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REVIEW ARTICLE

COMPLEX REGIONAL PAIN SYNDROME: AN UPDATE

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ABSTRACT: Complex Regional Pain Syndrome or CRPS is a chronic disabling heterogenous pain disorder due to trauma, resulting in sensory changes, motor function impairment, psychological changes. Diagnosis is based on clinical features and investigations. The patho-physiology is not clearly known. There is no single drug therapy, only combinations work. Treatment is multidisplinary involving medical, psychological and rehabilitation. Newer modes of spinal cord stimulations, neuraxial mode of analgesics and newer drugs are promising.
KEYWORDS: Complex Regional Pain Syndrome, Management, Rehabilitation, Newer modes.

INTRODUCTION: Complex Regional Pain Syndrome is a combination of regional pain and sensory changes following trauma which exceed in magnitude and duration of anticipated healing period. The International Association for the Study of Pain defined it as "A variety of painful conditions following injury which appears regionally having a distal predominance of abnormal findings, exceeding in both magnitude and duration, the expected clinical course of the inciting event often resulting in significant impairment of motor function, and showing variable progression over time". There are two subtypes, CRPS I (Reflex Sympathetic Dystrophy) and CRPS II (Causalgia).[1,2]

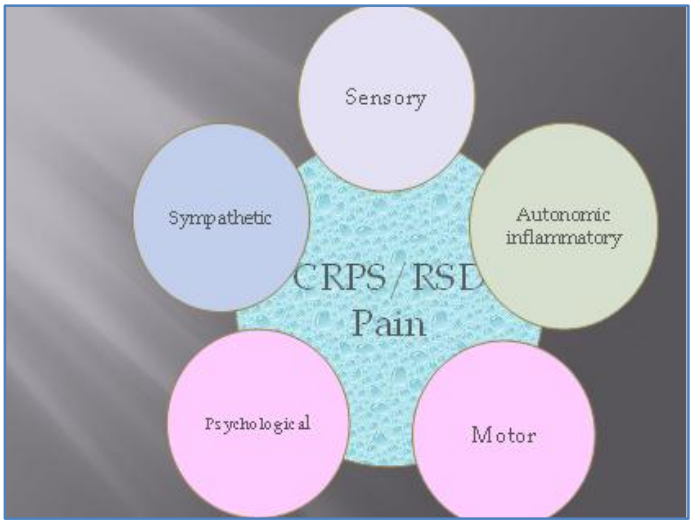

Figure 1

CRPS I (R S D): It is a syndrome of pain with hyperalgesia after an initiating, noxious event with symptoms disproportionate to inciting event and not limited to a single peripheral nerve. There is evidence of edema, skin blood flow abnormality or abnormal sudomotor activity. The diagnosis is by exclusion of condition that account for the degree of pain and dysfunction. CRPS

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II(Causalgia) is a syndrome of pain where a known nerve injury is responsible because not all pains are sympathetically maintained. The pain can be Sympathetically Maintained Pain (SMP) where the pain is dependent on the sympathetic activity in the affected area and is relieved by the blockade of the efferent sympathetic nervous system and Sympathetically Independent Pain (SIP) where pain is unresponsive to sympathetic blockade. Therefore, clinically a patient may present with either SMP or SIP or both i.e., part of chronic pain maybe SMP or part of chronic pain maybe SIP.

Figure 2

INCIDENCE: CRPS can occur at any age, highest being among 50-70 years and upper limb being affected more commonly in adults and the lower extremity in adolescents. Children below 7 years of age are more prone. It affects both men and women, although some studies show that it is more common in women (W:M = 4:1 ratio) and incidence in girls around 13 years is 80%. CRPS is seen with increasing frequency in injured workers, following surgery, myocardial infarction and stroke.

SYMPTOMS: CRPS presents with a wide range of symptoms and the hallmark of pain is that it is out of proportion to the inciting event[2]. It usually occurs in hands and feet which are rich in nerve innervations but can also present anywhere in the body. Pain can be spontaneous or stimulus evoked and does not progress sequentially. The disease progression is very variable and not time limited. Symptoms can be in the form of:

Allodynia – pain evoked by mechanical or thermal stimulus that usually does not cause pain, as light touch.

Hyperalgesia - exaggerated response to a normally non-painful stimulus.

Hyperpathia - abnormal painful reaction to a stimulus.

There are three stages of CRPS:

STAGE ONE: 3 months from onset.

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There is severe, burning pain at the site of injury. Muscle spasm, joint stiffness, restricted mobility rapid hair and nail growth and vasospasm, affecting colour and temperature of skin[3,4].

STAGE TWO: 3 – 12 months from onset.

This stage presents with more intense pain, swelling spreads, hair growth diminishes and nails become cracked, brittle, grooved and spotty. Osteoporosis becomes severe and diffuse, joints thicken and muscles atrophy.[1,2,4]

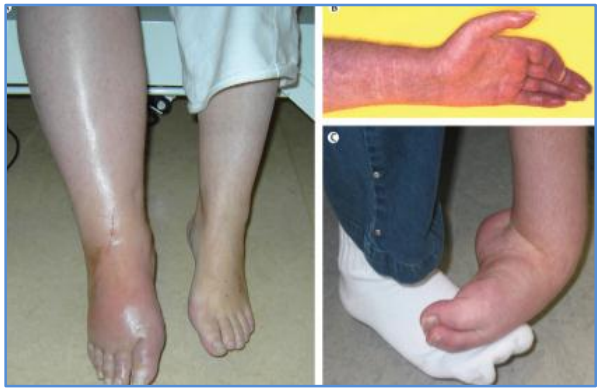

Figure 3: Vascomotor Changes and signs of CRPS

STAGE THREE: In this stage the pain is unyielding with irreversible changes in skin and bone, marked muscle atrophy, severely limited mobility of affected area and may involve the entire limb. Flexor tendon contractions with occasional limb displacement from normal position and marked bone softening and thinning are observed.[2,4]

PATHOPHYSIOLOGY 0F CRPS:

1. **Autonomic Nervous System mediated: Exact pathophysiology is not clear, but there are several theories[1,2,4]**:
    - Primary afferents thought to affect receptors endings of myelinated (A) and unmyelinated (C) afferent fibres– documented for inflammatory process.
    - Vascular bed consisting of arterioles, capillaries, venules.
    - Micromillieu (micro-environment) depends on several interacting components:
    - Neural activity in post-ganglionic nor-adrenergic fibres supplying blood vessels cause release of nor-adrenaline and other substances and vasoconstriction
    - Excitation of Primary afferents (Aα& C fibres) cause vasodilatation in pre-capillary arterioles and plasma extravasation in post-capillary venules (C-fibres only) by release of substance P (SP) and other vasoactive components (calcitonin gene-related peptide)
    - Some of these effects can be mediated by non-neuronal cells – mast cells and macrophages
    - Change of temperature – a metabolic state of tissues
    - Sympathetic Nerve fibres interact in three levels:

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- Via adrenoceptors (mainly alpha) in blood vessels -→vasoconstriction
- Via adrenoceptors (mainly beta) in macrophages →release of cytokinins
- Via adrenoceptors (mainly gama) on afferents (further sensitisation of these fibres)

2. **Autoimmune etiology:** An autoimmune etiology had been suggested and 30 – 40 % patients of CRPS have surface binding auto-antibodies against inducible Autonomic Nervous System auto-antigens.

3. **HLA System (Human Leukocyte Antigen):** Evidence showed that HLA system plays a role, especially the HLA – B62, HLA – DQ8, HLA – DQ1, HLA – DR13 related dystonia and women with HLA system were more prone.

4. **Psychological factors:** Being a chronic condition, CRPS definitely has an impact on certain personality traits, especially in adolescents.

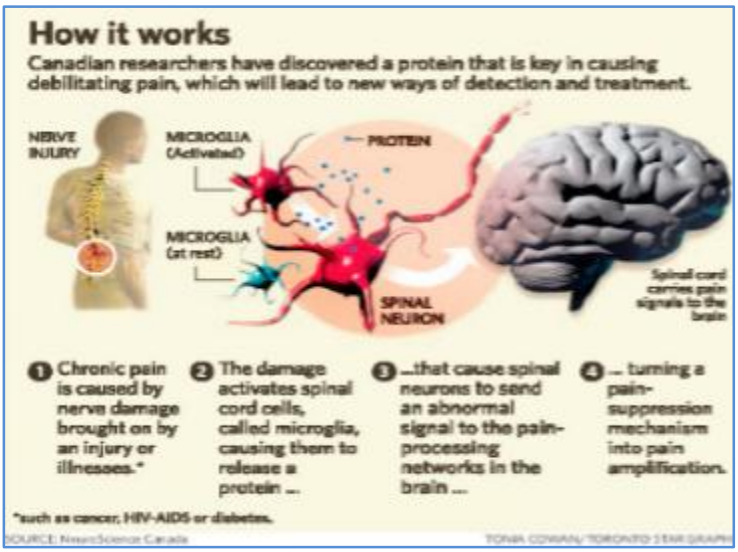

Figure 4

DIAGNOSIS: Diagnosis is mainly dependent on the clinical course. A detailed medical history of the initial trauma, history of sensory, autonomic, motor disturbances, development, distribution and characteristic of pain and time course help in clinching the diagnosis. Detection of any swelling, sweating, trophic, temperature and motor abnormality in disturbed area are important. Muscle strength of affected limb, somato-sensory abnormalities, characteristic or distribution details, elicitation of pain on movement and pressure at joints must be tested[3]. The other diagnostic methods include:

1. **Bone Scintigraphy:** This is positive in Sub-acute period about (1 year) showing vascular bone changes. Radio-labelled technetium anti-TNF α to image TNF α scintigraphically and found uptake in clinically affected hands.

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2. **Radiography:** This is useful in chronic cases of CRPS only. It shows patchy osteoporosis due to disuse, two weeks after onset of CRPS. Bone scan and Bone densitometry are useful guide for follow up.
3. **QST – Quantitative Sensory Testing:** Testing of thermal and thermal pain threshold gives information about functioning of unmyelinated and small myelinated afferent fibres of spinothalamic tracts.
4. **Autonomic Functions:** Infrared thermometry, Laser Doppler flowmetry, Infrared thermography and quantitative sudomotor axon reflex test (QSART) are new methods.
5. **Thermography:** Skin temperature differences of 1.0 C between two symmetrical body parts are significant.
6. **Sudomotor testing:** QSRT tell of function of sudomotor reflex loops and resting sweat output test may be used.

All the above investigations are used to follow the progress and response to treatment.

IASP Diagnostic Criteria for CRPS:

- Presence of an initiating noxious event, or a cause of immobilization
- Continuing pain, allodynia or hyperalgesia with pain disproportionate to inciting event
- Edema, changes in skin blood flow, abnormal pseudomotor activity in the region of pain
- Diagnosis is excluded by the existence condition that would otherwise account for the degree of pain and dysfunction

Research Diagnostic Criteria for CRPS: Budapest Criteria.
(Modified IASP Research Diagnostic Criteria for CRPS)

1. Continuing pain disproportionate to any inciting event.
2. Report at least one symptom in each of the four following categories.
    a. Sensory: Hyperesthesia an orallodynia.
    b. Vasomotor: Temperature asymmetry and or skin colour changes and or skin colour asymmetry in the affected region.
    c. Pseudomotor / edema: Edema and or sweating changes and or sweating symmetry in the affected region.
    d. Motor /Trophic: Decreased range of motion and or motor dysfunction(Weakness, tremor, dystonia) and or trophic changes (hair, nail, skin) in the affected region Presence of 2 symptoms and 2 signs gives 80% accurate diagnosis and presence of 4 symptoms and 2 signs as diagnostic criteria for CRPS is most effective criteria to rule in and rule out CRPS across different population.[4,5]

In conclusion, the diagnostic value of TPBS as a confirmatory test for CRPS according to the Budapest research criteria is low. The current study supports that no specific test is available for CRPS, which is diagnosed primarily through absent of the symptoms and signs.

Differential Diagnosis: It includes Deep Vein Thrombosis, Thrombophlebitis, Thoracic Outlet Syndrome, Myofascial Pain Syndrome, Cumulative Trauma Disorder, Peripheral Pain of Central Origin.

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MANAGEMENT of CRPS: The general strategy of the management of CRPS is multi-disciplinary. The goal being aimed at restoration of full function of the extremity with 50% pain relief and 30mm of 100mm VAS of pain scale along with improvement of quality of life. A team of Pain Specialists, Neurologists, Hand Surgeons, Orthopedic Surgeons, Physiotherapists, Psychologists, Occupational therapists are in need for effective management of CRPS patients. Severity of symptoms determines the therapeutic regime and 20 to 30% of the treated patients return to normalcy.[5,6]

Pharmacotherapy Guide:

- Mild – Moderate Pain: Simple analgesics and or blocks.
- Excruciating, intractable Pain: Opioids and or blocks or more experimental interventions.
- Inflammation, Swelling, Edema: Steroids or NSAIDS, immunomodulators.[7]
- Depression, Anxiety, Insomnia: Sedation, analgesic anti-depressants anxiolytics and or psychotherapy.[6,8]
- Significant Allodynia/ Hyperalgesia: Anticonvulsants and or other Na+channel blockers and or NMDA receptor antagonists.[9]
- Significant Osteoporosis, immobility, trophic changes: Calcitonin or Bisphosphonates.
- Profound vasomotor disturbance: Ca+ channel blockers, sympatholytics and or blocks.

Treatment of Inflammatory Process:

- NSAIDS – naproxen, ketorolac + lidocaine (IVRA)
- Corticosteroids – prednisone, methyl- prednisolone + lidocaine (IVRA)
- Immunoglobulins– IVIG-0.5g/kg (refractory cases)
- Monoclonal antibodies – Anti TNF (tumour necrosis factor) alpha antibody "Infliximab" was given as a low dose IV regional block and significant improvement was observed within 24 hours. "Remicade" in stage I of CRPS I was found supportive when given as infusion under a strict protocol at 0 week, 2 week, 6 week then once in 2 months for 1 year. Complete remission was reached within 8 weeks but sensory signs improvement came only after 6 months.
- Sensitisation of Pain.
- Baclofen intrathecal- GABA agonist (dystonia in Reflex Sympathetic Dystrophy
- Capsaicin (0.05% - 0.075%) – Topical application QID for 1 month
- Carbamazepine: oral for peripheral neuropathic pain[10]
- Anticonvulsants: Gabapentine– oral – 1200-3600mg/day
- Pregabaline oral 150-600mg/day
- Calcium channel blockade: Nifedipine– oral – limited role
- NMDA receptor blockers: Ketamine topical application in acute early dystrophic state showed beneficial and Ketamine infusion of 10-90mg/hour as awake or as sub-anaesthesia technique and high doses of 600-900mg for medically induced coma. Low dose continuous infusion of 5mg/hour to 30mg/hour in 70kg individual for4 days reduces pain for nearly 11 weeks.
- Na+ Channel Blockers: Lidocaine IV for Allodynia[10]

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- Opioids: Morphine was effective in upper limb CRPS[11]
- Tricyclic anti-depressants: amitriptyline – for impaired descending nociceptive inhibition
- Sympatholytic Agents:
- α2 agonists – clonidine for topical and epidural use[12].
- Guanethidine proved best in early stages
- Phenoxybenzamine
- Free radical Scavengers:
- DMSO –topical application in warm CRPS
- NAC (N-acetyl cysteine) – topical in cold CRPS
- Vit. C orally 1500mg/50 days for Colles fracture
- Bisphosphonates: decreases pain associated with bone loss in CRPS
- Intranasal Calcitonin: relieves pain in early CRPS with or without bisphosphonates
- INTERVENTIONAL THERAPIES: Interventional therapies for CRPS patients are for those who face difficulty either in starting or progressing of the functional restoration or interdisciplinary management[13]. If the patients are not responding, then stepwise therapy is recommended- from less invasive blocks to infusions or catheter infusion or neuro-stimulation for functional improvement and pain control. The outcomes were seldom assessed with validated tools and the evidence level for invasive therapies in the treatment of CRPS in children is weak.
- Sympathetic Ganglion Blocks: Sympathetic Ganglion Blocks remains an important diagnostic (SMP vs. SIP) as well as therapeutic aids (SMP). Sometimes only a single block is necessary to produce permanent relief from pain. Stellate ganglion block was found to give good results by enhancing anti-oxidant defences.

Treatment maybe initiated with minimally invasive therapies followed by sympathetic nerve blocks, intravenous regional nerve blocks and somatic nerve blocks. Further more invasive ones like epidural and plexus catheter block, neuro-stimulation-spinalcord stimulation(SCS), peripheral nerve stimulation(PNS) and finally sympathectomy or endoscopic thoracic sympathectomy(ETS), motor cortex stimulation(MCS) are recommended. In chronic stage, many symptoms are related to so-called neuroplasticity; these include hyperalgesia, sensory loss, motor symptoms, body perception disturbances, autonomic symptoms and learned incorrect behaviour such as nonuse. At this stage, the only medical treatment that is effective against pain without improving the function is ketamine infusion, but this has side effects.[13,14]

Treatment Phases: 6 week phases:

- Maximum 3 phases are authorized.
- 1st 6 week phase – 5 sympathetic blocks along with medication.
- 2nd 6 week phase – 3 sympathetic blocks.
- 3rd 6 week phase -upto 3 sympathetic block.

Pulsed Radiofrequency (PRF) Neurolysis: Pulsed Radiofrequency Neurolysis is being used by pain specialists. In this the tip Temperature of electrode should not exceed 42 C (critical threshold).Advantage of this over chemical and surgical sympathectomy is, decreased incidence

of neuritis, tinnitus, blindness and urethral stricture. It causes minimal neuron destruction, avoids post sympathetic neuritis, has precise sympatholysis, avoids chemical neuritis and selective action on myelinated nerve fibres with no risk for de-afferentation.

Physical and Occupational Therapy: CRPS I patients: Physical therapy under light anaesthesia is an attempt to remobilize the extremity cautiously, avoiding damage to the atrophied muscle or tissue or bone.

Rehabilitation of CRPS patients: These patients need vocational and functional rehabilitation for stress relief, normalization of use, flexibility, gentle increase in range of movement, edema control, treatment of myofacial pain and postural normalization[15].

Psychological Intervention in CRPS: Emotional factors have great impact in these cases because of the chronicity of the condition[16]. Care of physical and mental health, staying connected with friends and family, pursuing hobbies may help in raising pain threshold[17].

Hospitalization is very rare except in co-existing orthopaedic conditions.

Prevention: Use of Vitamin C after fractures and early mobilization after stroke helps in preventing occurrence of this syndrome.

CONCLUSION: Complex Regional Pain Syndrome is a severe, disabling, heterogenous pain disorder resulting in physical, emotional, financial consequences.[18] Patho-physiology is not fully known. It presents with abnormalities throughout the neuraxis – peripheral, autonomic, central nervous system often ending with significant disability, anxiety and depression. Diagnosis is purely based on clinical features and diagnostic tests are not validated. It is distressing to note that no single drug or combinations work for all. Management of CRPS is multidisciplinary involving medical, psychological, physical and rehabilitation interventions.[12,19] The advent of newer drugs and spinal cord stimulation and motor cortex stimulation and neuraxial route of analgesia are promising for these patients with intractable CRPS. Recently it is termed as "Pain of Unknown Origin."

REFERENCES:

1. G.P.Dureja, Rashmi Madan, H.L.Kaul Regional Anaesthesia and Pain Management- current perspective 2000; pg: 219-239.
2. Siddiqui OA, Usmani H, Zafar L, Khan MM, Ahmad M N Continous infraclavicular brachial plexus block with bupivacaine and clonidine in CRPS type 2 of the upper extremity: a case report. Indian Journal of Pain 2010; vol 24, pg: 16-27.
3. Steven D. Waldman MD, JD Pain Review, Saunders Elsevier;2009; pg: 328-329.
4. Baron R. CRPS: McMohan S. Koltzenburg. M(ed): Wall and Melzack's Text Book of Pain,ed.5.Philadelphia, Churchill Livingston, 2006.
5. Dr.Craig W. Martin, Senior Medical Advisor CRPS- Towards the development of Diagnostic criteria and treatment guidelines. (by evidence based practice group) Jan 2004.

DOI: 10.18410/jebmh/2015/1051

6. Janne Ludwig, Ralf Baron Complex Regional Pain Syndrome: an inflammatory pain condition ? Drug Discovery Today: Disease mechanism. Vol.I, Issue 4, Dec.2004, pg 449-455.
7. MrsulaWesselmann, Srinivasan N. Raja Complex Regional Pain Syndrome pg:219-239
8. E.Eisenberg, A.V.Chistyakov, M.Yudaskin – Evidence for cortical hyperexcitability of the affected limb representation area in CRPS: a psychological and transcranial magnetic stimulation study. Pain2005
9. Frank Birklein, Martin Schmelz. Neuropetides, neurogenic inflammation and complex regional pain syndrome (CRPS) Neuroscience letter, vol 437, Issue 3; 6 June 2008 pg; 199-202
10. Perz R. Kwakkel G, Zuummonal W, de Lange J. Treatment of Reflex Sympathetic Dystrophy (CRPS type I): a Research Synthesis of 21 randomized Clinical Trials. Journal of Pain Symptoms Management. 2001: 511-26
11. Harden R N, A clinical Approach to CRPS. The Clinical Journal of Pain. 2000; 16: 526-532
12. Scadding J W. CRPS. From the Text Book of Pain. P. Wall and R. Melzack. Edition: 835-848
13. Perz et al. "Evidence based guidelines for CRPS type I. BMC Neurology 2010: 10-20
14. Levine J. Taiwo Y. Inflammatory Pain. In: Wall P D. Melzack R (eds): Text book of Pain. 3rd ed. Churchill Livingstone Edinburgh, 1994; 45-56
15. Wilder R T. Reflex Sympathetic Dystrophy in Children and Adolescents: Difference from Adults. In: Janig W, Stanton-Hicks M (ed). Reflex Sympathetic Dystrophy: A Reappraisal, Progress in Pain Research and Management. IASP Press. Seattle, 1996: 67-78
16. Baron R, Blumberg H et al. Progress in Pain Research and management. Seattle, WA:IASP Press; 1996: 25-48
17. Becker WJ, Ablett DP, Harris CJ, et al. Long term treatment of intractable reflex sympathetic dystrophy with intrathecal morphine. Can J Neural Sa 1995; 22:153-9
18. Birklein F, O'Neill D, Schlereth T. Complex Regional Pain Syndrome: An optimistic perspective. Neurology, 2015 Jan 6; 84(1): 89-96.
19. J.Y. Moon, S.Y. Park, et al. Analysis of pattern of three- phase bone scintigraphy for patients with CRPS diagnosed using the proposed research criteria (the 'Budapest Criteria'). BJA vol 108, issue 3; Jan 2012: pgs 655-661.

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