

Kompleksni regionalni bolni sindrom

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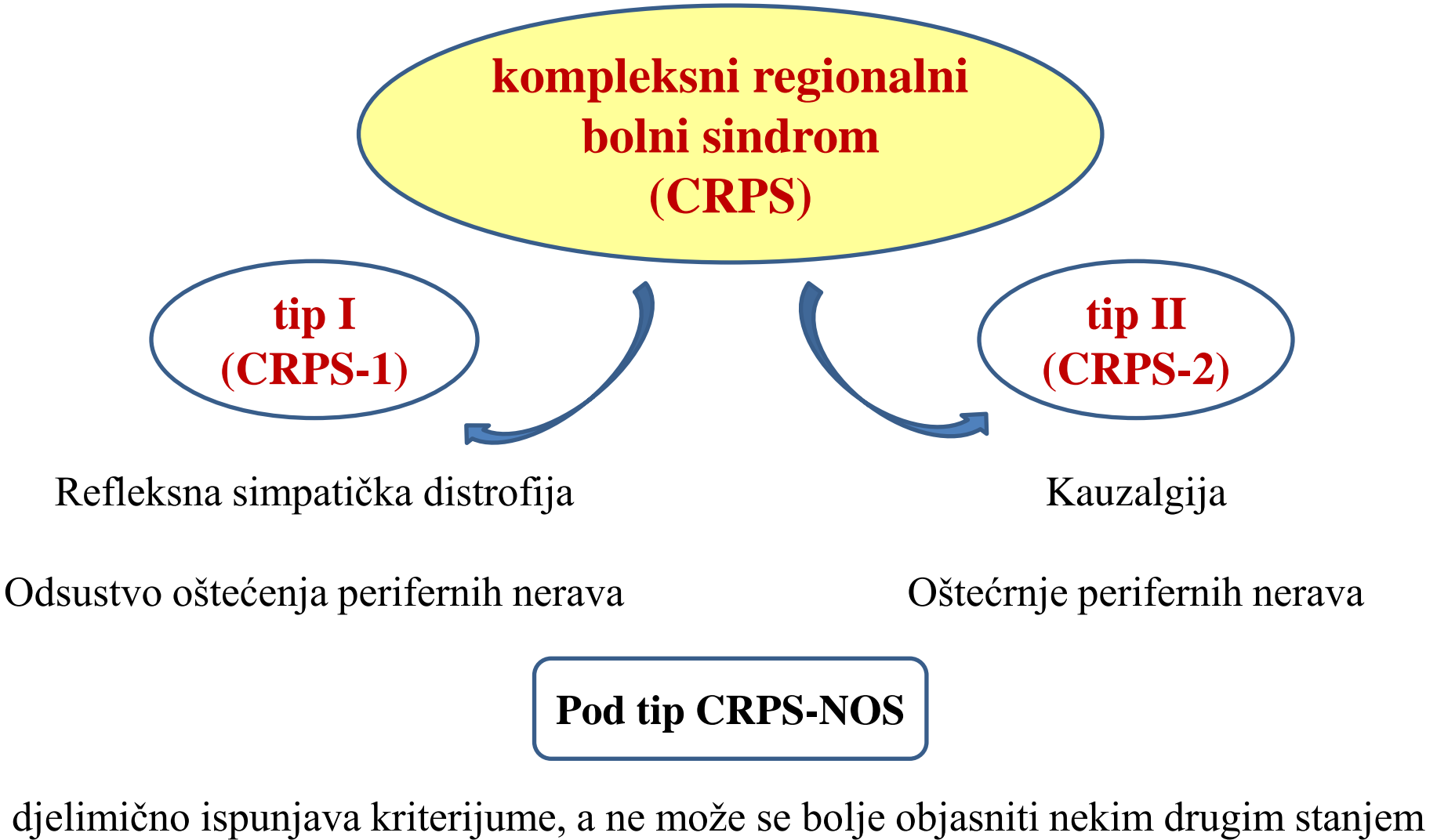
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Kompleksni regionalni bolni sindrom (CRPS) predstavlja hronično bolno stanje koje karakterište progresivno pogoršanje spontanog regionalnog bola bez dermatomske distribucije.

- bolno iskustvo je neproporcionalno vremenu i ozbiljnosti inicijalnog uzročnog događaja,
- udruženo sa simptomima, koji variraju u ozbiljnosti uključujući promjene na koži, autonomnu disfunkciju, abnormalne motorne i senzorne promjene, kao i trofičke promjene

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Harden i saradnici:

Budimpeštanski kriterijumi

Bolno stanje, gdje je bol disproporcionalna inicijalnom događaju u vremenu i stepenu, sa distalnom predominantnosti i postojanjem senzornih, motornih, sudomotornih, vazomotornih i/ili trofičkih promjena i nemogućnosti da se patologija objasni nekim drugim stanjem

Harden RN, Bruehl S, Perez RSGM, Birklein F, Marinus J, Maihofner C, et al. Validation of proposed diagnostic criteria (the “Budapest Criteria”) for complex regional pain syndrome. *Pain*. 2010;150(2):268–74. Revision of diagnostic criteria

The Budapest Criteria. Diagnostic criteria for CRPS as defined by an international consensus meeting held in Budapest

Budapest Criteria: clinical diagnostic criteria for CRPS

Continuing pain, which is disproportionate to any inciting event.

Must report at least 1 symptom in 3 of the 4 following categories:

- Sensory: reports of hyperalgesia and/or allodynia
- Vasomotor: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
- Sudomotor/edema: reports of edema and/or sweating changes and/or sweating asymmetry
- Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin)

Must display at least 1 sign at time of evaluation in 2 or more of the following categories:

- Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
- Vasomotor: evidence of temperature asymmetry and/or skin color changes and/or asymmetry
- Sudomotor/edema: evidence of edema and/or sweating changes and/or sweating asymmetry
- Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin)

There is no other diagnosis that better explains the signs and symptoms

- A sign is counted only if it is observed at the time of diagnosis.
- Research criteria for CRPS are recommended that are more specific, but less sensitive than the clinical criteria; they require that 4 of the symptom categories and at least 2 sign categories be present.

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Kontinuirana bol neproporcionalna veličini inicijalnog događaja.

- ◆ Pacijent mora prijaviti najmanje jedan simptom u tri od četiri navedene kategorije:
 - ◆ Pacijent mora imati najmanje jedan znak u vrijeme pregleda u dvije ili više navedenih kategorija:
 - senzorni: postojanje alodinije i/ili hiperalgezije,
 - vazomotorne: postojanje temperaturne asimetrije i/ili promjene boje kože i/ili asimetrije u boji kože,
 - sudomotorne/edem: prisustvo edema i/ili znojenja i/ili asimetrije u znojenju,
 - motorni/trofički: postojanje smanjenje obima pokreta i/ili motorne disfunkcije (slabost, tremor, distonija) i/ili trofičke promjene (koža, nokti, kosa).
 - ◆ Ne postoji druga dijagnoza koja bi objasnila simptome i znakove.
- Znak se uzima u obzir samo ukoliko postoji u trenutku postavljanja dijagnoze.

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- ❖ Incidenca CRPS tip I je 5,46 na 100000 stanovnika, CRPS tip II 0,82 na 100000 stanovnika godišnje
- ❖ Žene su pogođene četiri puta više nego muškarci, odnosno 71% u odnosu na 29%, sa prosjekom godina 46, uz veću incidencu u postmenopauzalnom periodu,
- ❖ Gornji ekstremiteti su zahvaćeni dva puta više nego donji (na gornjim ekstremitetima 70%.)
- ❖ CRPS tip I se javlja češće u odnosu na CRPS tip II (88% u odnosu na 12%)

Urits I, Shen AH., Jones MR, Viswanath O, Kaye AD. Complex Regional Pain Syndrome, Current Concepts and Treatment Options. *Current Pain and Headache Reports*, **2018**; 22(2):10.

Ott S, Maihofner C. Signs and symptoms in 1,043 patients with complex regional pain syndrome. *J Pain* **2018**; 19: 599e611

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- ❖ Ekstremne frakture su najčešće inicirajući događaji CRPS-1, 7% pacijenata koji su doživjeli frakturu ručnog zgloba, skafoidne kosti, skočnog zgloba ili pete metatarzalne kosti razviju CRPS-1.
- ❖ Udruženost između razvoja CRPS-1 i reumatoidnog artritisa ili drugog muskuloskeletnog komorbiditeta. CRPS-1 se obično razvija unutar osam nedelja nakon inicijalnog događaja.

Beerthuisen A, Stronks DL, Van't Spijker A, Yaksh A, Hanraets BM, Klein J, et al. Demographic and medical parameters in the development of complex regional pain syndrome type 1 (CRPS1): prospective study on 596 patients with a fracture. *Pain*. **2012**;153:1187–92

- ❖ CRPS-1 se može razviti i nakon hirurgije na ekstremitetima, 4,36 % pacijenata će razviti oboljenje nakon elektivne hirurgije stopala i/ili skočnog zgloba.

RewhornMJ, Leung AH, Gillespie A, Moir JS, Miller R. Incidence of complex regional pain syndrome after foot and ankle surgery. *J Foot Ankle Surg*. **2014**;53(3):256–8.

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❖ CRPS se u 8,3% pacijenata razvija nakon operacije karpalnog kanala

Da Costa VV, De Oliveira SB, Fernandes M d CB, Saraiva RÂ. Incidence of regional pain syndrome after carpal tunnel release. Is there a correlation with the anesthetic technique? Rev Bras Anesthesiol. **2011**;61:425–33.

❖ Kao komplikacija operacije ramena i gornjeg ekstremiteta CRPS se javlja od 3 do 11,1%.

Chalmers PN, Slikker Iii W, Mall NA, Gupta AK, Rahman Z, Enriquez D, et al. Reverse total shoulder arthroplasty for acute proximal humeral fracture: comparison to open reduction–internal fixation and hemiarthroplasty. J Shoulder Elb Surg. **2014**;23(2):197–204



Figure 1. Etiology of CRPS type I and II. The width of the bars represents the relative amount of primary triggers being responsible for the emergence of CRPS. Note that incidence (eg, surgery) initiated by the primary trigger (eg, fracture) are not included.

Ott S, Maihöfner C. Signs and Symptoms in 1,043 Patients with Complex Regional Pain Syndrome. The Journal of Pain, Vol 19, No 6 (June), **2018**.

Patofiziologija – nejasna i kontroverzna

multifaktorijalan uticaj: imunološki, autonomna disregulacija, neuronska plastičnost, psihološki faktori, genetika...

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- **imunološki uticaj** – fundamentalan u razvoju CRPS-a

- Citokini i NGF → ekscitacija nociceptora → indukuju retrogradno depolarizaciju primarnih aferentnih vlakana malog dijametra → oslobađanje neuropeptida (supstanca P i CGRP) iz senzornih terminala u koži → vazodilatacija i ekstravazacija proteina u tkivo rezultirajući znacima neurogene inflamacije – crvenilo, toplota i edem. Neuropeptidi → oslobađanje proinflamatornih medijatora TNF- α , IL-1 β , IL-6 → pojačavaju perifernu senzitivaciju na štetne stimulse
- CRPS kao autoimuna bolest (u 70% dokaz o postojanju antiautonomnih IgG antitijela u serumu).

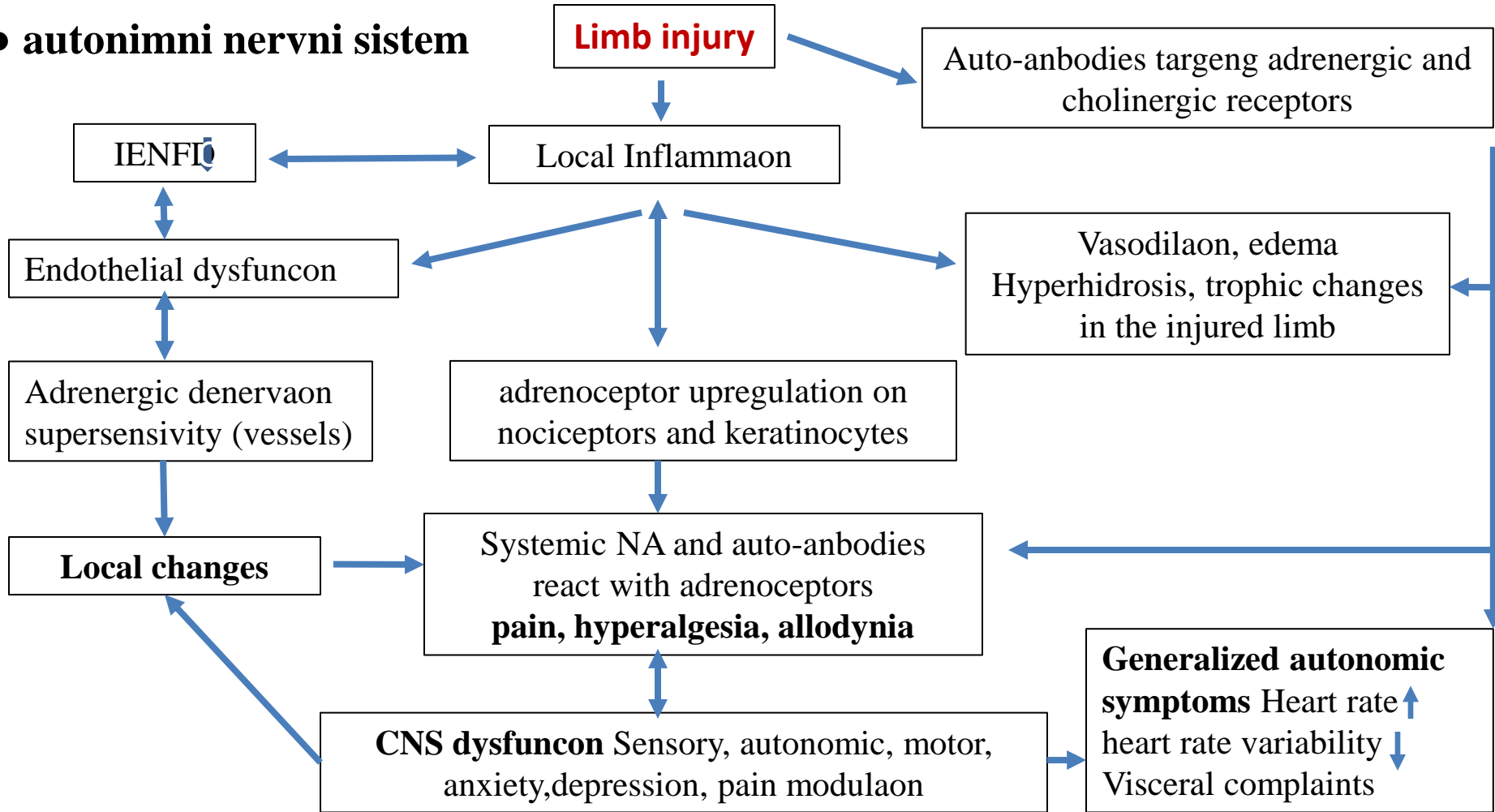
Shim H, Rose J, Halle S, Shekane P. Complex regional pain syndrome: a narrative review for the practicing clinician. **2019** British Journal of Anaesthesia, Published by Elsevier. Accepted: 22 March **2019**.

Marinus J, Lorimer Moseley G, Birklein F, Baron R, Maihöfner C, Kingery WS, van Hilten JJ. Clinical features and pathophysiology of complex regional pain syndrome. *Lancet Neurol* **2011**; 10: 637–48

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● **autonimni nervni sistem**

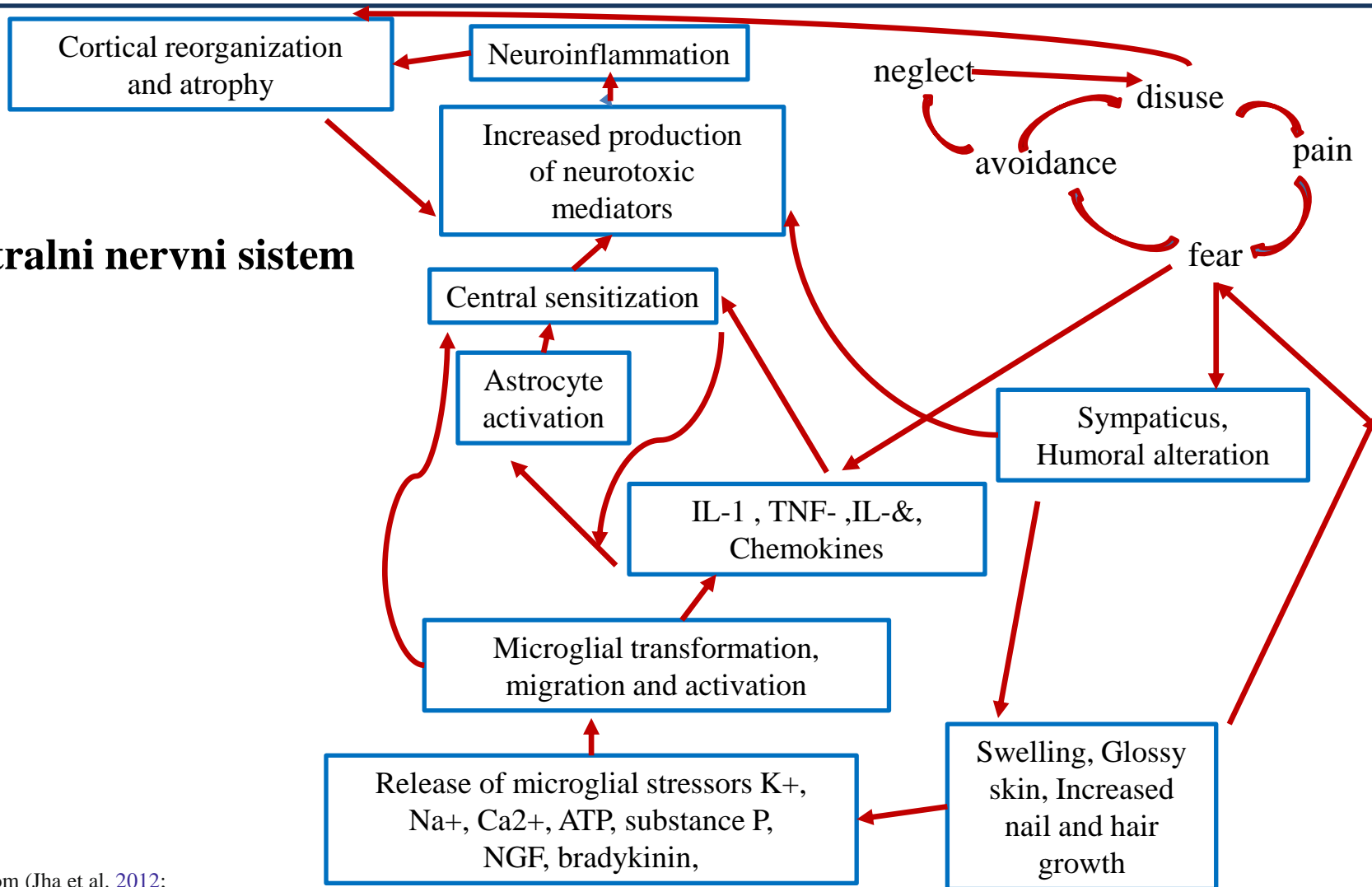


Knudsen LF, Terkelsen AJ, Drummond PD, Birklein F. Complex regional pain syndrome: a focus on the autonomic nervous system. Clin Auton Res 2019 May 18,

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● **centralni nervni sistem**



Adapted from (Jha et al. 2012;
Vlaeyen and Linton 2012;
Marinus et al. 2011)

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Senzibilizacija CNS-a od suštinskog značaja za razvoj CRPS.

Kontinuirana aktivacija perifernih živaca nakon povrede povećava efikasnost sinaptičkog nociceptivnog pražnjenja u dorzalnom rogu. Ova senzibilizacija se smatra posredovani neuropeptidima kao što je glutamat i supstanca P, smanjujući prag odgovora na mehaničke i toplotni stimuluse, koji dovode do hiperpatije i alodinije.

Schwartzman RJ, Alexander GM, Grothusen J. Pathophysiology of complex regional pain syndrome. *Expert Rev Neurother* **2006**; 6: 669e81

Ovo je takođe pokazano na životinjskim modelima, gdje intratekalno apliciran antagonist supstance P dovodi do smanjenja alodinije.

Guo TZ, Offley SC, Boyd EA, Jacobs CR, Kingery WS. Substance P signaling contributes to the vascular and nociceptive abnormalities observed in a tibial fracture rat model of complex regional pain syndrome type I. *Pain* **2004**; 108: 95e107

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CNS inflammation and somatosensory function – thalamus and somatosensory cortex

Funkcionalna reorganizacija primarnog somatosenzornog korteksa dovodi do razvoja i progresija CRPS-a.

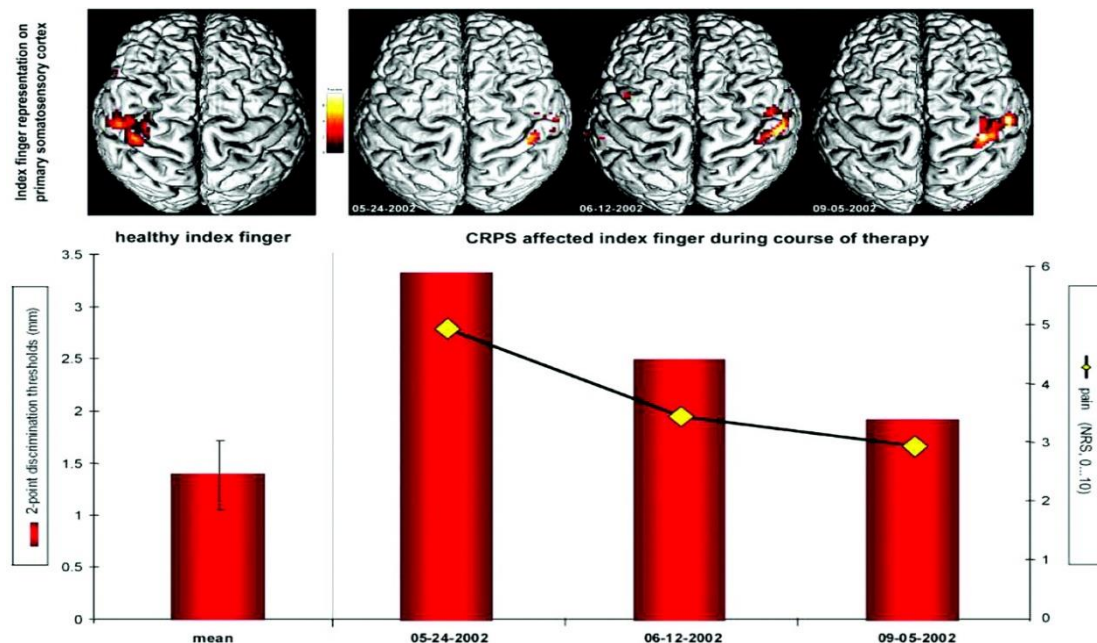
Maihöfner C, Neundörfer B, Birklein F, Handwerker HO. Mislocalization of tactile stimulation in patients with complex regional pain syndrome. *J Neurol.* **2006**;253(6):772–9.

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Zahvaćeni dijelovi tijela imaju manju zastupljenost u primarnom somatosenzornom korteksu u odnosu na nezahvaćenu stranu i pojedince koji nisu imali CRPS, iako nisu postojale razlike u latenciji i aktivacijskoj snazi.

Di Pietro F, McAuley JH, Parkitny L, Lotze M, Wand BM, Moseley GL, et al. Primary somatosensory cortex function in complex regional pain syndrome: a systematic review and meta-analysis. *J Pain.* **2013**;14:1001–18. Systematic review.



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CNS inflammation and autonomic function – hypothalamus

Jedna od najčešćih simptoma u CRPS-u je autonomna disfunkcija koja se manifestira izmjenjenom temperaturnom regulacijom, otokom i promjenom boje kože što ukazuje na moguću disfunkciju hipotalamus-a

Poremećaji spavanja prisutni u hroničnoj boli smatra se da mogu biti u odnosu sa hipotalamusnom (*nc. suprachiasmaticus*) regulacijom ciklusa spavanja.

Linman C, Becerra L, Borsook D. Inflaming the Brain: CRPS a Model Disease to Understand Neuroimmune Interactions in Chronic Pain. *J Neuroimmune Pharmacol.* **2013** Jun;8(3):547-63

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Inflammation cognition and memory – hippocampus, frontal lobes

Pacijenti sa CRPS imaju redukciju volumena hipokampus-a

Promjena markera glijalne aktivacije je primjećena u hipokampusu što je u korelaciji sa povećanjem anksioznosti kod ovih pacijenata

Kod pacijenata sa CRPS-om postoji atofija sive mase (*insula, nc. accumbens, prefrontalni korteks*) i promjena bijela mase (*cingulum i corpus callosum-u*). Jaka je veza između atrofičnih regiona u odnosu na anksioznost, što sugeriše da abnormalna anatomija mozga kod CRPS-a može dati kognitivne simptome.

Linman C, Becerra L, Borsook D. Inflaming the Brain: CRPS a Model Disease to Understand Neuroimmune Interactions in Chronic Pain. *J Neuroimmune Pharmacol.* **2013** Jun;8(3):547-63

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CNS inflammation and motor function – basal ganglia

- pareza,
- tremor (akutna faza 82%, nakon 12 mjeseci 44%),

- distonija (ručni zglob i prsti-GE; plantarna fleksija i inverzija-DE-u bilo kojoj fazi bolesti, uz širenje na ostale ekstremitete)-uključene bazalne ganglije
(GABAergička presinaptička inhibicija uočena u CRPS pacijenata sa distonijom)

- mioklonus,
- pojačani tetivni refleksi.

van Rijn MA, Marinus J, Putter H, et al. Onset and progression of dystonia in complex regional pain syndrome. *Pain* **2007**;130:287–93.

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CNS inflammation and inattention – parietal lobe

fMR i neuropsihološka testiranja ukazuju na promjenu funkcije parijetalnog režnja u CRPS-u.

Uočen je visoki neglect skor kod pacijenata sa CRPS-om, ali nije dokazana signifikantna razlika između CRPS-a i drugih stanja.

Kolb L, Lang C, Seifert F, Maihofner C (2012) Cognitive correlates of "neglect-like syndrome" in patients with complex regional pain syndrome. *Pain* 153(5):1063–1073.

Druge karakteristike parijetalnog režnja uključujući neadekvatnu procjenu veličine šake i agnoziju za orijentaciju objekta sugerišu na postojanje abnormalnosti u procesu vizuospacijalnih informacija.

Peltz E, Seifert F, Lanz S, Muller R, Maihofner C (2011) Impaired hand size estimation in CRPS. *The Journal of Pain: Official Journal of the American Pain Society* 12(10):1095–1101.

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CNS inflammation and pain modulation – periaqueductal gray

Promijenjena endogena modulacija bola u CRPS ukazuje na abnormalnosti facilitatorne modulacije bola kod ovih pacijenata, moguće kroz periakveduktnu sivu masu (PAG).

Povećanje citokina u PAG-u dovode do pojave hiperalgezije

Kod pacijenata sa CRPS-om značajno je manja aktivnost u PAG-u tokom supresije bola u poređenju sa zdravim kontrolama.

Benamar K, Geller EB, Adler MW (2008) Elevated level of the proinflammatory chemokine, RANTES/CCL5, in the periaqueductal grey causes hyperalgesia in rats. *Eur J Pharmacol* 592(1–3):93–95

Freund W, Wunderlich AP, Stuber G, Mayer F, Steffen P, Mentzel M, Schmitz B, Weber F (2011) The role of periaqueductal gray and cingulate cortex during suppression of pain in complex regional pain syndrome. *Clin J Pain* 27(9):796–804.

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- **genetski uticaj**

Genetska veza nije sigurna. U studijama u 2016. godini posmatran je pojedinačni nukleotidni polimorfiza, na preko 200 000 uzoraka i nije nađena razlika između CRPS pacijenata i kontrolnih grupa.

Janicki PK, Alexander GM, Eckert J, Postula M, Schwartzman RJ. Analysis of common single nucleotide polymorphisms in complex regional pain syndrome: genome wide association study approach and pooled DNA strategy. *Pain Med* **2016**; 17: 2344e52

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● uticaj psihološke strukture i stanja

Kod pacijenata sa posttraumatskim stresnim poremećajem (PTSP) značajno povećana učestalost CRPS-a u poređenju sa kontrolama.

Pacijenti sa višim nivoima anksioznosti, percepcijom invalidnosti i straha od boli pokazuju lošiji tok bolesti. To je vjerovatno sekundarno uz porast oslobađanja kateholamina povezane sa anksioznošću, što dovodi do povećane nociceptivne senzibilizacije i adrenergičkih simptoma.

Speck V, Schlereth T, Birklein F, Maihofner C. Increased prevalence of posttraumatic stress disorder in CRPS. *Eur J Pain* **2017**; 21: 466e73

Urits I, Shen AH, Jones MR, Viswanath O, Kaye AD. Complex regional pain syndrome, current concepts and treatment options. *Curr Pain Headache Rep* **2018**; 22: 10

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Pretjerano negativan psihološki odgovor na štetne podražaje takođe može imati značajan uticaj na razvoj CRPS-a. Pokazalo se da vodi ka povećanju proinflamatorne aktivnost citokina kao odgovor na bolni podražaji i nivo negativnog odgovora je bio u korelaciji sa skorom bola kod pacijenata sa CRPS-om.

Harden RN, Oaklander AL, Burton AW, et al. Complex regional pain syndrome: practical diagnostic and treatment guidelines, 4th edition. *Pain Med* **2013**; 14: 180e229

Velika multicentrična prospektivna studija nije uspjela pokazati psihološke faktore, tj. agorafobiju, depresiju, i somatizacija, kao predikciju razvoja CRPS-a.

Beerthuizenl A, Stronksl DL, Huygenl FJPM, Passchierl J, Kleinl J, van't SpijkerlA. The association between psychological factors and the development of complex regional pain syndrome type 1 (CRPS1)—a prospective multicenter study. *Eur J Pain*. **2011**;15(9):971–5.

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Generalno CRPS je lokalizovan na primarno zahvaćen ekstremitet

Istraživanje obuhvatilo 185 pacijenata, 89 pokazala razvijeni CRPS u više ekstremiteta.

Kod 72 pacijenta širenje CRPS na drugi ekstremitet, kontralateralno 49%, ipsilateralno 30% i dijagonalni obrazac 14%.

Trauma na drugom ekstremitetu prethodila u 37%, 44% i 91%.

Opasnost od širenja se povećava sa brzojem zahvaćenih ekstremiteta

- Pacijenti sa CRPS u više ekstremiteta su bili u prosjeku 7 godina mlađi i češće se imali poremećaje kretanja
- Spontanost širenje obično slijedi kontralateralni ili ipsilateralni obrazac, dok je dijagonalno širenje rijetko i obično mu prethodi nova trauma.
- Pretpostavka je da su procesi u kičmenoj moždini kao i supraspinalne promjene odgovorne za spontano širenje CRPS-a.

van Rijn MA, Marinus J, Putter H, et al. Spreading of complex regional pain syndrome: not a random process. *J Neural Transm* **2011**; 118-1301-9

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Dinamički tok CRPS-a.

U akutnoj toploj fazi, ekstremitet je izuzetno osetljiv, često edematozan i topao. Kroz vrijeme, uglavnom se razvija hladna (hronična) faza, ostavljajući samo tragove očigledne upalne geneze dok se zadržava bol koji je obično goreći, najčešće ozbiljan. Uporan bol tokom hronične faze je povezana sa tipičnim atributima hroničnog bola koji uključuje depresiju, ali i kognitivne promjene i reaktivne simptome anksioznosti i beznađa.






Uticaj na izbor liječenja



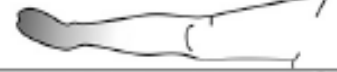


Antiinflamatorne i imunološke mjere mogu biti najefikasnija terapija u akutnoj fazi prije centralne senzibilizacije i razvitka mehanizama koji vode u hroničan proces.

Bruehl S. An update on the pathophysiology of complex regional pain syndrome. *Anesthesiology* **2010**;113:1–725.

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arm	left	right	total
none	700 67.2%	657 63.1%	
	0 0.0%	1 0.1%	1 0.1%
	9 0.9%	8 0.8%	17 1.6%
	301 28.9%	327 31.4%	628 60.3%
	5 0.5%	12 1.2%	17 1.6%
	27 2.6%	37 3.6%	64 6.1%
total arm	342 32.8%	385 37.0%	727 69.8%

leg	left	right	total
none	884 84.8%	881 84.6%	
	12 1.2%	14 1.3%	26 2.5%
	1 0.1%	0 0.0%	1 0.1%
	128 12.3%	133 12.8%	261 25.1%
	6 0.6%	5 0.5%	11 1.1%
	11 1.1%	9 0.9%	20 1.9%
total leg	158 15.2%	161 15.5%	319 30.6%

exceptions


trunk		3 0.3%
all highlighted areas originate from different patients		
more than one location		7 0.7%

Figure 2. Localization of symptoms. Overview of the affected areas, separated in left and right, as well as upper limb, lower limb, and trunk (all marked areas are from different patients).

Ott S, Maihöfner C. Signs and Symptoms in 1,043 Patients with Complex Regional Pain Syndrome. The Journal of Pain, Vol 19, No 6 (June), 2018.

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Bol, alodinija, hiperalgezija,

Promjene u senzitivnim funkcijama

Vazomotorne: promjena boje kože, izmjenjeno lučenje znoja, izmjenjena temperatura kože,



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trofičke promjene: poremećaj u rastu dlake, noktiju, demineralizacija kostiju (trofičke komplikacije, infekcija, tromboza, spontani hematomi, kožni ulkus..) i motorne abnormalnosti: distonija, smanjenje snage mišića, gubitak izdržljivosti

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I akutna faza:

najmanje 6-8 nedelja i do šest mjeseci. Bol, edem, koža topla i crvena. Osteoporoza nije vidljiva.

II distrofična faza:

3-6 mjeseci uz žareću i pulsirajuću bol, atrofične promjene tkiva, vidljiva osteoporoza.

III atrofična faza:

nakon 6 mjeseci uz izražene atrofične i osteoporotične promjene, često ireverzibilne. Uz bolove prisutna ankiloza i kontraktura zglobova.



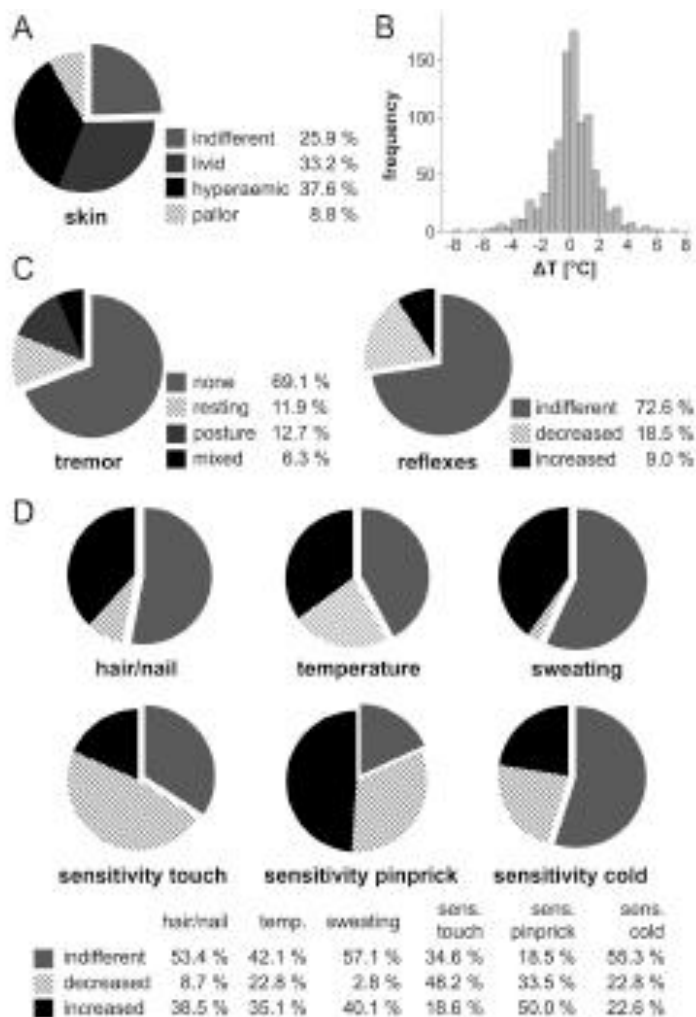


Figure 4. Prevalence of typical symptoms (trophic, sensory, motor). (A) Prevalence of the skin color of the affected limb. (B) Histogram of the difference in skin temperature between affected and unaffected (range -8.0° to $+7.26^{\circ}$ C, mean: $+0.8^{\circ}$ \pm 1.65° C, $n_s = 942$). (C) Prevalence of motor signs (tremor, reflexes). (D) Prevalence of trophic, autonomic, and sensory signs. Abbreviations: temp., temperature; sens., sensitivity.

Ott S, Maihöfner C. Signs and Symptoms in 1,043 Patients with Complex Regional Pain Syndrome. The Journal of Pain, Vol 19, No 6 (June), 2018.

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Liječenje

Farmakoterapija, fizikalna terapija, botulinski toksin A, intratekalna aplikacija Baklofena, simpatički nervni blok, stimulacija kičmene moždine, stimulacija spinalnog dorzalnog gangliona..

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Table 1. Rational pharmacological therapy for CRPS.

Drug category	Drug	Dosage	Evidence-based efficacy/effectiveness (GRADE like)
NSAIDs	Ketorolac	Weekly IVBs (30–120 mg plus 50 mL lidocaine 0.5%) for 1 month	May be slightly effective in reducing early nociceptive pain at short term without reduction of edema
	Piroxicam	Oral 20 mg daily for 2 weeks	May make little or no difference on overall symptoms and functional independence
	Corticosteroids	Parecoxib	iv 80 mg/day for two consecutive days
Prednisolone		Oral 40 mg daily for 2 weeks followed by a tapering to 10 mg daily in the following 2 weeks and continuing this dose for 2 months	Probably slightly reduces overall symptoms and improves functioning at short term; may slightly reduce overall symptoms and CRPS recurrence at long term
Opioids	Morphine	Oral 10 mg tid, titrated to 30 mg tid, for 56 days	May make little or no difference on pain
NMDA receptor antagonist	Memantine	Oral 5 mg daily, titrated to 40 mg for 56 days	May make little or no difference on pain
Calcium metabolism modifiers	Calcitonin	Intranasal or im, 100–300 IU daily for 2–4 weeks	May slightly reduce pain and improves mobility at short term
Amino-bisphosphonates	Neridronate	iv, 100 mg every 3rd day, 4 times over 10 days; im 25 mg daily for 16 consecutive days (<i>ongoing trial</i>)	Provides pain relief and better QoL at both short and long terms (<i>high quality of the evidence</i>)
	Alendronate	iv 7.5 mg for 3 consecutive days for 2 times, 2 weeks apart; oral 40 mg daily for 2 months	Probably provides slight pain relief and probably slightly increases mobility (<i>moderate quality of the evidence</i>)
	Pamidronate	iv 60 mg, single dose	Probably provides slight disease severity reduction and slightly improves QoL at medium term (<i>moderate quality of the evidence</i>)
Nonamino bisphosphonates	Clodronate	iv, 300 mg daily for 10 consecutive days	Probably provides pain relief at medium–long term (<i>moderate quality of the evidence</i>)
GABA-receptor	Gabapentin	Oral 600 mg once a day on first 2 days, titrated to 600 mg bid	May slightly reduce pain, sensory impairment, and

Iolascon G, Moretti A. Pharmacotherapeutic options for complex regional pain syndrome. expert opinion on pharmacotherapy. (2019)

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GABA analogs	Gabapentin	Oral, 600 mg once a day on first 2 days, titrated to 600 mg bid on days 3-4 and to 600 mg tid from 5th day to 3rd weeks; oral, 300 mg tid per day	May slightly reduce pain, sensory impairment, and sleep disturbances at short medium term
TCA	Amitriptyline	Oral (10 mg at bedtime)	May slightly reduce pain and sleep disturbances at short-medium term
Anesthetics	Lidocaine	iv infusions (to increase plasma levels of lidocaine of 1, 2, and 3 mg/ml)	Probably makes little or no difference in terms of pain relief
NMDAR antagonists	Ketamine	iv continuous infusion rate started at 1.2 µg/kg/min, titrated to a maximum of 7.2 µg/kg/min over 4 days	Probably provides pain relief at short- and medium-terms, without functional improvement
Calcium channel blockers	Nifedipine	Oral, 10 mg tid for 2 days titrated to 2 tabs tid	It is uncertain if intervention might reduce pain
α-Sympathetic blocker	Phenoxybenzamine	Oral 10 mg at night to maximal 3 tablets qid	It is uncertain if intervention might reduce pain
α2-Adrenergic agonist and imidazoline receptor agonist	Clonidine	Topical, transdermal patch	It is uncertain if intervention might reduce hyperalgesia
Immune globulins	Immunoglobulins	iv, total dose of 9-18 g, divided in 3 infusions over 1 week; 0.25 g/kg/day for 2 consecutive days; 0.5 g/kg on days 1 and 22	Probably make little or no difference on pain relief and QoL
TRPV1 agonists	Capsaicin	Topical, 5-10% concentration, 1-8 applications daily	It is uncertain if intervention might reduce pain
α1-Adrenergic antagonist	Prazosin	Topical, 1% concentration	May reduce hyperalgesia and allodynia
Neuromuscular blockers	Botulinum toxin	Subcutaneous, 300 U every 3 months, twice; 5 U/site, mean total dose/session 79.5 U; electromyography (EMG)-guided im injection (10-20 U/muscle, total dose 100 U)	May provide pain relief

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Botulinski toksin A

Uprkos nejasnom mehanizmu kako BTX-A utiče na CRPS, studija ukazuje na njegov efekat u redukciji samoprocjene bola kod pacijenata sa CRPS-om refrakternim na tradicionalno liječenje.

Lessard L, Bartow MJ, Lee J, Diaz-Abel J, Tessler OES. Botulinum Toxin A: A Novel Therapeutic Modality for Upper Extremity Chronic Regional Pain Syndrome. *Plas Reconstr Surg Glob Open* **2018** Oct 16;6(10).

Terapija ozonom

Rowen RJ Robins H. Ozone Therapy for Complex Regional Pain Syndrome: Review and Case Report. *Current Pain and Headache Reports* (2019) 23:41

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Fizikalna terapija

Fizikalna i okupaciona terapija mogu dovesti do redukcije bola i poboljšanja pokretljivosti kod pacijenata sa CRPS-om.

Harden RN, Oaklander AL, Burton AW, Richardson K, Swan M, Otr L, et al. Complex regional pain syndrome: practical diagnostic and treatment guidelines, 4th edition. *Pain Med.* **2013**;14(2):180–229.

Mirror terapija kao deo kompleksnog integrativnog tretmana je efikasan za korekciju šeme tijela i poremećaja percepcije kod pacijenata koji pate od CRPS I

Kotiuk V, Burianov O, Kostrub O, Khimion I, Zasadnyuk I. The impact of mirror therapy on body schema perception in patients with complex regional pain syndrome after distal radius fractures. *British Journal of Pain.* **2018**.

Manuelna limfna drenaža, elektroprocedure (IFS, TENS..), laseroterapija, UZV terapija, taktilni diskriminacioni trening, elektroakupunktura, pulsno magnetno polje...

Smart KM, Wand BM, O'Connell NE. Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II (Review). *Cochrane Database Syst Rev.* **2016** Feb 24;2.

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Simpatički nervni blok

Rezultati ovog ažuriranja slični su prethodnim verzijama ovog sistematskog pregleda, ostaje nedostatak objavljenih dokaza i nedostatak kvalitetnih dokaza, koji podržavaju ili opovrgavaju upotrebu lokalne simpatičke nervne blokade za CRPS. Iz postojećih dokaza, nije moguće donijeti čvrste zaključke u pogledu efikasnosti ili sigurnosti ove intervencije, ali ograničeni dostupni podaci ne sugeriraju da je LASB djelotvoran u smanjenju bolova kod CRPS-a.

O'Connell NE, Wand BM, Gibson W, Carr DB, Birklein F, Stanton TR. Local anaesthetic sympathetic blockade for complex regional pain syndrome. *Cochrane Database Syst. Rev.* **2016** Jul 28;7:CD004598

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Intratekalna aplikacija baklofena

Intratekalni baclofen (ITB) je uspješno primjenjen u liječenju pacijenata sa tvrdokornim CRPS-om.

Stimuliše GABA B receptore na primarnim aferentnim vlaknima i deluje na nociceptivne jedinice dorzalnih rogova u inhibiciji neurtransmitterske aktivnosti.

ITB smanjuje bol i poboljšava distoniju i kvalitet života .

Van Der Plas AA, Van RijnMA, Marinus J, Putter H, Van Hilten JJ. Efficacy of intrathecal baclofen on different pain qualities in complex regional pain syndrome. *Anesth Analg.* **2013**;116(1): 211–5.

van RijnMA, Munts AG, Marinus J, Voormolen JHC, de Boer KS, Teepe-Twiss IM, et al. Intrathecal baclofen for dystonia of complex regional pain syndrome. *Pain.* **2009**;143:41–7.

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Stimulacija kičmene moždine (SCS)

Nakon ugradnje sistema uočeno je smanjenje angiogenog faktora rasta u zahvaćenom ekstremitetu, vodeći poboljšanje hipoksije tkiva.

95% pacijenata je zadovoljno sa svojim sistemom nakon 5 godina.

Nakon 88 mjeseci nađeno je da je sistem SCS bio efikasniji ukoliko je ugrađen u prvoj godine nastanka bolesti i ispod 40 godina starosti.

Smanjeno korištenje antikonvulziva, antidepresiva i/ili NSAIL za najmanje 25% i prijavljuju smanjenje bola, poboljšanje funkcionalnosti i kvaliteta života.

Kumar K, Rizvi S, Bnurs SB. Spinal cord stimulation is effective in management of complex regional pain syndrome I: fact or fiction. *Neurosurgery*. **2011**;69(3):566–78.

Visnjevac O, Costandi S, Patel BA, Azer G, Agarwal P, Bolash R, et al. A comprehensive outcome-specific review of the use of spinal cord stimulation for complex regional pain syndrome. *Pain Pract*. **2017**;17(4):533–45. Efficacy of SCS

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Kvalitet dokaza za smanjenje bola je nivo 1B+, kvaliteta žkivota 1B+ i ukupnog zadovoljstva 2C+.

Početakom 2019.godine javlja se prvi izvještaj u slučaju ugradnje hirurških elektroda SCS sistema kod CRPS na nivou C1-C2 sa vrhom do C4 sa bilateralnim pokrićem gornjih dermatoma za gornje ekstremiteta koji su ukazali na signifikantno smanjenje bola i kompletno odsustvo spinalnog mioklonusa.



Bosea R, Banerjee AD. Spinal cord stimulation for complex regional pain syndrome type I with spinal myoclonus – a case report and review of literature. *Br J Neurosurg.* **2019** Jan 12:1-3

Visnjevac O, Costandi S, Patel BA, Azer G, Agarwal P, Bolash R, et al. A comprehensive outcome-specific review of the use of spinal cord stimulation for complex regional pain syndrome. *Pain Pract.* **2017**;17(4):533–45. Efficacy of SCS

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Stimulacija dorzalnog spinalnog ganglija (DRG)

Studija sa 8 pacijenata nakon implantacije sistema za stimulaciju dorzalnog ganglija pokazala je smanjenje bola i poboljšanje funkcionalnosti.

- Nakon 1 mjeseca bol smanjena za 62% i perzistira 12 mjeseci.
- Nakon 12 mjeseci kvalitet života poboljšan kod svih ispitanika, u 6 od 8 smanjen bola za preko 50% u odnosu na početne vrijednosti.

Van Buyten JP, Smet I, Liem L, Russo M, Huygen F. Stimulation of dorsal root ganglia for the management of complex regional pain syndrome: a prospective case series. *Pain Pract* **2015**; 15: 208e16

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Studija 152 pacijenta sa CRPS DE podijeljena u grupu sa SCS i grupu DRG stimulacijom.

Nakon 3 mjeseca kod 81,2% pacijenata sa DGR stimulacijom smanjena bol za više od 50%, u grupi sa SCS kod 55,7% pacijenata smanjena bola za više od 50%.

Nakon 12 mjeseci statistički veće oslobađanje bola u grupi DGR stimulacije (74,2% vs 53,0%).

U obe grupe grupi nije bilo ozbiljnih neželjnih efekata.

Deer TR, Levy RM, Kramer J, et al. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12months: a randomized comparative trial. *Pain* **2017**; 158: 669e81

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Vitamin C

Zbog različitih ishoda studija i ukupnog kvaliteta dokaza, nejasno je da li je vitamin C efikasan u smanjenju prevalence CRPS-a nakon određenih preloma i operacija ekstremiteta.

Zbog niskog rizik pri upotrebi i pozitivnih rezultata u nekim studijama, upotreba vitamina C kod distalnog preloma radius-a ili nakon operacija stopala ili gležnja još uvijek može biti moguća intervencija koja bi se mogla koristiti.

Shim H, Rose J, Halle S, Shekane P. Complex regional pain syndrome: a narrative review for the practicing clinician. **2019** British Journal of Anaesthesia, Published by Elsevier. Accepted: 22 March **2019**.

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Psihološka terapija može biti od pomoći u tom smislu da pomogne pacijentima u prevazilaženju bola i u treninzima opuštanja.

Harden RN, Oaklander AL, Burton AW, et al. Complex regional pain syndrome: practical diagnostic and treatment guidelines, 4th edition. Pain Med **2013**; 14: 180e229

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