Review Article

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Clinical Traits and Underlying Pathophysiological Mechanisms of Complex Regional Pain Syndromes

Abstract

Aim of the work

To study relationship between clinical pattern of complex regional pain syndromes (CRPS) and inflammatory and sympathetic parameters.

Materials and methods

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

Results

Fourteen patients had increased serum TNF 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 TNF were found.

Conclusion

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

Keywords: CRPS • TNF • SSR • Sympathetic skin response • Sympathetic dysfunction

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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. 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. In CRPS type II there is major nerve damage, i.e., a partial lesion of a peripheral nerve is necessary for the diagnosis. Several pathophysiological mechanisms have been proposed to explain CRPS. These mechanisms include facilitated neurogenic inflammation, pathological sympatho-afferent coupling, neuroplastic changes within the CNS and genetic factors. Inflammation has been proposed as a mechanism for CRPS because many clinical symptoms of acute CRPS resemble inflammation. 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). However, inflammation in CRPS may not always be neurogenic in nature. Regional local inflammation was demonstrated in patients with CRPSI as evidenced by increased TNF and interleukin without a concomitant increase of neuropeptides. Sympathetic dysfunction in CRPS has been addressed. Skin temperature

abnormalities have been attributed to either inhibition of norepinephrine-mediated sympathetic control over cutaneous blood vessels (as in the acute stage) or their supersensitivity to circulating catecholamines (as in the chronic stage with vasoconstriction) [1]. In addition, abnormal sudomotor function was also found in CRPS patients. Patients with sympathetically mediated pain (CRPSII) are suggested to have sympathetic-afferent coupling triggered by NGF and TNF in response to peripheral nerve lesion. Such coupling may be responsible for the sensitization of the C nociceptive neurons mediated by locally released norepinephrine and epinephrine. In CRPSI, similar coupling may take place as a result of subclinical traumatic nerve lesions of the cutaneous and deep somatic tissues. 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 TNF 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 [2].

Materials 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 electrophysilogical study were included. The study was approved by the local ethical committee of Faculty of Medicine, Alexandria University [3]. Patients were diagnosed according to the revised Budapest criteria (research diagnostic criteria), 2004. Patients were excluded from the study if one or more of the following were present: hypertension as it affects the level of catecholamines 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 TNF, acute phase proteins and blood picture, intake of drugs that affect the vascular system, corticosteroids and immunosuppressive drugs and delayed bone healing. Moreover, smokers were also excluded from the study. 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) [4]. (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.

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 nerve, brachial plexus, triple nerve injuries (median, ulnar and radial) as well as a painful neuroma due to old ulnar nerve injury at the wrist (total = four; 19%). Sixteen patients (76.2%) were females and five (23.8%) were males. Their mean age was 43 ± 15.17 years (ranging from 17 to 61) and the mean disease duration was 3.75 ± 2.21 months (ranging from 1 to 7). Twenty patients had different combinations of manifestations suggestive of acute (warm) CRPS while only one patient (4.76%) had primary cold CRPS with bluish hand discoloration, decreased local temperature and increased sweating of seven month duration [5].

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. Low density of nociceptive C and A™ fibers in CRPS I provide further support of such pathophysiologic similarity [6].

Localized inflammatory processes (peripheral afferent mechanism) as well as autonomic abnormalities (peripheral efferent mechanism) are among the proposed pathogenic mechanisms of CRPS. In the present study, TNF was found elevated in 2/3 of the studied patients. This reflects a significant inflammatory component of the pathogenic mechanism [7]. TNF is

a key cytokine contributing to CRPS features. Tissue injury leads to production of TNF (which also induces other proinflammatory cytokines) by endothelial cells, fibroblasts, lymphocytes and tissue macrophages which can lead to sensitization of nociceptors and amplification of neurogenic inflammation. Proinflammatory cytokines can be operant in CRPS independent of neurogenic inflammation. The increased TNF level in CRPS patients was proved in many studies whether in patients' sera or locally in blister fluid. However, in a study performed by van de Beek [8]. Serum TNF was within-normal limits in CRPS patients. This is in agreement of one-third of our patients who had normal serum TNF 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 TNF 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 TNF 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 TNF level and disease duration in our study [9]. Also there was no significant difference between patients with elevated serum TNF and those without regarding disease duration in our study. However, Huygen et al found serum TNF to be normal in their patients while elevated in suction blister fluid in the affected side representing strictly local inflammation. This may explain the normality of serum TNF among some of our patients and if so, inflammation can still be considered as an operating mechanism of such patients [10].

Conflict of Interest

None

Acknowledgment

None

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