

Update on Evidence Based Management of CRPS

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Introduction

- Complex regional pain syndrome (CRPS) is a disorder of the extremities.
- A diagnosis of CRPS requires the presence of regional pain and sensory changes following a noxious event.
- The pain is more severe than expected from the injury which caused it.

Introduction

- CRPS frequently begins following:

- An injury
- Surgery
- A vascular event such as a stroke

- It is characterized by:

- Pain
- Swelling/edema
- Limited range of motion
- Vasomotor instability
- Skin changes/abnormal skin color
- Patchy bone demineralization
- Temperature changes
- Atrophy

Introduction

- Two types of CRPS have been recognized:

- Type I:

- No definable nerve lesion is present.
- Represents about 90% of clinical cases.

- Type II:

- A definable nerve lesion is present.
- Formerly termed causalgia.

CRPS TODAY

- Multi-system syndrome characterized by chronic pain usually affecting one limb, but may spread to remote region(s)
- Considered to emerge from CNS with additional peripheral disease mechanisms: ANS, somatic nervous system, neurogenic inflammation, hypoxia, psychological factors
- Can begin/affect any part of the body
- Blood supply to the limb is affected
- Hand, knee, hip and shoulder most commonly affected
- Early diagnosis & Tx bring best prognosis

Etiology (1)

- The pathogenesis of CRPS is unclear.
- It is thought to involve the formation of a reflex arc after an inciting event.
- The reflex arc follows the routes of the sympathetic nervous system.
- It is modulated by cortical centers which produce peripheral vascular changes.

Etiology (2)

- **There is decreased, rather than increased, sympathetic outflow to the affected limb.**
- **Autonomic features are thought to be due to catecholamine hypersensitivity and include:**
 - Cyanosis
 - Mottling
 - Increased sweating
 - Abnormal growth of hair
 - Diffuse swelling
 - Coldness

Etiology (3)

- **A proposed mechanism for the persistent pain and allodynia is the release of inflammatory mediators and pain producing peptides by peripheral nerves, including:**
 - Substance P
 - Neuropeptide Y
 - Calcitonin gene related peptide
 - IL-6, IL-8, IL-1beta
 - Tumor necrosis factor alpha

Inciting events

- Soft tissue injuries (sprain, etc): 65%
- Fractures
- Myocardial infarctions
- Cerebrovascular accidents
- Arthroscopic procedures
- No precipitating event
- Emotional stress at the time of the event may also be an important precipitating factor.

Risk Factors & Determinants

- **Demographic: USA 5.5/100,000/yr, EU 26.2**
 - Female: 3.5 times, mostly 50s-70s
- **Injury-Related Factors**
 - Mainly in Caucasian & Japanese (?)
 - Wrist fx 1-37%
 - Total knee prosthesis surgery: 0.7-21%
 - Stroke: 1.6-48.8%
 - Spontaneous CRPS: rare but occur
 - Severity of injury: not related to risk of CRPS
 - Cast immobilization: increased pressure, early complaints of tightness-predictive factors for onset of CRPS

- A retrospective study of 146 pts (Zyluk A, 2001)
 - ✓ 64% good, only 29% pain free,
 - ✓ only 15% grip strength >50% of normal
- A series of CRPS (Low P, et al 1996):
 - 64 % severe pain >12 months VAS>7/10
- Tibial shaft fx: 10% in 1 yr
- Colle's fx: 9% in 10 yrs
- Kemler et al (2000)
 - upper ext. CRPS: self- care issues
 - lower ext. CRPS: mobility/control issues

■ Genetics

- Warm CRPS: polymorphism in one of TNFa promotor genes
- ACE/ID polymorphism in Japanese CRPS
- HLA-DR, HLA-DQ polymorphisms: as with MS and narcolepsy

■ Antecedent Infections

- Infection-induced cross reactivity against autoantigens
- Parvo B19 IgG, herpes simplex, Campylobacter jejuni, Lyme borreliosis, spirochetal, hepatitis B vaccination

■ Related Disorders

- Osteoporosis, osteomalacia, osteogenic imperfecta: more susceptible for CRPS
- Rheumatic disease, ALS, Ehlers-Danlos synd.
- Headache: 2 times
- Psychiatric: depression, anxiety, somatoform disorders

Clinical Manifestations

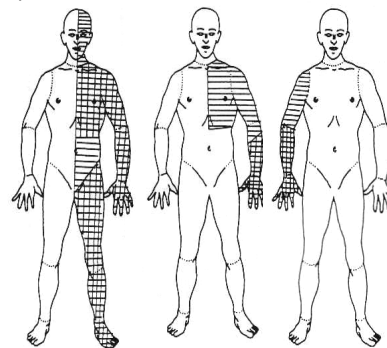
- CRPS may occur in either the upper or lower extremities.
- Involvement of both upper and lower extremities in the same patient is unusual.
- It may be recurrent.
- Three clinical stages can occur during the course of illness.

Recurrence or Spread

- Spread to other extremity; 10%
- Recurrence: 1.8%/ year
- Mean onset of spread: 78 days
- Independent/mirror image spread: 2.6, 2.5 yrs

Hemisensory impairment
(Rommel O et al., Pain 80;1999)

- 24명의 CRPS(I) 환자 중 Sensory 장애
A: 8(33%), B: 4(17%) C: 8(83%)
- 17명의 환자 중 spontaneous pain
5명은 손상부의 limb 전체, 2명은 손상부의
체부 전체



How soon after precipitating event will a patient develop CRPS?

- Usually begins days to weeks after the inciting event.
- In about 80% of cases it occurs within 3 months of a traumatic episode, but
- In many cases, CRPS begins over 6 months later.

Patterns of Spread

1. Contiguous spread (SC) [Commonest].
Enlargement of initial area from distal to proximal.
2. Independent spread (IS): To a non-contiguous distant site.
3. Bilateral or mirror image spread (MS)
[18-100% of cases]: Symmetric, less (patchy) signs & symp.s on opposite side.
4. Generalized CRPS [Small % of patients]:
Affecting the entire body

Stage 1. ACUTE/HYPEREMIC STAGE

- The patient develops pain in a limb following an event or without apparent cause.
- Symptoms include burning or throbbing pain, diffuse aching, sensitivity to touch or cold, and localized edema.
- The distribution of the pain is not compatible with a single peripheral nerve, trunk, or root lesion.
- Vasomotor disturbances occur with variable intensity, producing altered color and temperature.
- Radiographs are usually normal but may show patchy demineralization of the involved bones.



Stage 2 (Dystrophic Stage)

- **Is characterized by:**
 - Progression of soft tissue edema
 - Thickening of the skin and articular soft tissues
 - Muscle wasting
 - Development of brawny skin
- **Symptoms typically last for three to six months.**



Stage 3 (Atrophic Stage)

- The most severe stage.
- It is characterized by:
 - Limitation of movement
 - Shoulder-hand syndrome
 - Contractures of digits
 - Waxy trophic skin changes
 - Brittle ridged nails
- Radiographs reveal severe bone demineralization.



Stage 4 (Immunologic Stage)

- Failure of immune system, reduction of helper T-cell lymphocytes, inc of killer T-cells
- Hypertension and orthostatic hypotension
- Intractable generalized edema, involving pelvis, abdomen, lungs and extremities
- Cutaneous lesions
- Increased risk for Cancer

WHEN TO SUSPECT CRPS

- "Excruciating pain, stiffness, inflammation following a minor trauma..."
- "...Persistent pain and swelling of unexplained origin aggravated by bed rest or upon awakening. ..."Hooshmand, H MD CRPS: Diagnosis and Therapy Spring Verlager 1999
- "Injury that has not healed, (past normal healing time) and pain out of proportion to the injury".

EARLY DIAGNOSIS CRITICAL

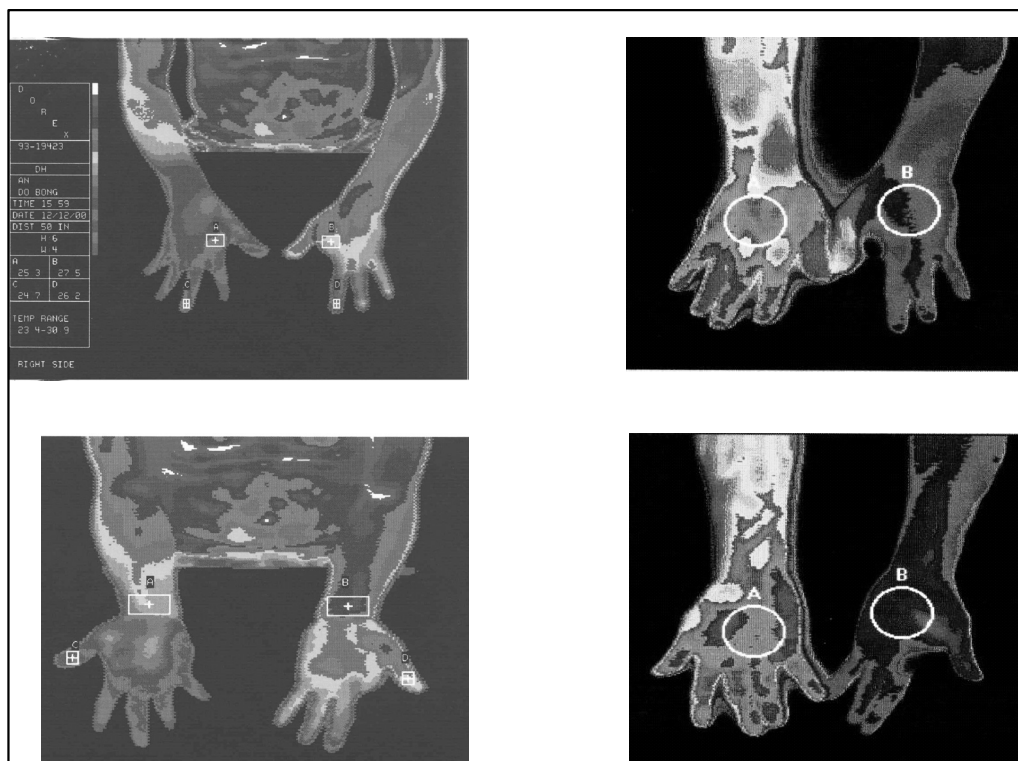
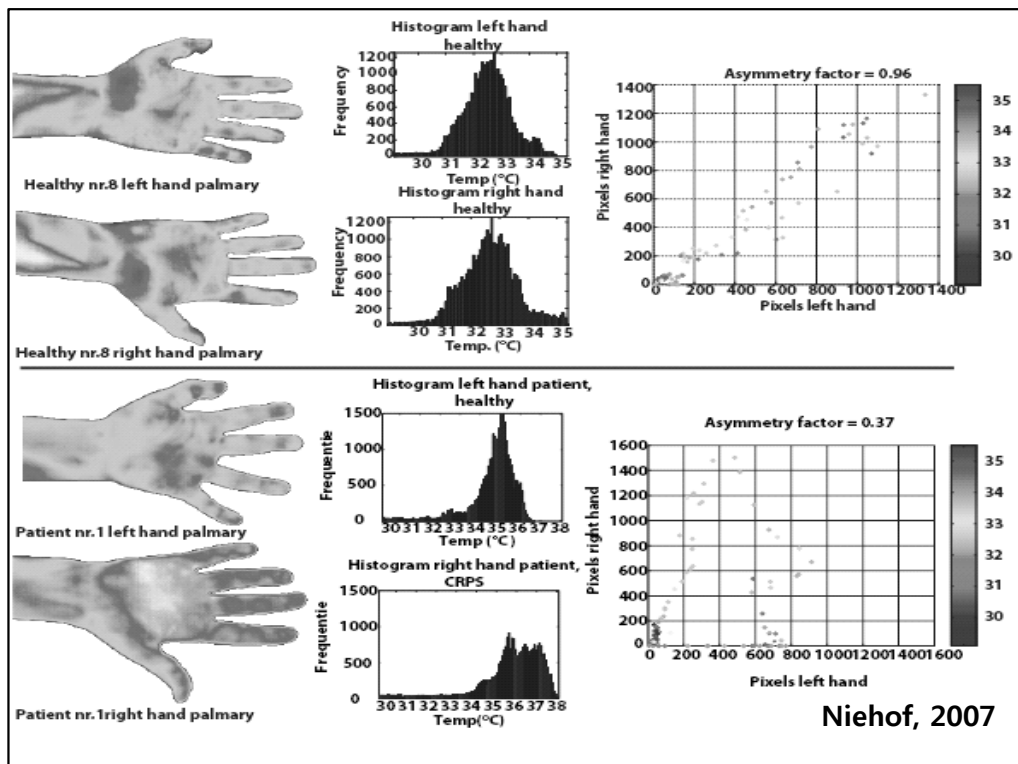
- Early diagnosis (<3 mo.) with PROPER treatment, success rate is highest, the best prognosis
- If left untreated, can lead to lifetime of severe, intractable, chronic pain
- First 3-6 months after onset: 80-90% recovery rate
- 6 months to 2 years 70-80%, after 2 years: 20%

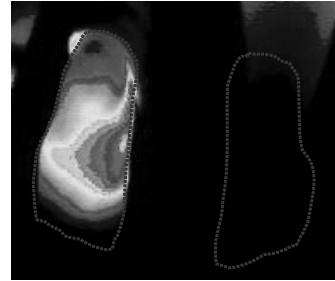
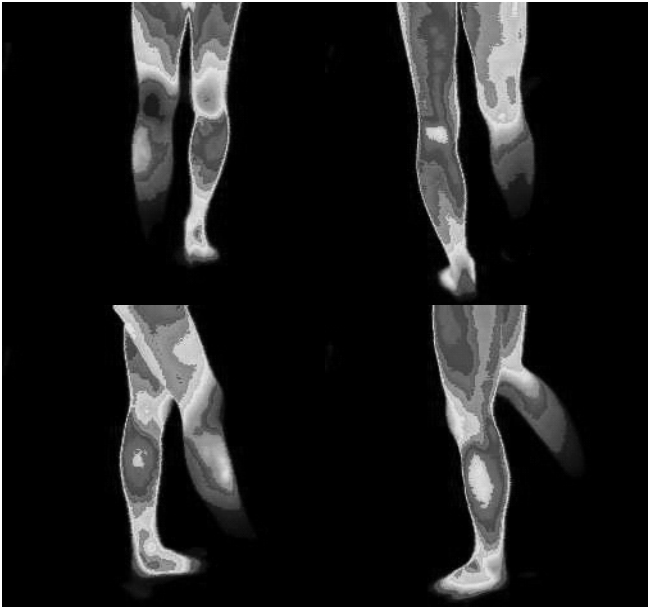
Autonomic Testing

- Includes:
 - Resting sweat output (RSO)
 - Resting skin temperature (RST)
 - Quantitative sudomotor axon reflex test (QSART)
- These tests are typically performed by neurologists and psychiatrists.
- Only recommended in patients in whom the diagnosis is in doubt or where medicolegal issues are involved.

Autonomic Testing

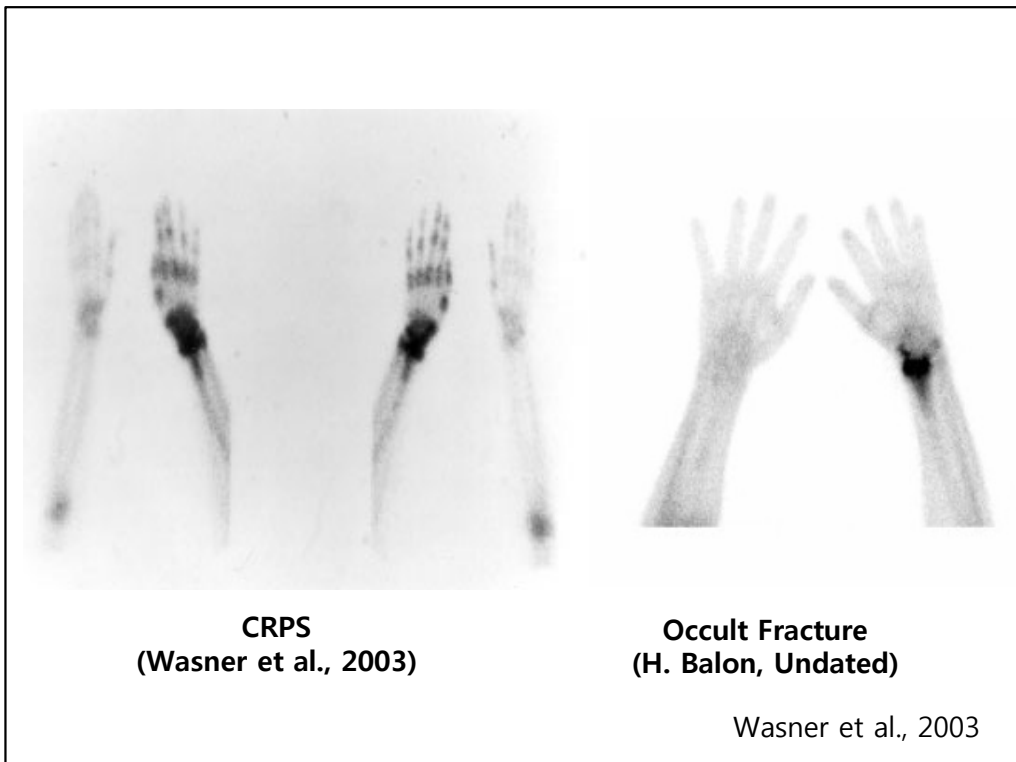
- Measurement of skin temperature, and sensory changes can be performed and are less costly, but less sensitive.
- Imaging studies may be helpful diagnostically including:
 - Bone scintigraphy
 - Plain radiographs
 - Magnetic resonance imaging





Bone Scintigraphy

- Shows decreased perfusion of the affected area and increased uptake in the peripheral joints of the extremity.
- Has a higher sensitivity and specificity than plain radiography, especially in stage 1.
- Is of limited value when performed more than six months after the onset of symptoms.



THREE PHASE BONE SCAN

	Stage 1	Stage2	Stage3
1 st phase = blood flow (within 2 min)	+	N	-
2 nd phase = blood pool (after 10 min)	+	N	-
3 rd phase = bone phase (2-3hrs)	++	+	-

Plain Film Radiography

- Most useful during stage 3 and often stage 2.
- Frequently show patchy osteopenia.
- Demineralization ranges from very limited to extensive and is often most marked in the subchondral region.
- Less common findings include:
 - Destruction of the joints and adjacent bones
 - Subluxation
 - Proliferative new bone formation
 - Extensive degenerative changes

Magnetic Resonance Imaging

- May show changes in all stages of disease.
- Especially useful for identifying stage 1 and stage 3 disease.
- Is able to identify:
 - Skin thinning/thickening
 - Tissue enhancement
 - Soft tissue edema
 - Muscle atrophy

CT Scanning

- May show focal areas of osteoporosis in a Swiss cheese-like appearance most obvious in stage 3.
- Unclear whether it is more sensitive or specific than bone scintigraphy or plain film radiography for CRPS at any stage.
- Is not recommended as a diagnostic test.

Response to Therapy

- A regional sympathetic nerve block or regional perfusion block can be useful both therapeutically and diagnostically.
- Abrupt relief from pain and dysesthesia is typically transient and suggests a diagnosis of CRPS.

IASP diagnostic criteria for CRPS-I (1)

1. Initiating noxious event, or a cause of immobilization.
2. Continuing pain, allodynia, or hyperalgesia
3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity
4. This diagnosis is excluded by the existence of conditions
(Exclusion criteria)

IASP diagnostic criteria for CRPS-I (2)

- Spontaneous pain or allodynia/hyperalgesia
 - not limited to the territory of a single peripheral n.
 - disproportionate to the inciting event.
- Evidence of edema, skin blood flow abnormality, or abnormal sudomotor activity
 - in the region of the pain
 - since the inciting event.

IASP diagnostic criteria for CRPS-I: associated Sgs and Sxs

1. Atrophy of the hair, nails, and other soft tissues
2. Alterations in hair growth
3. Loss of joint mobility
4. Impairment of motor function, including decrease in
ROM, weakness, tremor, myoclonic activity, and dystonia
5. Sympathetically maintained pain may be present

New Diagnostic Criteria (1) - IASP 2003 -

New Clinical Dx Criteria (1 Sx in 3/4 factors, 1 sg in 2 or more factor)

New Research Dx Criteria (1 Sx in 4/4 factors, 1 sg in 2 or more factor)

* 4 Subsets of Symptoms/Signs: Sensory changes/ Vasomotor-/
Sudomotor-, edema/ Movement disorder, dystrophy

1. Continuing pain that is disproportionate to any inciting event.
2. Must report at least 1 Sx in three of the 4 following categories.
3. Must display ≥ 1 sign in ≥ 2 of following categories.
4. There is no other diagnosis that better explains the Signs and Symptoms.

New Clinical Diagnostic Criteria for CRPS-I (2)

2. Must report at least 1 Sx in three of the 4 following categories:

Sensory: reports of hyperesthesia (spontaneous pain).

Vasomotor: reports of temperature asymmetry &/or skin color changes &/or skin color asymmetry

Sudomotor/Edema: reports of edema &/or sweating changes &/or sweating asymmetry.

Motor/Trophic: reports of ↓ ROM &/or motor dysfunction (weakness, tremor, dystonia) &/or trophic changes (hair, nails, skin)

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- Skin: 자발통, 통각과민(기계적, 열적, 심부체성)
- Vasomotor: 혈관(확장, 수축), 피부변화(온도, 색깔)
- Sudomotor/Edema: 부종, 발한이상(증가, 감소)
- Motor/Trophic:
 - 근력약화, 근긴장이상, 진전, 협응기능장애, 관절강직,
 - 연부조직변화, 피부위축, 손발톱변화/털변화(증가, 감소)

New Clinical Diagnostic Criteria for CRPS-I (3)

3. Must display ≥ 1 sign in ≥ 2 of following categories:

Sensory: evidence of hyperalgesia &/or allodynia.

Vasomotor: evidence of temperature asymmetry &/or skin color changes &/or skin color asymmetry

Sudomotor/Edema: evidence of edema &/or sweating changes and/or sweating asymmetry.

Motor/Trophic: evidence of \downarrow ROM &/or motor dysfunction (weakness, tremor, dystonia) &/or trophic changes (hair, nails, skin)

Sensitivity and specificity

	Sensitivity	Specificity
IASP criteria	98%	36%
New (C/R) IASP criteria	85/70%	60/94%

Proposed clinical diagnostic criteria for CRPS (*Harden et al., Pain Medicine, 2007*)

To make the clinical diagnosis, the following criteria must be met:

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in three of the four following categories:
 - Sensory:** Reports of hyperesthesia 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, nail, skin)
3. Must display at least one sign at time of evaluation in two or more of the following categories:
 - Sensory:** Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
 - Vasomotor:** Evidence of temperature asymmetry ($>1^{\circ}\text{C}$) 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, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms

Harden et al./Pain Medicine 2007;8(4);326-331

Validation

Criteria/Decision Rules for Proposed Criteria	Sensitivity	Specificity
2+ sign categories & 2+ symptom categories	0.94	0.36
2+ sign categories & 3+ symptom categories	0.85	0.69
2+ sign categories & 4 symptom categories	0.70	0.94
3+ sign categories & 2+ symptom categories	0.76	0.81
3+ sign categories & 3+ symptom categories	0.70	0.83
3+ sign categories & 4 symptom categories	0.86	0.75

DIAGNOSIS OF CRPS

(2004년 수정본)

임상적 증상이나 징후의 4범주

감각이상

- 자발통(spontaneous pain)
- 기계적 통각과민(mechanical hyperalgesia)
- 열적 통각과민(thermal hyperalgesia)
- 심부 체성 통각과민(deep somatic hyperalgesia)

혈관이상

- 혈관확장(vasodilation)
- 혈관수축(vasoconstriction)
- 피부온도의 비대칭(skin-temperature asymmetries)
- 피부색의 변화(skin-color changes)

부종, 발한 이상

- 부종(swelling)
- 다한증(hyperhidrosis)
- 저한증(hypohidrosis)

운동 또는 이영양성 변화

- 근력저하(motor weakness)
- 떨림(tremor)
- 근육긴장 이상(dystonia)
- 협조운동 부족(coordinate deficits)
- 손톱 또는 모발변화(nail or hair changes)
- 피부위축(skin atrophy)
- 관절강직(joint stiffness)
- 연부조직의 변화(soft-tissue changes)

판정

임상 적용 시(감수성 0.85, 특이성 0.60) : 3범주 이상에서 각각 1개 이상의 증상과 2개 이상의 범주에서 각각 1개 이상의 징후가 있어야 한다.

연구목적적으로 사용 시(감수성 0.70, 특이성 0.96) : 4범주 모두에서 각각 1개 이상의 증상과 2개 이상의 범주에서 각각 1개 이상의 징후가 있어야 한다.

Disability of CRPS by 5th Ed of AMA: 40-50%

What about definitive Dx? When & how?

- In AMA Guides 6th edition, there are 4 categories and 11 objective diagnostic criteria points for CRPS:

- 1) mottled or cyanotic skin color,
- 2) cool skin temperature,
- 3) edema,
- 4) dry or overly moist skin,
- 5) smooth and non-elastic skin texture,
- 6) soft tissue atrophy,
- 7) joint stiffness and decreased passive motion,
- 8) nail changes,
- 9) hair growth changes,
- 10) radiographic trophic bone changes or osteoporosis, and
- 11) bone scan consistent with CRPS

- The number of points determines the impairment rate of the CRPS. However, if the number is less than 4, the impairment rate is 0%.
- Although the number of objective signs may increase the accuracy of the diagnosis, not the impairment, of the CRPS, it can be used as an alternative measurement of the immeasurable subjective symptom.
- The rate of physical impairment due to the PRD can be from 0% to 40% (for the lower extremity) or 60% (for the upper extremity), by the AMA 6th edition.

- According to AMA Guides 6th edition, a sign is counted only if it is observed and documented at time of the impairment evaluation.
- Needs at least of 1 year after Dx based on IASP guideline
- Disability determination from at least 2 Pain Specialists should be required
- Also should include full psychiatric evaluation and to R/O compensation traits
- Other considerations:
 - Impacts when too early definitive Dx given
 - Proper education to pt and families
 - Proper timing and types of management with multidisciplinary approach
 - **Drug abuse, addiction, compensation, overdiagnosis, etc**

Table 1. Pain related disability by the Workmen's Compensation Insurance Act

Grades	Criteria	Labor loss
7	Pain always interferes with one's job except easy work	60%
9	Workable, but pain limits range of jobs significantly	40%
12	Workable, but pain often interferes with one's work	15%
14	Workable, but pain or abnormal sensory is present	5%

Table 2. Pain related disability by the Patriots and Veterans Welfare Corporation Act

Grades	Criteria	Labor loss
5	Pain always interferes with one's job except easy work	80%
6	Workable, but pain limits range of jobs significantly, with objective signs such as osteoporosis, joint contracture and muscle atrophy corresponding to the CRPS	70%
7	Workable, but pain limits range of jobs significantly, with objective signs on physical examination or tests corresponding to the CRPS Workable, but often severe pain interferes with one's work	60%

CRPS : complex regional pain syndrome

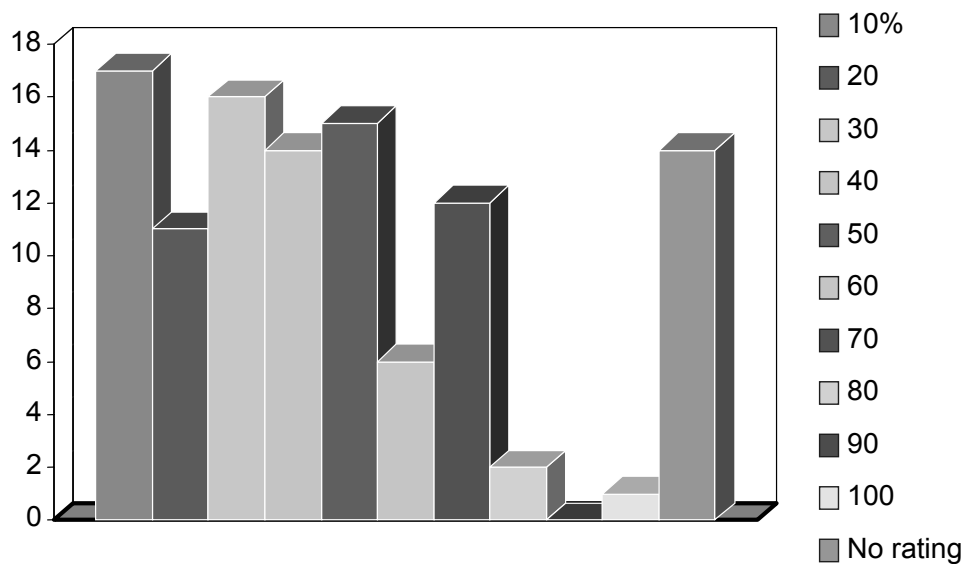
Differential Diagnosis

- ✓ Infectious arthritis (CBC, ESR, SF culture)
- ✓ Rheumatoid arthritis (ESR, CRP, RF, S.C nodules)
- ✓ SLE (Rash, serositis, renal, CBC, ESR, ANA, C3& C4)
- ✓ Scleroderma (Esophageal dysmotility, pulmonary, ANA, Scl 70)
- ✓ Peripheral neuropathy (no edema, glove & stock hyposthesia)
- ✓ Rotator cuff tear (drop arm, localized)
- ✓ Paraneoplastic syndrome (ovarian carcinoma)
- ✓ Remitting seronegative symmetrical synovitis with pitting edema (ESR, CRP, MRI, dramatic response to steroids)

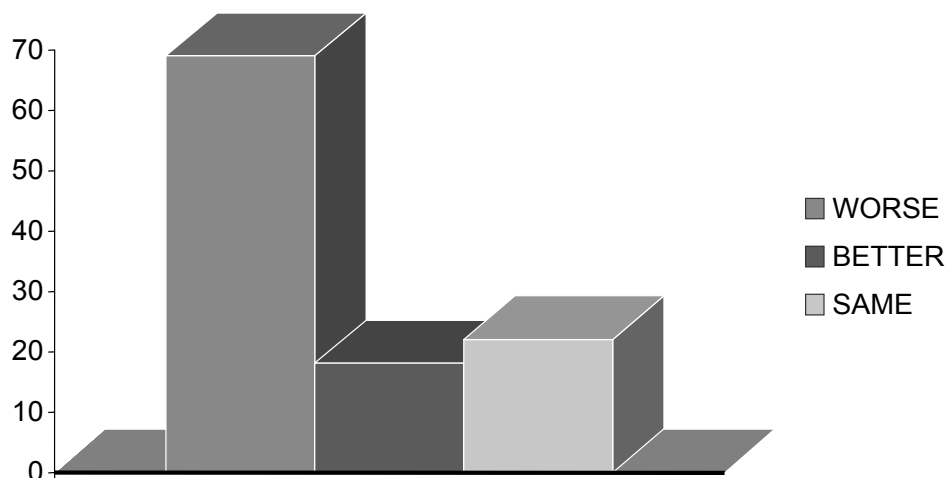
Prevention

- The best treatment of CRPS is prevention.
- Early mobilization after stroke or MI is recommended to reduce the risk of developing CRPS.
- The prophylactic use of vitamin C after wrist fracture is recommended to lower the risk of developing CRPS.
 - The postulated mechanism of action is the prevention of damage from toxic free radicals via an antioxidant effect.

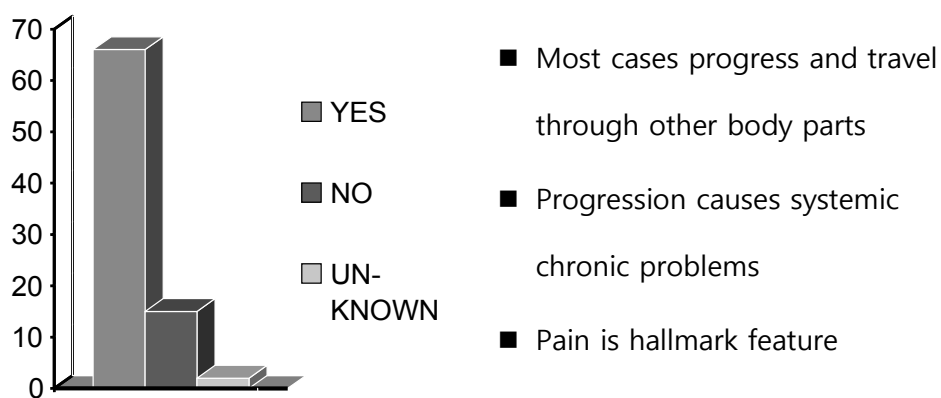
OVERALL SUCCESS RATING



PROGRESSION: IS YOUR CRPS WORSE, BETTER OR SAME?



HAS YOUR CRPS SPREAD?



- Most cases progress and travel through other body parts
- Progression causes systemic chronic problems
- Pain is hallmark feature

Management of CRPS

- A multidisciplinary management approach of CRPS has been recommended by a consensus of experts.
- Treatment is more effective when initiated in stage 1, as soon as the diagnosis is established, and before radiographic changes appear.
- The prognosis of CRPS type 1 is generally favorable.

Summary

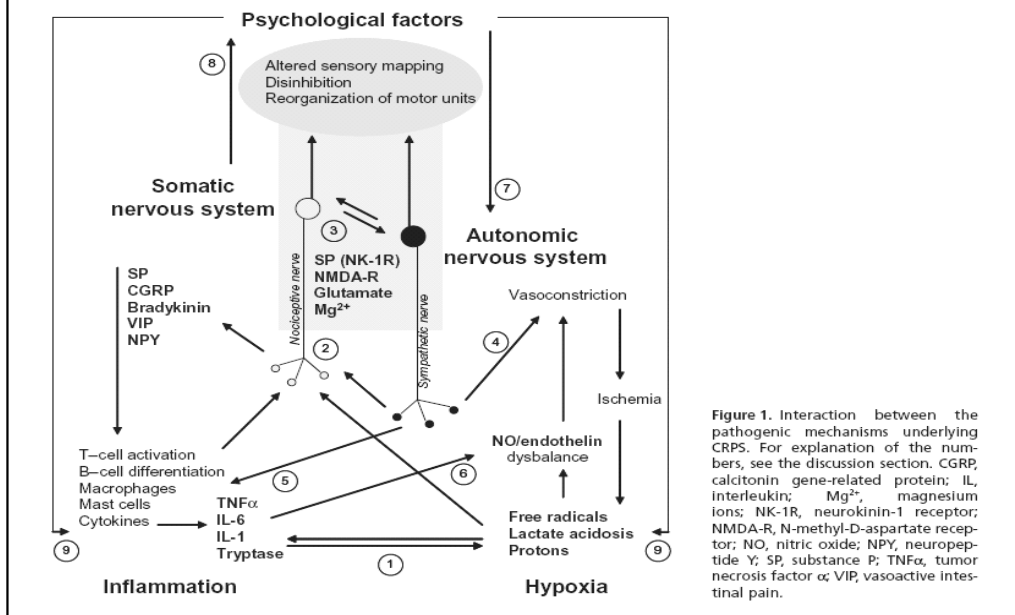
- Goals of physical and pharmacologic therapies:
 - Normalize sensation
 - Promote normal positioning
 - Decrease muscle guarding
 - Minimize edema
 - Increase movement and functional use of the extremity
 - Increase independence in all areas of activity of daily living

Management Based on Updated Pathogenesis & Etiology

- Autonomic Nervous System
- Somatic Nervous System
- Inflammation
- Hypoxia
- Psychological Factors

Marissa de Mos et al.(2009). Pain Practice Based on Review of 419 Papers

Interaction between pathogenic mechanisms underlying CRPS



1. Autonomic Nervous System

- Sympathetic hyperactivity or SMP: debatable & not obligatory part of CRPS
- Sweating & trophic change: can also be neuropeptide effect
- SMP may also due to pathological failure of spinal inhibitory mechanism to suppress nociceptive input by normal, instead of increased sympathetic stimulation
- Many pts do not benefit from sympatholytic blocks
- Abnormal sensitivity of adrenergic receptors for normal sympathetic outflow(intradermal inj ->pain)
- Catecholamin in serum of CRPS pt usually decreased
- But, sympathetic blocks still effective in subset of pts

2. Somatic Nervous System

- 29% reduction of axonal density in CRPS(C, A-delta) with presence of aberrantly branched endings
- Spinal Sensitizers: NMDA, NK-1
 - Memantine(NMDA antagonist): effective for pain and motor sx
 - Antiepileptics(gabapentin): increase neuronal excitation threshold-only moderately effective
- Supraspinal alterations
 - CBF change esp. in hypothalamus
 - Some pts experience referred sensation or body perceptive disturbance, impaired tactile discrimination
- Efferent Motor Alterations
 - Hyperexcitability in sensory & motor cortex
 - Graded motor imagery & Mirror therapy: effective

3. Inflammation

- Classic mediators (lymphocytes, mast cells, etc) excrete pro-inflammatory cytokines: IL-6, TNFa, tryptase, etc (25 types)
- Systemic parameters of inflammation (WBC, ESR, CRP): normal
- Neurogenic inflammation: by neuropeptides secreted by C-fiber after various triggers in periphery
 - But, it can also be released after primary afferent depolarization in dorsal horn
 - Cardinal mediators: SP, CGRP, bradykinin (4배 증가), neuropeptide Y, ACE, VIP- even in unaffected limb
- Successful response from immunomodulating agents
 - Inflixmab, thalidomide, corticosteroid

4. Hypoxia

- Decreased capillary oxygenation & increased lactate in skin
- In muscle: acidosis & impaired high-energy phosphate metabolism
- Affected limb: histopathologically, oxidative stress
- Hypoxia -> acidosis & free radical formation -> trigger primary afferent to cause severe painful sensation
- Hypoxia in CRPS proposed to be caused by extreme vasoconstriction either by sympathetically thriven or resulting fro a local dysbalance between endothelial factors

- Endothelial factors: NO (vasodilatin) and endothelin (ET-1) (vasoconstriction)
 - ET-1 in CRPS increased & NO decreased in affected limb
- Role of HYPOXIA induced by endothelial dysfunction in ongoing CRPS (chronic CRPS)
- NO donors proposed as therapeutic agents
- Acute hypoxic injury (eg tourniquet apply in rats followed by reperfusion) develop CRPS-like Sxs without microscopic nerve damage: triggering aff. & initiation of inflammatory response by free radical under oxidative stress (proposed mechanism?)
- Positive outcome (RCT) from scavengers (DMSO, N-acetylcysteine, Vit C) in early Tx of CPRS pts

5. Psychological Factors

- One extreme view CRPS as "pseudoneurological disease(somatoform disorders, malingering, psychiatric pathology)- now generally disregarded but still controversial
- Many agree psychological factors and personality in the *maintenance* (instead of onset) of CRPS
 - 1) Anger-out: influence pain intensity by reactive muscle activity and by inhibition of endogenous opioid antinociceptive system activation
 - 2) Stress-induced release of catecholamines: vicious cycle from emotional stress and pain
 - 3) Extreme fear for pain: disuse of affected extremity, prolonged immobilization, decreased blood flow, trophic alteration
- Physical therapy with graded activity to overcome movement anxiety: great value since it stimulates desensitization for mechanical allodynia & prevents against accumulation of catecholamines, neuropeptides, inflammatory mediators

Psychologic Assessment and Counseling

- Job and interpersonal relationships should be evaluated in all patients.
- Stress-management techniques may reduce the effect of stress on the autonomic and central nervous system.
- Consulting a clinical psychologist is recommended if:
 - CRPS has been present for more than two months duration.
 - There is no response to treatment.
 - There is a suspected comorbid psychologic or psychiatric disorder.

Physical and Occupational Therapy

- PT/OT are effective in preventing CRPS.
- There is conflicting data on whether PT/OT in patients with CRPS is effective.
- However, there is little downside to PT/OT evaluation and treatment.
- PT/OT referral is recommended soon after the diagnosis is established.
- PT should be performed twice daily at home for patients in all stages of CRPS and should begin before limitation of movement occurs.
- If PT/OT is delayed to stage 3, impairment is not likely to improve.

Smoking Cessation

- Cigarette smoking appears to be a risk factor for CRPS.
- However, the beneficial effect of smoking cessation has not been assessed in patients with CRPS.
- Nevertheless, the risk enhancing effect of smoking provides rationale for advising smoking cessation.

Pharmacologic Therapy

- Only a few pharmacologic agents have been studied in well designed clinical trials to treat CRPS.
- Currently, there are no drugs that have FDA approval specifically for the treatment of CRPS.
- Medications that appear to resolve pain significantly better than placebo include agents in the following classes:
 - Anticonvulsants
 - Bisphosphonates
 - Oral glucocorticoids
 - Nasal calcitonin

Pharmacologic Therapy

- Antidepressant medications, including tricyclic antidepressants, are often effective in reducing neuropathic pain, but not definitive in CRPS.
- Selective serotonin reuptake inhibitors (SSRIs) are not recommended in recent neuropathic pain guidelines and have shown much less efficacy when compared to the heterocyclic antidepressants.
- However, the serotonin-norepinephrine reuptake inhibitors (SNRIs) duloxetine and venlafaxine are currently recommended in neuropathic pain guidelines as first-line neuropathic coanalgesics

- **Guidelines developed by a consensus of CRPS experts suggest beginning treatment for pain with:**
 - A tricyclic antidepressant (eg, amitriptyline or nortriptyline)
 - An anticonvulsant (eg, gabapentin)
 - A nonsteroidal antiinflammatory drug
 - And an opioid for those with severe pain : A fair trial of other therapies should be tried before opioids in this population. Opioids are not the preferred or initial therapy in patients with CRPS.

Pharmacologic Therapy

- Topical application of capsaicin cream four times daily over painful areas can be used for treating neuropathic pain.
 - Side effects include local burning and skin irritation
 - 3-5 days is sufficient to assess effectiveness and tolerability
- Other approaches with some evidence of efficacy but more invasiveness include:
 - IV ketamine
 - Epidural clonidine injections and infusions
 - Intravenous regional sympathetic block with bretylium
 - Local sympathetic blocks with local anesthetic

Anticonvulsants

- Beneficial in chronic pain, especially pain that is lancinating, burning, or sharp.
- Gabapentin has been used successfully in some cases of CRPS.
- Carbamazepine 600 mg/d 1 wk
- Newer agents include pregabalin (75 mg bid) and lamotrigine (25 mg bid).

Bisphosphonates

- Have been used to prevent bone resorption & bone modeling in patients with CRPS.
- May also be useful for pain relief.
- Examples include: daily for 8 weeks(oral), 10 d(IV)
 - Clodronate
 - Pamidronate IV
 - Alendronate IV or po
- Potential side effects include:
 - Hypocalcemia
 - Esophageal ulceration
 - Osteonecrosis of the jaw

Glucocorticoids

- A short course, that is tapered quickly as the patient responds, has been shown to have a beneficial effect.
- 30 mg/d for 12 wks
- May be significantly more effective than NSAIDs, but should be reserved for patients who do not respond to NSAIDs and antidepressants first.
- Continued low-dose corticosteroid treatment may be needed for a prolonged period in severe cases.
- Patients with stage 3 disease usually do not respond to steroids.

NMDA Antagonists (1)

Ketamine:

- gradually increasing (3-5 mg/kg/hour) dose over a 5-day period.
- Midazolam was given concomitantly to counteract the psychiatric side effects, which included agitation, anxiety, and nightmares.
- This method was used in a patient with severe refractory CRPS that was spreading. Complete remission had been maintained for 8 years according to the case report.
- Another study by the same author also used anesthetic doses of ketamine. An open-label phase II trial of 20 patients with refractory CRPS showed that anesthetic doses (over 5 days) of ketamine provided a benefit in reducing pain, improving quality of life and the ability to work. All 20 patients experienced complete remission within 1 month of treatment, 17 patients maintained complete remission at 3 months, and 16 patients maintained complete remission at 6 months. In those who relapsed, there was still a significant relief in pain at 3 and 6 months.

NMDA Antagonists (2)

■ **Amantadine**

- 200 mg/IV

■ **Dextromethopphan**

- Oral dose of 400 mg/day
- should not be administered with tricyclic antidepressants or agents that inhibit CYP2D6, as a drug interaction can result in toxicity

Alpha-adrenergic Antagonists and Antihypertensives

- Clonidine transdermal patch: some benefit in four CRPS patients with sympathetically maintained pain & substantial reduction in hyperalgesia to mechanical and cold stimuli occurred.
- Terazosin may be effective in treating sympathetically maintained pain in patients with CRPS. One patient had complete relief of sympathetically maintained pain and vasospasm on terazosin.
- Oral nifedipine (up to 60 mg/day) or phenoxybenzamine showed benefit for the control of extreme vasoconstriction in two uncontrolled case series of patients with CRPS (n=59). Three out of four patients with CRPS responded to phenoxybenzamine 10 mg/day on a daily or every other day basis for a duration of 6 weeks up to 60 months.
- Intravenous phentolamine is not typically used clinically; however, it may be used diagnostically.

Calcitonin

- Appears to be effective in studies in CRPS patients.
- Retards bone resorption.
- Has a putative analgesic effect, of which the mechanism is unknown.
- 300 to 400 IU/day via injection or nasal spray is the typical recommended dose (3-4잔).
- There is a low risk associated with use.
- It is recommended in combination with PT for patients with mild to moderate symptoms of CRPS despite use of NSAIDs and tricyclic antidepressants.

Other Drugs for CRPS

- Thalidomide up to 300 to 400 mg daily has shown improvement in pain in case reports of patients (n=43) with CRPS.
- IV and subcutaneous lidocaine have also been used.
- Topical treatments that have been used for CRPS include capsaicin, the 5% lidocaine patch, eutectic mixture of local anesthetics (EMLA) cream, and dimethyl sulfoxide (DMSO).
- Dworkin et al recommended oral mexiletine as a third-line option for treating neuropathic pain.
- Treatment for dystonia or muscle cramps may include use of oral baclofen or clonazepam.[†]

Response to Treatment

- Patients with stage 1 disease should be seen on a weekly basis.
- The treatment should be changed if the response is suboptimal.
- Goals of therapy are:
 - Decreased pain
 - Improved mobility
 - Better function

Response to Treatment

- Patients in stage 1 who are not improving despite two weeks of oral treatment in addition to PT should be considered for invasive forms of treatment.
- Patients in stages 2 and 3 of CRPS are also candidates for invasive therapies if pain and function have not rapidly improved.

Invasive Treatment

- Invasive treatments include:
 - Tender point injections
 - Nerve stimulation
 - Epidural clonidine
 - Regional sympathetic nerve block
 - Ganglion blocks
 - Intravenous regional blocks
 - Spinal cord stimulation
 - Motor cortex stimulation
 - Sympathectomy

Invasive Treatment

- Patients receiving noninvasive therapy who are not improving are offered increasingly invasive interventions, allowing 2 weeks for improvement before moving on to the next treatment type.
- In tertiary care centers, spinal cord stimulation is considered if the patient has not responded within 12 to 16 weeks of the initiation of therapy.

Indications for SCS

- Failed Back Surg/Post Lami. Syndrome - leg pain of neuropathic type
- CRPS I & II
- Peripheral vascular disease - microvascular disease
- Angina - chronic resistant
- Neurogenic Bladder/Urge Incontinence
- Perineal/Pelvic/Coccygeal Pain
- Post-amputation pain



Patient Selection ...

- Pt is willing to work with the treatment team on a long term
- Life expectancy of >3-6 months
- Trial screening is successful >50% reduction in pain level

Patient Selection Criteria

- More conservative therapies have failed
- An observable pathology exists that is concordant with the pain complaint
- Further surgical intervention is not indicated
- No serious untreated drug habituation exists
- Psychological evaluation and clearance for implantation has been obtained
- No contraindications to implantation exist
- A Screening Test has been successful

by Elliot Krames M.D., in The Journal of Pain and Symptom Management
(*J Pain & Symptom Mgt.*, 1996):

복합부위통증증후군에 대한 척수자극술 인정 기준

항목	저621 척수신경자극기 설치술(Implantable of Spinal Neurostimulator Electrodes)의 보험 급여 기준
제목 1	저621 척수신경자극기 설치술의 세부사항 인정기준
세 부 인 정 사 항	<p>저621 척수신경자극기 설치술의 인정기준은 다음과 같은 경우에 요양급여를 인정하며, 동 인정기준 이외 시행하는 경우에는 전액 본인 부담토록 함.</p> <p style="text-align: center;">- 다 음 -</p> <p>가. 6개월 이상의 적절한 통증치료(약물치료와 신경차단술 등)에도 효과가 없고, 심한 통증(VAS 통증점수 7 이상)이 지속되는 불인성 통증이 있는 경우</p> <p>나. 약물치료, 신경차단술, epidural morphine injection 등 적극적인 통증치료를 6개월 이상 실시함에도 불구하고 심한 통증(VAS 통증점수 7 이상)이 지속되는 만성통증으로 여명이 1년 이상으로 예상되는 경우</p>

척수신경자극기설치술 산재보험 인정기준

‘척수신경자극기설치술’은 보건복지부장관이 고시하는 “요양급여의 적용기준 및 방법에 관한 세부사항”에서 정한 범위내에서 인정하되, 동 기준 중 “6개월 이상의 적절한 통증치료(약물치료와 신경차단 술 등)에도 효과가 없고, 심한 통증(VAS 통증점수 7 이상)이 지속되는 불인성 통증”에 대한 적응증과 시술 전 평가 및 영구 자극기설치술 실시기준은 다음과 같다.

1. 적응증
 - 가) 척추수술 후 실패증후군. 다만, 경추 및 요추에 대하여만 인정하며, 최초의 척추수술 후 6개월 이상에서 3년을 초과하지 않은 시점에서 시행한 경우에 한함
 - 나) 복합부위통증증후군 제1형 및 제2형
 - 다) 상완신경총의 부분적 손상
2. 시술 전 평가 및 영구 자극기설치술 실시기준
 - 가) 다면적 인성검사(MMPI)를 포함한 임상 심리검사를 실시하고 정신과 전문의가 정신상태 검사 결과 등을 종합 평가하여 심리적인 요인이 없음을 확인하여야 한다.
 - 나) 영구적인 척수신경자극기설치술은 시험적 거치술 후 환자의 증상호소 정도 및 시각통증척도(VAS)등을 종합하여 최소 50% 이상의 통증감소 효과가 있어야 한다.
3. 시행: 2007. 06. 15. 진료분부터

- ※ 복합부위통증증후군(CRPS) 제1형 및 제2형의 구분
- 제1형 : 반사성교감신경위축증(reflex sympathetic dystrophy, RSD)
 - 제2형 : 말초신경의 외상후성 신경통(작열통과 외상성 말초신경손상후 신경통, csusalgia, post-traumatic neuralgia)
- ※ 제외되는 적응증
- 요통과 경부통이 주 증상인 축성통증(axial pain), 항문주위 및 회음부 통증(anorectal & perineal pain), 마미충 증후군(cauda equina syndrome)의 통증
 - 말초혈관 폐색으로 인한 혈관성 통증 및 협심증(angina pectoris)
 - 포진 후 신경통(post-herpetic neuralgia, PHN) 및 개흉술 후 신경통(post-thoracotomy neuralgia), 늑간 신경통
 - 상완신경총과 요천추 신경총의 적출 손상 후 신경통(brachial & lumbosacral plexus avulsion pain)
 - 환상지통(phantom limb pain) 및 단지통(stump pain)
 - 중추성 통증(central pain)
 - 중풍 후 신경통(central post-stroke pain, CPSP, 기존의 thalamic syndrome)
 - 척수신경(spinal cord를 의미함, not spinal root)손상에 따르는 척수마비의 통증(central pain following spinal cord injury)
 - 척수손상으로 인해 척수신경자극술을 시행할 후주(dorsal column)의 기능이 이미 소실된 경우
 - 척수신경의 완전 절단(spinal cord transection)

참고 문헌 -----
 Neurosurgery 58:481-496, 2006 / Journal of Neurosurg (Spine 3) 100:254-267, 2004 / Surg Neurol 1998:50:110-121 / SPINE Volume 30, Number 1, pp152-160 / J Neurosurg (Spine 3) 100:254-257, 2004 / European Journal of Pain 10(2006):91-101 / The British Pain Society 2005:1-32

Other Modalities

- Intrathecal baclofen may relieve dystonia in patients with CRPS.
- A skilled hypotherapist can be helpful for patients with heightened arousal including fear, anxiety, excessive sweating, and weakness.
- Hypnosis has allowed physical therapy to progress in some patients with otherwise intractable disease.

Treatment of Relapse

- Individual episodes of CRPS may last 6 to 9 months.
- These may be followed by spontaneous resolution or successful therapy.
- However, sequelae may persist and recurrences can occur.
- Cold or emotional trauma can cause an exacerbation several months after treatment.
- Small doses of TCAs and oral guanethidine have been helpful in treating recurrences.

CRPS FACTS

- When not caught early, CRPS can be progressive (70% of cases)
- NEED to find single diagnostic test
- Early recognition through education
- Early diagnosis equals BETTER prognosis
- Sometimes invasive treatments without success can cause worsening of symptoms
- Watch out for additional injury

WHAT CAN A MEDICAL PROFESSIONAL DO?

- EARLY RECOGNITION IS ESSENTIAL TO PATIENT RECOVERY
- ATTEND CRPS INFORMATION SESSIONS
- IF YOU SUSPECT CRPS, REFER IMMEDIATELY FOR TREATMENT
- BELIEVE THE PATIENT'S PAIN: IT IS REAL
- LISTEN/SUPPORT PATIENT

Conclusions

- If left untreated, CRPS can result in permanent deformities and chronic pain requiring a range of long-term pharmacologic and nonpharmacologic treatments.
- If the condition is caught early, physical therapy is a valuable tool to mobilize the affected body part, and sympathetic nerve blocks may be used to stop the progression of or cure the disease.
- Other therapies used to treat patients with CRPS are psychotherapy, surgical sympathectomy, spinal cord stimulation, and intrathecal drug pumps.

- The absence of well-defined criteria for the diagnosis of this syndrome has resulted in a lack of RCTs for the Tx of CRPS.
- In some of the cases, data have only been reported on oral presentations or posters during clinical meetings.
- The medications that have been used or tried in this population include certain antidepressants, anticonvulsants, anesthetics, antihypertensives, anti-inflammatories, opioids, calcitonin, bisphosphonates, and neuropathic coanalgesics, among others.
- There are no medications that are FDA approved for the treatment of CRPS at present time.
- To avoid polypharmacy, it is important to remove agents from the regimen that are not resulting in an improvement in pain or function.