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PhD THESIS

Complex regional pain syndrome – diagnostic and treatment –Summary–

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Complex regional pain syndrome (CRPS) is the current name of the syndrome known in the past under the name of reflex sympathetic dystrophy or causalgia. In addition to the classic particularities of neuropathic pain – burning sensation, hyperalgesia and allodynia, CRPS is associated with local edema and modifications that suggest autonomous involvement – hyperhidrosis, changes in color and temperature of the skin of the affected region. Consequently, trophic changes of the skin, hair and nails as well as impaired motor function – loss of muscle strength, decreased active range of movement and tremor, may appear.

Although CRPS can practically appear after any type of lesion, the most common documented trigger factors are surgery, fractures and sprains. Patients with CRPS experience not only intense pain, but also significant functional deficits and psychological distress. CRPS is one of the most difficult painful chronic diseases to treat, because there is no defined drug treatment and the clinical studies are not able to support the effectiveness of the frequently used interventions. Due to the absence of effective drug treatment, expensive and invasive palliative interventions are often used, such as spinal cord stimulation and intrathecal drug administration. The lack of a suitable treatment for CRPS results in general from the incomplete understanding of its physiopathological mechanisms.

The clinical stage and severity of the condition determine the therapeutic attitude. In the acute stage of CRPS, when the patient presents quasi-permanent severe pain, intense physical work is not recommended, because it can cause the exacerbation of symptoms. Thus, the immobilization of the affected limb, pain relief and physical therapies are justified. The painkillers of choice are opioids, tricyclic antidepressants and anticonvulsants. In addition, glucocorticoids should be taken into account if symptoms and signs of inflammation are present. The sympatholytic procedures – the sympathetic blockade – identify the component of the pain that is maintained by the sympathetic nervous system (SNS). Psychological counseling needs to be included in the treatment arsenal on one hand to detect aggravating factors and on the other hand to strengthen the therapeutic obtained response. Thus, it is important, in the daily practice, to train the patients and health staff regarding the risk factors and the initial signs of CRPS, in order to early establish the diagnosis.

Taking into account the considerations above, we focused the study on the identification of biological markers with high sensitivity and specificity for CRPS. The inflammation signs, such as the increase temperature of the skin, edema, skin color changes and pain have justified the evaluation of the inflammatory profile in CRPS. To highlight the inflammatory profile

specific for CRPS we quantified the proinflammatory cytokines – tumor necrosis factor α (TNF), interleukin-1 β (IL-1 β) and interleukin-6 (IL-6) – and the anti-inflammatory cytokine – interleukin-10 (IL-10). In addition, CRPS is also associated with neurogenic inflammation, which mainly depends on the intervention of neuropeptides, such as calcitonin gene-related peptide (CGRP) and substance P (SP).

Considering that the inflammation which contributes to the development of CRPS can have two sources, both cytokinic and neurogenic, the main target of our study was to quantify the amount of proinflammatory (TNF, IL-1 β , IL-6) and anti-inflammatory (IL-10) cytokines, as well as neuropeptides (SP, CGRP), in the serum of patients with CRPS. The classic mechanisms of inflammation include various immune cells, such as lymphocytes and mast cells, which after damage to the tissue, produce proinflammatory cytokines that will generate local edema, characteristic to early phases of CRPS. In addition, the inflammation is also enhanced by a lower concentration of anti-inflammatory cytokines. Moreover, the release of neuropeptides directly from the nociceptive fibers as a response to trigger factors increases the extravasation of plasma and vasodilation, causing swelling of the affected segment.

Furthermore, we correlated the inflammatory markers with the clinical aspect characteristic to the three stages of CRPS. One of the secondary objectives of the study was pointing out the importance of early diagnosis and treatment in order to improve symptoms and reduce the functional deficit. Thus, following the tissular lesion, an inflammatory response is generated by the local macrophages amplifying the migration of blood cells. Various inflammation mediators act synergistically to induce and maintain the appearance of pain.

Some patients may present increased susceptibility in developing abnormal reactions to painful stimuli, extended over a longer period of time, with a higher predisposition for CRPS. In this regard, another important objective was to evaluate the involvement of demographic factors (age and sex), preexisting pathologies, CRPS etiology, characteristics and severity of the lesions, non-specific biological inflammatory syndrome, lipid and glucose profile and psycho-emotional status in the CRPS examined group.

Taking into account the incomplete knowledge of the ethiopathogenic process involved in CRPS and the administration of a predominantly symptomatic treatment, the purpose of this research thesis has been:

- identifying the predisposing and triggering factors of CRPS,
- highlighting the involved pathogenic pathways,

- to establish new therapeutic targets.

We conducted an observational, longitudinal and prospective study, over a period of four years: from 2016 to 2019 and included a group of 60 patients from the Clinic of Rheumatology of the Emergency County Hospital of Craiova. The procedures and evaluations have been carried out in the same unit.

Initial instructions provided to the patients have been to continue their medication, without any modifications for at least one week prior to enrollment in the study. The severe pain caused by discontinuation of the therapy and the rebound effect, may prevent the specific determination of the cytokine activity. Eligibility screening has been conducted through detailed health questionnaires. The control group included 12 women and 8 men with ages between 20 and 52, similar to the age of the patients with CRPS (23-72 years). The average height and weight have been comparable between the two groups (control: 168 ± 7 cm, 76.5 ± 10.1 kg; patients: 166 ± 9 cm, 81.2 ± 15.3 kg) with the body mass index slightly increased in the patients' group (25.2 vs. 29.4).

Besides cytokine and neuropeptide determination, usual blood tests have been carried out. These tests included a complete blood count, C reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen (FB), total cholesterol (CHL), triglycerides (TG), total lipids (LT), glucose (GL) and were determined in the laboratory of the Emergency County Hospital of Craiova.

Patients' data was divided into three groups: acute (A), chronic, which includes the atrophic and dystrophic clinical stages (C) and the control/reference group (R), as follows: a number of 20 patients both in the control and the acute group and 40 patients in the chronic group. We tested the resulted values for normal distribution using the Shapiro-Wilk test. The differences between the control, acute and chronic patients, we used the nonparametric Kruskal-Wallis test. In addition, the Mann-Whitney test was used to compare each pair of samples. In order to differentiate cases with CRPS and normal subjects, we used the receiver operating characteristic curve test (ROC curve).

Regarding demographics, female sex has been one of the risk factors for the onset of CRPS, the ratio women/men was about 3:1. Women aged 54-66 years, in the postmenopausal period, have been predominantly affected. Background of senile osteoporosis, together with bone demineralization subsequent to prolonged immobilization and the increase of osteoclast activity under the action of inflammation cells led to an increased incidence of osteoporosis

among patients with CRPS. Few differences have been observed, without statistical significance, regarding the origin of patients with CRPS. We believe that more patients from urban areas addressed to healthcare services than people living in rural areas, even though the incidence of trauma is greater in rural areas.

Smoking status has also been strongly associated with the development of CRPS; a percentage of 61.67% of the patients were smokers. This aspect is probably explained by the vasoconstrictor action on microcirculation, and also by the accelerated process of atherosclerosis in smoking patients. Changes in the size and integrity of the blood vessels will thus enhance the vaso and sudomotor clinical changes.

The etiology of CRPS in the examined group has been mainly represented by trauma (fractures, dislocations, sprains, contusions), followed by abarticular conditions –rotator cuff injuries, carpal tunnel syndrome, cardiovascular pathology – stroke and myocardial infarction, and in a minority of cases postherpetic neuralgia and neoplasms.

CRPS development depends firstly of the trigger event. Trauma caused by medium or high intensity forces, that induce in particular fractures is frequently associated with CRPS. Additionally, comminuted or intraarticular fractures and nerve damage incurred after severe trauma will increase the risk of development as well as the severity and duration of clinical events. A rare entity, but with severe evolution and unfavorable prognosis, dependent on the preexisting pathology is paraneoplastic CRPS.

Psycho-emotional status of the patient has also been correlated with the occurrence and severity of CRPS. Disability and severity of pain have been strongly associated with psychological factors (depression, anxiety and kinesiophobia) in CRPS, but a cause and effect relationship could not be established in this observational study. Sleep disorders have been strongly associated with the susceptibility to develop CRPS. In addition, patients who experienced many stressful events in life –family conflicts, workplace caused stress, deaths of relatives – are more likely to develop CRPS.

History of chronic back pain or headaches have represented risk factors. Of the patients diagnosed with migraine associated CRPS, 61.2% have reported the occurrence of severe headaches since before the onset of CRPS symptoms. Thus, migraine may be a risk factor for CRPS, and the its presence may be associated with a more severe form. Fibromyalgia is independently associated with CRPS.

Usual blood tests screening revealed the association of CRPS with metabolic syndrome. Statistically significant high levels of triglycerides and cholesterol were determined, dyslipidemia representing an important factor of risk. This result sustains the early development of atherosclerosis compromising the vascular flow and emphasizes the clinical manifestations.

Trying to explain the ethiopathogenic processes involved in CRPS, we started from the assumption that the inflammatory response from the central and peripheral nervous system plays an important role in the development and persistence of the pain pathology.

The inflammation involved in the development of CRPS is of two types: cytokinic and neurogenic. Even if we observe certain trends (higher levels of proinflammatory and lower anti-inflammatory activity) in the obtained cytokine profile, the results have not been statistically significant. The p values for TNF, IL-1 β , IL-6 and IL-10 were high (0.4497, 0.0768, 0.2337 and 0.6300, respectively), but cannot be used in diagnostic purposes. A cytokine with anti-inflammatory properties is represented by IL-10. It inhibits the expression of pro-inflammatory cytokines such as IL-1, IL-6 and TNF α . In addition, IL-10 may reduce the receptors of proinflammatory cytokines. Although the results of our study have not been significant statistically and cannot be used for diagnosis, we can still see a decrease tendency of IL-10 in the patients group.

Neuropathic pain (NP) is a debilitating disorder produced by the mechanical/chemical deterioration of the tissues, infections or peripheral/central system nervous condition. Common features of NP involve sensorial disorders, including spontaneous pain, increased sensitivity to painful stimuli (hyperalgesia) and painful sensitivity to harmless stimuli (allodynia).

Most of the post-traumatic inflammatory changes observed in patients with CRPS are mostly mediated by two neuropeptides – CGRP and SP. The serum levels that we identified have been significantly higher in patients with CRPS than the control group.

In the conducted study, CGRP has significantly higher values ($p < 0.0001$) in patients with CRPS. CGRP is the main transmitter that induces neurogenic vasodilation of arterioles. This is mainly due to its actions on the endothelial cells and vascular smooth muscle. Features commonly found in CRPS like excessive hair growth and the activation of sweat glands are also stimulated by CGRP. In addition, the cell types that are involved both in innate immunity (dendritic cells, keratinocytes, mast cells) as well as in the adaptive immune system (T lymphocytes), are directly activated by SP and CGRP.

We have identified significantly increased levels of SP ($p < 0.0001$) in patients with CRPS. Our data provides evidence that SP is involved in CRPS, being partly responsible for clinical aspects through its neuromodulator and immunomodulators properties.

We obtained higher levels of neuropeptides in patients with acute CRPS and slightly decreased concentrations in the chronic group. This aspect can be explained by the fact that in patients with chronic CRPS, central mechanisms are those who play an important role in maintained symptoms.

Early diagnosis of CRPS allows an appropriate treatment that has as purpose to completely restore the functionality of the affected segment. A chronic pain syndrome causes alterations both in the central and peripheral nervous system, leading to a decrease in the effectiveness of the administered therapy.

A highlighted aspect in this study revealed the susceptibility of patients to generate abnormal responses to painful stimuli, with predisposition to develop CRPS. Regarding the epidemiological data that we obtained an average age of development of CRPS between 54-66 years, the incidence increasing with the advancement in age. The distribution of the sexes has been in favor of female sex; the upper extremity being affected more frequently than the lower, and the fracture being the triggering event in over 44% of the cases. The dysfunction of the autonomic sympathetic nervous system involved in the pathogenesis of CRPS has been supported by evidence of dyslipidemia in the evaluated patients, as well as the presence of the nonspecific biologically inflammatory syndrome.

The evaluation of the CRPS trigger factors has revealed an increased frequency of trauma resulting in fractures or soft tissues lesions, cardiovascular or CNS pathologies, neoplasms representing an exceptional etiology.

In addition, results obtained from the inflammation profile analysis from patients with CRPS has shown that the neuropeptides (SP, CGRP) could be successfully used to confirm the CRPS diagnosis. In order to support this statement, we used the ROC curve method.

Thus, we conclude that neuropeptides could be used to support the CRPS diagnosis, a predominantly neurogenic condition. Starting from studies that have used CGRP antagonists for the treatment of migraines, the increased values of neuropeptides justify the administration of pathogenic therapy in CRPS. We support this affirmation because the neuropathic pain

remains refractory to available analgesics, and chronic use of these drugs, in particular opioids, was shown to exacerbate pain and inflammation.

Although the study offers significant evidence only for the increase in neuropeptides, the pro-inflammatory cytokines had also high values, but without statistical significance. A meta-analysis has revealed a relatively high heterogeneity of the inflammatory markers, in particular cytokines, since they act at particularly low concentrations. Consequently, we believe that longitudinal studies in patients with CRPS will be important for a better understanding of the complexity of this process. Moreover, a larger number of patients with acute stage of CRPS would be able to provide new perspectives on the role of cytokines, as they would be able to be increased in comparison to chronic patients, consecutive their short half time. Increased IL-1 β values justify the use of a specific IL-1 receptor antagonist, which is competitively bound on the same receptor as IL-1 β , but does not transmit cell signal, blocking cellular modifications. Thus, the administration of an antagonist of the IL-1 receptor, anti-TNF therapies and an antagonist of the IL-6 receptor can prevent or reduce hyperalgesia mediated by cytokines and mechanical allodynia induced by nerve lesions. The low levels of IL-10 in the serum of patients support the utility of therapies with of IL-10 agonists, regarding its anti-inflammatory and antinociceptive effects.

Thus, CRPS remains an exclusion diagnosis, established mostly on clinical criteria with favorable prognosis if early multidisciplinary treatment is applied. In addition, the period of recovery after injury is slightly different to each individual and depends on the severity of trauma and the predisposing factors, such as age, sex and the presence of other comorbidities.