Complex regional pain syndrome is a chronic neuropathic pain condition which usually arise after trauma. It is associated with some of the sensory, vasomotor, sudomotor, motor and trophic symptoms and signs.

Due to variability of symptoms and long-lasting pain, these patients are hard to rehabilitate. They exhibit activity related fear and so have pronounced functional limitations. Adequate rehabilitation procedures, frequently long lasting, are essential for their optimal recovery, so rehabilitation specialist should constantly update their knowledge on this issue.

Emerging researches on pathophysiology, diagnosis and treatment of CRPS created a need for systematization of current body of evidence. Available researches on efficacy of different treatment options are still insufficient to create precise therapy guidelines, so future researches are needed in order to promote better rehabilitation outcomes.

Key words: complex regional pain syndrome, treatment, rehabilitation

INTRODUCTION

Complex regional pain syndrome (CRPS) is a chronic neuropathic pain condition characterized by sudomotor and vasomotor disturbances, trophic and bone changes, as well as motor impairment. It has formerly been known as reflex sympathetic dystrophy (RSD), Sudeck atrophy or shoulder-hand syndrome. RSD is the most frequently used term for this condition pointing out the role of sympathetic nervous system in its etiology. In recent years, as knowledge about the condition improved, it was shown that sympathetic response is not specific for the entity and there were no evidences for its reflexive nature, neither.

In 1994 International Association for the study of pain (IASP) adopted new terminology better describing the condition and so the new term -CRPS was introduced. CRPS is subdivided into type I and type II, reflecting absence or presence of documented nerve injury, but without any difference between them regarding symptom presentation and response to therapy.

In recent years there has been much of progress in understanding the pathophysiology of the condition, defining diagnostic criteria and evidence based treatment. Since rehabilitation specialists are the ones that diagnose and treat majority of these patients, a necessity to systemize current knowledge on this topic emerged. Patients with CRPS are generally hard to rehabilitate due to severity of problems and long term need for rehabilitation process. Thus, a constant update on all relevant issues regarding this condition is important, for it should help us guide our treatment and allow maximal rehabilitation potential to our patients.

ETIOLOGY

Etiology of CRPS is still poorly understood, but there are evidences that certain events can trigger development of this condition. Incidence of CRPS in general population has recently been investigated and data show 26.2 new cases per 100 000 annually. Incidence of CRPS has been 11-18 % following fracture, total knee arthroplasty or 8% after carpal tunnel release, although large prospective studies on this issue are still missing. CRPS can also arise after minor trauma such as sprain or after conditions such as myocardial infarction, herpes zoster infection or stroke. CRPS affects female more than males at ratio approximately 4:1, with mean patient’s age at diagnosis over 52 years. Children can also develop CRPS that shows certain specificities in diagnosis and treatment. Susceptibility for developing CRPS after trauma has lately been partly explained by genetic risk, showing association of certain HLA and CRPS. Some authors had also presented its autoimmune nature characterized by elevated Ig G serum antibodies directed towards autonomic re-
Regarding psychological factors and their association with CRPS, there are no evidences to support causal relationship. It seems that an interaction between psychological status and CRPS exist and should be considered in the context of biopsychosocial model proposed for chronic pain conditions. Up to date there has not been well designed prospective studies analyzing natural history of CRPS. Available data are all from retrospective studies and show symptom and signs duration from 1-3 years for the majority of patients, without uniformity of impairment progression, ranging from no change to worsening of symptoms and signs.

**PATHOPHYSIOLOGY**

Exact pathophysiological mechanism of disease is still unknown, but it certainly involves multiple pathways. It was believed that CRPS represents sympathetically mediated peripheral pain, but nowadays evidences exist in favor of central nervous system involvement. Mechanisms involved in generation of CRPS includes altered cutaneous inervation with reduced density of C and Ad fibers in affected region, peripheral and central sensitization as well as brain plasticity which includes reduced representation of affected limb in somatosensory cortex. There is also important role of altered sympathetic nervous system with expression of adrenergic receptors on nociceptive fibers after injury, but without excessive sympathetic outflow, as commonly believed. The role of inflammation in development of CRPS is evident, including classic and neurogenic inflammatory mechanisms. Increased local, systemic and cerebrospinal fluid levels of proinflammatory cytokines (TNF-α, interleukin 1β, 2) and increased proinflammatory neuropeptides (substance P, bradykinin, calcitonin gene related peptide) are also seen among these patients.

**DIAGNOSIS**

Over the years several diagnostic criteria for CRPS were used: IASP, Bruehl, Valdman. In 2003 Budapest diagnostic and research criteria were established, which managed to overcome the disadvantages of previously used ones. Decision rule for clinical diagnosis requires two of four signs categories and three of four symptom categories and shows 0.85 sensitivity and 0.69 specificity. For research purposes, diagnostic rule is to obtain at least one symptom in all four symptom categories and one sign in two sign categories, reaching sensitivity of 0.70 and specificity of 0.94. Diagnostic criteria are given in Figure 1.

**TREATMENT**

**Pharmacological treatment**

According to the latest systematic review on treatment of CRPS we can classify evidences for certain therapy options in several categories depending on proofs strength for their efficacy.

There is strong evidence for the efficacy of bisphosphonates. Intravenous pamidronate (60 mg as a single dose) was used in long standing CRPS (more than 6 month of duration) while alendronate in high daily doses of 40mg for 8 weeks showed good results in patients with early CRPS.

Moderate evidences are found for low dose intra venous ketamine infusion (4.5 days of continuous treatment or 10 consecutive days of outpatient treatment) in long standing, refractory CRPS and can be integrated in treatment only in multidisciplinary pain centers were anesthesiologist is a part of a team.

Limited evidences exists regarding the efficacy of oral tadalafil and low dose intravenous immunoglobulin in long standing CRPS.

It should be mentioned that there are still no evidences for the treatment with antihyperalgesic drugs, despite neuropathic nature of pain.

Earlier systematic review presented evidences for good pain relief with oral steroids (30-40mg of prednisolon given 2-12 weeks) but data mainly concerned post stroke painful shoulder and trials have not been based on new diagnostic criteria. No studies were found evaluating paracetamol as a stand-alone treatment for CRPS-I. There is insufficient evidence on the degree of pain control achieved by NSAIDs and oral opioids in CRPS-I patients.

Effects of calcitonin are very contradictory, but having in mind that some positive effects are seen, it could be administered if other medication fail to reduce pain.

Regarding possible prophylactic measures there is one high quality trial in patients after wrist fractures for vitamin C (500mg for 50 days).

**PHYSICAL THERAPY**

Rehabilitation interventions for treatment of CRPS are widely used with no clear consensus on the content of procedures.

There are strong evidences from literature regarding graded motor imaginary program for pain reduction in CRPS after wrist fractures. This program consisted of recognition of hand laterality, imagined hand movement and mirror movement of the affected hand. Patient participated in program for 2 weeks in each stage, performing task hourly for 12 hours.

Effects of mirror therapy on pain, as stand-alone treatment, are analyzed only in post stroke CRPS and are found to be moderate.

Method of graded exposure is technique that forms a part of cognitive behavioral concept. It comprise of exposure to noxious stimuli under supervision of physiotherapists. The study evaluating this approach, although generated on very small sample size, showed decreased level of pain-related fear, pain intensity and disability. It is also shown that perceived fear of activities is linked to the functional limitations in CRPS-I. This finding signalize clinicians that cognitive-behavioral treatments for patients with CRPS should be customized. This kind of approach is closely related to another relevant is-
sue in rehabilitation of patients with CRPS - weather patient should exercise despite pain? Studies that analyzed functional improvement of patients neglecting pain as symptom that influence treatment decision, were also known under the name of "pain exposure exercises". They incorporated some elements of cognitive behavioral therapy and different therapeutic measures as desensitization, active and passive motion and showed very good results in improving functionality, decreasing disability and even reducing pain intensity. A multicenter randomized control trial has been announced to explore effects of pain exposure therapy compared to standardized care, so in future we expect to have even more valid data on this issue.

Desensitization procedures are widely accepted as the techniques to begin with rehabilitation program. Evidence for this treatment option in CRPs are based on one small trial where sensorymotor returning was associated with decreased pain, restoration of the impaired tactile discrimination and regaining of cortical map size in contralateral somatosensory cortex.

Stress loading is another therapeutic procedure known for years. Its effect on decrease of pain intensity and swelling is demonstrated and is believed to reverse sensory processing abnormalities by stimulating the large fiber receptors. Exercises include active traction and compression exercises without movement in affected joint( scrubbing and carrying activities).

Movement disorders are quite often seen in CRPS. It is estimated that dystonia is present in approximately 20% of patients with concurrent myoclonus and tremor and bradykinesia as a stand-alone sign. Despite their common presence, clinical trials investigated treatment options(benzodiazepines, botulinum toxin or baclofen) are all non comparative, so their effectiveness is yet to be established.

Regarding physical modalities in treatment of CRPS, there are limited evidences of superior effect of low level laser therapy to interferential currents in decreasing temperature in extremity, pain, swelling and disability compared with electrotherapy (TENS and stabilne galvanization).

Electromagnetic field therapy has been shown ineffective for CRPS in the high quality RCT. Interestingly, there are no studies on transcutaneous electrical nerve stimulation(TENS) although it is a physical modality widely used for pain control, compering effects of physical and occupational therapy for CRPS, it is shown that

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### FIGURE 1

#### BUDAPEST DIAGNOSTIC CRITERIA (adapted from Ref. 33.71)

<table>
<thead>
<tr>
<th>A</th>
<th>The patient has continuing pain which is disproportionate to the inciting event</th>
<th>Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Category</td>
<td>Sign</td>
</tr>
<tr>
<td>SENSORY</td>
<td>Alldynia and/or hyperalgesia</td>
<td>Hyperaesthesia</td>
</tr>
<tr>
<td></td>
<td>Temperature asymmetry (&gt;1°C) and/or skin colour changes and/or skin colour asymmetry</td>
<td>Yes/No</td>
</tr>
<tr>
<td>VASOMOTOR</td>
<td>Oedema and/or sweating changes and/or sweating asymmetry</td>
<td>Yes/No</td>
</tr>
<tr>
<td>SUDOMOTOR</td>
<td>Decreased ROM and/or motor dysfunction and/or trophic changes*</td>
<td>Yes/No</td>
</tr>
<tr>
<td>MOTOR/TROPHIC</td>
<td>At least one sign in minimum two categories needed</td>
<td>At least one symptome in minimum three categories needed</td>
</tr>
<tr>
<td>C</td>
<td>No other diagnosis can better explain the signs and symptoms</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>

A-C must apply

ROM - range of motion; *motor disfunction-tremor, weakness, dystinia, trophic changes-hair/nail/skin
both have positive effect on pain reduction and improved function, with some of the studies showing a slightly better effect and cost effectiveness for physical therapy.64,65

A meta analysis of acupuncture treatment in CRPS following stroke showed positive results in pain reduction, but there is still a need for higher quality trials to estimate its effectiveness.66

Occlusal splints and manual lymphatic drainage showed no reduction of pain intensity.57,68

Although not primarily a therapeutic device, repetitive transcranial magnetic stimulation (rTMS) has its place in rehabilitation, mostly after stroke, but it is shown that there is high level of evidence for its use in pain reduction in long standing CRPS.69,70

**DISCUSSION**

Up to date there has been published few clinical guidelines and systematic reviews on treatment of CRPS. Majority of them focused on all available therapeutic options, without special interests in rehabilitation procedures.34,42,71-34,42 There has been only one review article concerning rehabilitation issues, but it mainly focused on description of different kinesiotherapeutic approaches without giving clear review on evidences regarding most commonly used therapeutic procedures. So, the scope of our research was to summarize all available evidences on rehabilitation treatment, including kinesiotherapy, occupational therapy, physical modalities and special procedures used in CRPS treatment.

After analyzing available evidences, it is clear that majority of them are still of low level. Even the studies of high methodological quality47,49 are not replicated in another group of patients, so the high level of evidence they offer is only for specific group of patients. Current data offer high level of evidence only for graded motor imaginary treatment for CRPS patients after wrist fracture47,48 and it is based on minimum of evidences needed for fulfilling that criteria, meaning two high quality trials. In other words, majority of trails of rehabilitation procedures are either of low quality or restricted to one certain CRPS group of patients, so results of research could not be generalized. Nevertheless, we thought it was important to present all available evidences for they could certainly help us in some of the decision making and on the other hand, clearly demonstrate focus of future rehabilitation research. Rehabilitation specialist is the one that treat patients with CRPS through very demanding, long-term rehabilitation process. As majority of patients develop CRPS after trauma it is of great importance to timely recognize the condition and start appropriate rehabilitation procedures. It seems that our treatment should focus primarily on kinesiotherapeutic measures, especially the ones that promote activity.55

Rehabilitation process should start with active and passive exercises, despite the pain, along with procedures for alleviating pain. Although not evidence based, some experts suggest parallel cognitive behavioral therapy, emphasizing pain coping strategies which aim to help patients realize that pain accompanying physical activity does not mean tissue damage.25,55

Graded motor imaginary program, should also be incorporated in program from the beginning. It is advised to start pain control according to the WHO ladder72, because it is widely available, not expensive and with relatively low and controllable side effects.71 Low level laser therapy and acupuncture should be tried for additional pain relief. If neuropathic component of pain is dominant, desensitization techniques should be introduced. Antihyperalgezic drugs, especially pregabalin, as well as antidepressants, could be prescribed based on their use in other neuropathic pain conditions, although their effect on CRPS is yet to be established.

In the course of rehabilitation, progressive loading of the extremity should be encouraged. Duration of treatment is not limited, since rehabilitation is specially needed in long standing cases of CRPS. In the case conservative treatment fails, patients are advised for intervention procedures like spinal cord stimulation, anaesthetic blockade of sympathetic ganglia or sympathectomy.55 Although there are no yet evidences for multidisciplinary interventions in CRPS, experts suggest such an approach because of complex nature of the condition and its multifactorial cause.55,53

**CONCLUSION**

Available evidences suggest that rehabilitation treatment plays important role as pain relieving procedure, but also as therapeutic approach which lessen disability. Rehabilitation specialist should guide this complex treatment, timely recognizing the condition and including all available resources in its management.

Further research is needed to create higher level of evidence in all therapeutic fields so we could achieve maximal rehabilitation outcomes.

**SUMMARY**

Kompleksni regionalni bolni sindrom je hronično neuropatsko bolno stanje koje najčešće nastaje posle traume. Udržano je sa nekim od senzornih, vazomotornih, sudomotornih, motrnih i trofičkih znakova i simptoma.

Zbog raznovrsne simptomatologije i dugotrajnog bola ovi pacijenti se teško rehabilituju. Karakterističan je i izražen strah od aktivnosti, što doprinosi ograničenjima u funkcionalnosti. Ađekvatna rehabilitacija, koja vrlo često mora biti dugotrajna, omogućava u najvećoj meri optimiran oporavak ovih bolesnika. Ova činjenica ukazuje da lekar koji se bave rehabilitacijom treba pažljivo da prate novu saznanja vezana za ovo stanje.

U poslednje vreme objavljena su brojna isražavanja o patogenezi, dijagnozi i terapiji kompleksnog regionalnog bolnog sindroma. Sadašnji dokazi o efikasnosti različitih vidova terapija nisu dovoljni da bi se formirale jasne preporuke u terapijskom pristupu. Za postizanje boljih efekta rehabilitacije potrebna su dalja istraživanja u ovoj oblasti.

Ključne reči: kompleksni regionalni bolni sindrom, tretman, rehabilitacija
BIBLIOGRAPHY


