Review

Complex regional pain syndrome – diagnostic, mechanisms, CNS involvement and therapy

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Complex regional pain syndromes (CRPS, formerly reflex sympathetic dystrophy and causalgia) are neuropathic pain conditions of one extremity developing inadequately after a trauma. The initiating trauma affects primarily the extremity, but can also be a central lesion (e.g., spinal cord injury, stroke). CRPS is clinically characterized by sensory, autonomic and motor disturbances. Pathophysiologically there is evidence for functional changes within the central nervous system and for involvement of peripheral inflammatory processes. The sympathetic nervous system plays a key role in maintaining pain and autonomic dysfunction in the affected extremity. After a primary central lesion, secondary peripheral changes in the paretic extremity are suggested to be important in initiating a CRPS. Though there is no diagnostic gold standard, careful clinical evaluation and additional test procedures should lead to an adequate diagnosis. An early diagnosis and an interdisciplinary approach are important for optimal and successful treatment.

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Introduction

Complex regional pain syndromes (CRPS, formerly reflex sympathetic dystrophy and causalgia) are neuropathic pain disorders developing as a disproportionate consequence of painful trauma or a nerve lesion affecting the limbs, or a bone fracture, or as a consequence of a remote process like stroke, spinal cord injury and myocardial infarction.¹ Clinical features that occur in a distal generalized distribution are spontaneous pain, allodynia, hyperalgesia, autonomic and motor dysfunction. In 1872 the American Civil War physician, Weir Mitchell, was the first who describe a pain syndrome, named *causalgia*, developing in the distal extremity following traumatic partial nerve injury. The affected extremity was characterized by sensory and trophic symptoms spreading beyond the innervation territory of the injured peripheral nerve. Early in the last century Paul Sudeck described similar symptoms in an extremity pain syndrome that developed after distal bone fractures without affecting any peripheral nerve. Based on the experience that patients with Sudeck's syndrome obtained dramatic pain relief by sympathetic block, the term reflex

sympathetic dystrophy was introduced by Evans in 1946 to accommodate the suggested pathophysiological role of the sympathetic nervous system. Following the growing evidence from recent years that sympathetically maintained pain (SMP) is still an important symptom, but not obligatorily necessary for the diagnosis of these disorders, a new terminology was introduced based entirely on elements of history, symptoms and findings on clinical examination, with no implied pathophysiological mechanism.² According to the International Association for the Study of Pain (IASP) 'Classification of Chronic Pain', reflex sympathetic dystrophy and causalgia are now called complex regional pain syndromes (CRPS). In CRPS type I (reflex sympathetic dystrophy), minor injuries to a limb or lesions in remote body areas precede the onset of symptoms. CRPS type II (causalgia) develops after injury to a major peripheral nerve.³ Recent investigations of autonomic, motor and somatosensory abnormalities indicate that the whole picture of CRPS is considered to be a neurological disorder involving the central nervous system as well as a peripheral neurogenic inflammatory process.⁴ However, the general awareness of CRPS is still poor, because on average thirty months pass by until patients are admitted to a pain center for adequate therapy.⁵

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Clinical picture of complex regional pain syndromes

CRPS type I (reflex sympathetic dystrophy)

Noxious events, including minor trauma (eg sprains, bruises, soft tissue trauma, frostbite or skin lesions), bone fracture or surgery of the affected extremity often determine the onset of CRPS I. Occasionally the disease develops after other medical events such as shoulder trauma, myocardial infarction or a lesion of the central nervous system. A peripheral nerve lesion is not detectable,⁶ although one histopathological study demonstrated damage of small afferent fibers in CRPS after leg amputation.⁷ The clinical picture of CRPS I is characterized by sensory, autonomic, trophic and motor abnormalities, as well as sometimes inflammatory symptoms (Figure 1).^{8–12}

Sensory symptoms These include a burning spontaneous pain felt in the distal part of the affected extremity.¹³ Characteristically, the pain is disproportionate in intensity to the inciting event. The pain usually increases when the extremity is in a dependent position. Stimulus-evoked pains are a striking clinical feature; they include mechanical and thermal allodynia and/or hyperalgesia. These sensory abnormalities often appear early, are most pronounced distally, and have no consistent spatial relationship to individual nerve territories or to the site of the inciting lesion.^{14–16} Typically the pain can be elicited by movements and pressure at the joints, even if these are not directly affected by the inciting lesion. In addition, somatosensory deficits may be present.^{17,18}

Autonomic abnormalities These include swelling and changes of sweating and skin blood flow (Figure 1).^{19–25} At normal room temperature the skin temperature of the limbs shows an inconstant side difference in about 30–80% of the patients, ie the affected extremity is

Figure 1 Patient with acute CRPS. The patient developed CRPS of the left hand after a radial fracture. Marked swelling two weeks after the initial trauma. Adapted from ¹⁶⁹, with permission

either warmer or colder. In the acute stages of CRPS I the affected limb is more often warmer than the contralateral limb. It is likely that there is an inflammatory component of CRPS I in the acute phase that contributes to pain and skin warming. Sweating abnormalities are present in nearly all CRPS I patients. Either hypohidrosis or, more frequently, hyperhidrosis is present.^{19,23,26} The acute distal swelling of the affected limb depends very critically on aggravating stimuli. Since it often diminishes after sympathetic blocks, it is likely that it is maintained by sympathetic activity.¹¹

Trophic changes Trophic changes such as abnormal nail growth, increased or decreased hair growth, fibrosis, thin glossy skin and osteoporosis may be present, particularly in chronic stages. Restrictions of passive movement are often present in long-standing cases and may be related to both functional motor disturbances and trophic changes of joints and tendons.

Motor symptoms Weakness of all muscles of the affected distal extremity are often present.²⁷ Small accurate movements are characteristically impaired.¹¹ Nerve conduction and electromyography studies are normal, except in patients in very chronic and advanced stages. Therefore, the peripheral motor neuron and the neuromuscular junction are unlikely to contribute to the motor dysfunction. About half of the patients have a postural or action tremor that represents an increased physiological tremor.²⁸ In about 10% of cases dystonia of the affected hand or foot develops.^{29,30}

An important feature of CRPS I is that the severity of symptoms is disproportionate to the severity of trauma, with a tendency to generalize in the affected distal limb but not to be confined to the innervation zone of an individual nerve. Thus, all symptoms of CRPS I may occur irrespective of the type of the preceding lesion.³¹ Furthermore, the site of the lesion at the limb does not determine the location of symptoms.³²

CRPS type II (Causalgia)

CRPS II develops in the distal extremity following traumatic partial peripheral nerve lesion. In the earliest systematic description of causalgia, Weir Mitchell noted that in addition to spontaneous pain, patients reported exquisite hypersensitivity of the skin to light mechanical stimulation.^{33,34} Furthermore, movement, loud noises or strong emotions might trigger their pain. Distal extremity swelling, smoothness and mottling of the skin, and in some cases, acute arthritis was present. In most cases the limb was cold and sweaty. The sensory and trophic abnormalities spread beyond the innervation territory of the injured peripheral nerve and showed a distally generalized distribution. Since all symptoms show many similarities to those of CRPS I, this syndrome is now called CRPS II.

Post-traumatic neuralgia

It is important to recognize that in many post-traumatic neuropathy patients the pain is located largely within the innervation territory of the injured nerve.³⁵ Although these patients often describe their pain as burning, they exhibit a less complex clinical picture than patients with causalgia, and do not show marked swelling or a tendency for progressive spread of symptoms. The cardinal symptoms are spontaneous burning pain, hyperalgesia and mechanical and especially cold allodynia. These sensory symptoms are confined to the territory of the affected peripheral nerve although allodynia may extend beyond the border of nerve territories to a certain degree. Spontaneous and evoked pain are felt superficially and not deep inside the extremity, and the intensity of both is not dependent on the position of the extremity. Following the IASP classification it is possible to use the name 'neuralgia' for this type of neuropathic pain (pain within the innervation territory of a lesioned nerve, eg post-traumatic neuralgia). However, the definition of CRPS II includes the statement that symptoms may also be limited to the territory of a single peripheral nerve.³ Therefore, the term CRPS II provides space to include these localized post-traumatic neuropathies. An inherent weakness of this definition of CRPS II is that different syndromes with different underlying mechanisms are obviously included.

Despite the described symptoms one has to be aware of other clinical entities that demonstrate a similar clinical picture to CRPS, eg neuropathy.^{36,37}

Recent validation of the current IASP definition for CRPS indicated that modifications of the diagnostic criteria have to be performed in the near future to improve specificity and sensitivity.³⁸

CRPS after stroke and spinal cord injury

Stroke Interestingly, CRPS may also develop after central lesions. Gellman *et al.* reported that 12% of brain-injured patients complained about symptoms of reflex sympathetic dystrophy.³⁹ The incidence for CRPS in the affected paretic upper extremity after stroke ranges between 1.5 and 61%.^{40–43} One reason for this large variation of data is probably that many symptoms of CRPS are also found in stroke patients. Motor abnormalities like paresis, somatosensory abnormalities and neglect, are typical features in stroke patients. Furthermore, skin temperature of the paretic extremity decreases in more than 50% of the patients after stroke.^{44,45} Disuse might be an important factor for these cold hands.⁴⁶ The development of unilateral sweating abnormalities after stroke led to the hypothesis that autonomic disturbances in stroke and CRPS might share a common central pathophysiology.⁴⁷ Pain is also a frequent symptom after a central lesion. Central pain, eg after thalamic lesions, has a burning characteristic and is often associated with allodynia. Furthermore, peripheral traumatic injury of the

shoulder led to painful extremities after stroke, as demonstrated by shoulder joint capsules taken at autopsy.⁴⁸ Important risk factors for development of such a peripheral shoulder–hand syndrome are subluxation, paresis of the shoulder girdle, moderate spasticity and visual deficits for the paretic extremity. The peripheral lesion might initiate a self-perpetuating vicious cycle of pain followed by the full picture of CRPS in some patients (Figure 2).⁴⁸ Similarly, in brain-injured patients associated extremity injury appears to be at a significantly higher risk of developing CRPS.³⁹

Spinal cord injury Although chronic pain is a frequent symptom in patients with spinal cord injury, the association with CRPS seems to be relatively rare with an estimated incidence of about 5–10%.^{49–52} In a retrospective study of 125 patients with reflex sympathetic dystrophy only two patients had previous neck injury.⁵³ CRPS appears within a few months following injury, and most often affects unilaterally one upper extremity in tetraplegia patients, whereas bilateral involvement or CRPS at the lower extremity have rarely been reported.^{54–57} Similar to stroke, more patients seem to have some features of CRPS without developing the complete syndrome.⁵⁸ An important predisposing factor is a medullary gunshot wound, although it only represents 10% of the etiology of spinal cord injury.⁵⁴ The association of CRPS in tetraplegia with limb trauma and shoulder pain may

Figure 2 Hypothesis on the development of CRPS after stroke affecting the upper extremity. Stroke deficits due to the central infarction may lead to secondary peripheral lesions that might initiate a self-perpetuating vicious cycle of pain followed by the full picture of CRPS in a minority of patients. Many symptoms in a majority of stroke patients that are due to the central lesion are at least partially also found in CRPS (bold type). Risk factors for development of painful shoulder–hand syndrome are italicized

indicate that peripheral mechanisms are involved in initiating CRPS, similar to that described in stroke.^{48,50,54} CRPS may be one cause of contractures in patients with spinal cord injury.⁵⁹

CRPS and sympathetically maintained pain

The former term 'reflex sympathetic dystrophy' for CRPS was based on the experience that sympatholytic procedures relieved pain in many patients. However, it became clear in recent years that pain depending on sympathetic activity is not necessary for the diagnosis of CRPS, because not all patients respond to sympatholytic procedures. Furthermore, it is not specific, because other neuropathic pain conditions might benefit from sympathetic blocks (Figure 3). Therefore, the term sympathetically maintained pain was re-defined: Neuropathic pain patients presenting with similar clinical signs and symptoms, can be divided into two groups by the negative or positive effect of selective sympathetic blockade or antagonism of alpha adrenoceptor mechanisms.^{60,61} The pain component that is relieved by specific sympatholytic procedures is considered 'sympathetically maintained pain' (SMP). Thus, SMP is now defined to be a symptom or the underlying mechanism in a subset of patients with neuropathic disorders and not a clinical entity. The positive effect of a sympathetic blockade is not essential for the diagnosis. On the other hand, the only possibility to differentiate between SMP and 'sympathetically independent pain' (SIP) is the efficacy of a correctly applied sympatholytic intervention.²

Figure 3 Neuropathic pain conditions with the facultative symptom of sympathetically maintained pain (SMP). CRPS patients have the highest incidence of an SMP followed by patients suffering from acute herpes zoster or postherpetic neuralgia, phantom limb pain and polyneuropathy (PNP)

Pathophysiological mechanisms in CRPS

Although the entire pathophysiology of CRPS is not resolved, evidence from human experimentation and animal studies illuminate many aspects of the underlying pathophysiological mechanisms.

The sympathetic nervous system

The clinical picture of autonomic dysfunction with changes in skin blood flow, temperature and sweating, as well as the symptom of sympathetically maintained pain, suggests that the sympathetic nervous system is involved in the pathophysiology of CRPS. Physiologically, sympathetic preganglionic neurons, which are involved in regulation of effector cells in somatic tissues, project to the paravertebral ganglia of the sympathetic trunk and synapse with postganglionic neurons that innervate the effector cells. These preganglionic sympathetic neurons are under central control, and the pattern of ongoing and reflex discharges is characteristic for each type of sympathetic pathway, eg skin vasoconstrictor, muscle vasoconstrictor and sudomotor neurons, and varies according to the innervated target cells.^{62,63} Under normal conditions sympathetic activity does not interact with the nociceptive neurons in the periphery.^{64,65}

Autonomic disturbances A partial nerve lesion is the important preceding event in CRPS II. Therefore, it has generally been assumed that abnormalities in skin blood flow within the territory of the lesioned nerve are due to peripheral impairment of sympathetic function and sympathetic denervation. During the first weeks after transection of vasoconstrictor fibers, vasodilatation is present within the denervated area. Later the vasculature may develop increased sensitivity to circulating catecholamines, probably due to upregulation of adrenoceptors.⁶⁶ Similar observations were recently described in the chronic nerve constriction injury model in rats.^{67,68} The skin on the lesioned side was abnormally warm for about the first post-operative week and then evolved to a chronically cold status. The late-stage cold skin was present despite a complete absence of fluorescence for norepinephrine. Thus, in this animal model, the skin is cold due to denervation supersensitivity of adrenoceptors rather than excessive sympathetic vasoconstrictor activity.

Sympathetic denervation and denervation hypersensitivity cannot completely account for vasomotor and sudomotor abnormalities in CRPS. First of all, in CRPS I there is no overt nerve lesion.⁶⁹ Furthermore, in CRPS II the autonomic symptoms spread beyond the territory of the lesioned nerve.

Studies on skin blood flow and temperature in CRPS I demonstrated that the warmer affected extremity in the acute stage of the disease (<6 months) is due to a functional inhibition of cutaneous sympathetic vasoconstrictor activity, leading to cutaneous vasodilatation.^{24,25} Consistently, direct measure-

ments of norepinephrine levels from the venous effluent above the area of pain show a reduction in the affected extremity.^{24,25,70,71} These data support the idea that CRPS I is associated with disturbed sympathetic reflex patterns in the affected extremity.^{20,22} The locus of pathophysiological changes underlying such disturbed reflex activity must be in the central nervous system. Abnormalities in central autonomic control are consistent with experimental findings in animals, which show that the reflex pattern in single cutaneous vasoconstrictor neurons may change after peripheral nerve injury.^{64,72}

Measurements of skin temperature and blood flow over time demonstrated a change according to the duration of CRPS.²¹ In more advanced stages (>6 months), there is an increased number of patients in whom skin temperature and blood flow in the affected limb are decreased.²⁵ There is evidence that cutaneous sympathetic vasoconstrictor activity returns with the duration of the disease.²⁴

The initial functional inhibition of vasoconstrictor activity in the acute stage might have led to secondary end-organ supersensitivity (decentralization supersensitivity) in the absence of structural damage to sympathetic fibers.^{62,66,69,73} Such supersensitivity could lead to increased vasoconstriction and reduced skin temperature, even though sympathetic postganglionic neuron activity is reduced. In fact, alpha-adrenoceptor density has been reported to be increased in skin biopsies of patients with CRPS.^{74,75} Accordingly, the few micro-neurographic studies of small sympathetic nerve fascicles that have been performed so far in patients with chronic CRPS with cold affected limbs showed that the average skin sympathetic activity was not different between the affected and contralateral side.^{76,77}

Further important signs of sympathetic dysfunction in CRPS are unilateral sweating abnormalities.⁷⁸ Quantitative measurements of sudomotor activity show enhanced sweat production in the disturbed limb in the acute and chronic stage of the disease in many CRPS patients.^{23,26} This unilateral hyperhidrosis indicates enhanced sympathetic sudomotor activity.

In conclusion, the combination of increased sudomotor and decreased cutaneous sympathetic vasoconstrictor outflow is a well known centrally regulated thermoregulatory function to keep body core temperature constant in different environments. However, under physiological conditions all extremities are involved. Therefore, the unilateral activation of sudomotor and inhibition of cutaneous sympathetic vasoconstrictor neurons indicates a centrally located thermoregulatory dysfunction in CRPS.

Sympathetically maintained pain Under physiological conditions there is no interaction between the sympathetic and the afferent nociceptive system; stimulation of the sympathetic trunk does not induce any activity in afferent neurons.^{65,79} However, under pathophysiological conditions the situation dramatically changes.⁸⁰ Neurophysiological and neuroanatomical experiments

in animals show that a pathologic coupling of sympathetic and afferent activity may follow a mechanically induced peripheral nerve lesion. This may take place between sympathetic fibers and regenerating or intact nociceptive C-fibers in the periphery, or between sympathetic vasoconstrictor fibers and afferent somata within the dorsal root ganglion.⁸¹ The interaction is chemically via noradrenaline from sympathetic endings and adrenoreceptors that are expressed on afferent neurons under pathophysiological conditions (Figure 4A). Accordingly, mRNA for α_2 -adrenoceptors is up-regulated in DRG neurons after nerve lesion.⁸²

Clinical studies in humans support the idea that nociceptors develop catecholamine sensitivity after complete or partial nerve lesions. After limb amputation, injection of epinephrine around a stump neuroma is reported to be intensely painful.^{83,84}

Furthermore, intraoperative stimulation of the sympathetic chain induces an increase of spontaneous pain in patients with CRPS II but not in patients with hyperhidrosis.^{85,86} In CRPS and post-traumatic neuralgias, intracutaneous application of norepinephrine into a symptomatic area rekindled spontaneous pain and dynamic mechanical hyperalgesia that had been relieved by sympathetic blockade, supporting the idea

Figure 4 Influence of sympathetic activity and catecholamines on primary afferent neurons (PAN). (A) After nerve transection a sympathetic-afferent interaction occurs in the neuroma and in the dorsal root ganglion. It is mediated by norepinephrine (NA) released from sympathetic postganglionic neurons (SPGN) and α -adrenoreceptors expressed at the plasma membrane of afferent neurons. PGN, preganglionic neuron. (B) After tissue inflammation intact but sensitized primary afferents acquire norepinephrine sensitivity. Norepinephrine is not acting directly on afferents but induces the release of prostaglandins (PG) from sympathetic terminals that sensitize the afferents. In accordance, bradykinin and nerve growth factor (NGF) induced nociceptor sensitization is also mediated by the release of prostaglandins from sympathetic postganglionic neurons. Adapted from ¹⁶⁹, with permission

that noradrenergic sensitivity of human nociceptors is present after a partial nerve lesion.⁸⁷ Also, in postherpetic neuralgia, spontaneous pain and mechanical hyperalgesia are enhanced after injection of epinephrine or phenylephrine.⁸⁸ A potential criticism of the above mentioned studies, where pain was rekindled with exogenous adrenergic agonists, is that the doses of norepinephrine (NE) used were much higher than are likely to exist *in vivo*. Therefore, the algesic effects of peripheral administration of NE in physiologically relevant doses was compared in patients with SMP and normal subjects.⁸⁹ Intradermal NE, in physiologically relevant doses, was demonstrated to evoke greater pain in the affected regions of patients with SMP, than in the contralateral unaffected limb, and in control subjects. In accordance with this, spontaneous pain and dynamic as well as punctate mechanical hyperalgesia was augmented in patients with CRPS I when sympathetic cutaneous vasoconstrictor neurons were activated physiologically by thermoregulatory and respiratory stress.^{90,91} Interestingly, this applies also to acute CRPS patients who demonstrate a functional inhibition of cutaneous sympathetic vasoconstrictor activity in the affected extremity (see above). This is not necessarily a paradox, because a reduced sympathetic activity might be sufficient to maintain the pain, in particular if functional α -adrenoceptors at the membrane of intact afferent fibers are up-regulated acutely. Furthermore, animal experiments have demonstrated that the sympathetic influence on inflammatory processes does not depend on sympathetic activity itself, but on the anatomical integrity of postganglionic fibers.⁹²

Peripheral inflammation

Paul Sudeck postulated an exaggerated inflammatory response as an important pathophysiological mechanism in CRPS.⁶

Indeed, some of the clinical features of CRPS, particularly in its early phase, could be explained by an inflammatory process.^{93–95} Consistent with this idea, corticosteroids are often successfully used in acute CRPS.⁹⁶

There is increasing evidence that a localized neurogenic inflammation might be involved in the generation of acute edema, vasodilatation and increased sweating. Scintigraphic investigations with radiolabelled immunoglobulins show extensive plasma extravasation in patients with acute CRPS I.¹⁰ Analysis of joint fluid and synovial biopsies in CRPS patients have shown an increase in protein concentration, synovial hypervascularity, and neutrophil infiltration.^{97–99} Furthermore, synovial effusion is enhanced in affected joints as measured with MRI.¹⁰⁰ In acute untreated CRPS I patients protein extravasation elicited by strong transcutaneous electrical stimulation was only provoked on the affected extremity as compared with the normal side, indicating that substance P might be involved.¹⁰¹

As further support of a neurogenic inflammatory process, serum concentrations of calcitonin gene-related peptide were elevated in CRPS patients as a marker for neurogenic inflammation.¹⁰² Venous blood samples of the affected extremity showed increased cytokine levels of interleukin-6 and tumor necrosis-alpha as evidence for a local inflammation.¹⁰³ The production of nitric oxide in peripheral blood monocytes was significantly increased after stimulation with interferon-gamma in patients compared with controls.¹⁰⁴

Thus the weight of evidence indicates that inflammatory processes are involved in the pathogenesis of early CRPS. However, the exact mechanisms of the initiation and maintenance of these inflammatory reactions are still far from clear. The central issue is whether there is a sympathetic as well as an inflammatory component and whether the sympathetic nervous system may contribute to the early inflammatory state. Animal studies have demonstrated that the sympathetic nervous system can influence the intensity of an inflammatory process,^{105,106} and studies indicate that sympatholytic procedures can ameliorate both pain and inflammation in humans (Figure 4B).¹⁰⁷ However, this concept has yet to be proven in patients with CRPS.

The central nervous system

Autonomic disturbances indicate a centrally located thermoregulatory dysfunction in CRPS (see The sympathetic nervous system). Also other symptoms of CRPS I favour a central origin of the disorder, or at least a substantial role of central pathways. Impairment of muscle strength involving all muscles of the affected distal extremity that is not due to pain, oedema or severance of peripheral nerves is likely to be the result of a centrally mediated impulse abnormality in the motoneurone pool. Furthermore, patients complain about a neglect-like syndrome responsible for severe motor dysfunctions.^{108,109} In about 50% of the patients an increased physiological tremor is found that is due to central changes.²⁸ Kinematic analysis of the upper extremity in CRPS revealed motor deficits probably due to impaired integration of visual and sensory afferent inputs to the parietal cortex.¹¹⁰

Based on numerous animal experimental findings, spontaneous pain and various forms of hyperalgesia at the distal extremity^{16,111} are thought to be generated by processes of peripheral and central sensitization (for review see¹¹²). Clinical and quantitative sensory testing of the nociceptive system demonstrated hemisensory impairment and hyperalgesia that frequently extends far beyond the area affected by spontaneous pain, indicating changes in central afferent processing that have been recently demonstrated by functional imaging studies.^{16–18,113–115} Furthermore, it is suggested that prefrontal networks are involved in SMP in CRPS patients.¹¹⁶ In one chronic CRPS patient symptoms resolved after a traumatic cerebral contusion in the left temporal lobe.¹¹⁷

All these data indicate that alterations of the central nervous system play an important role in CRPS. However, it is not clear, whether these are primary abnormalities in the disease or whether they are changes secondary to the pain.

Genetic considerations

The observation that many patients suffered from similar peripheral extremity trauma that is followed, in only a few by a CRPS, raises the question whether genetic factors are involved in the pathophysiology. Two studies revealed differences between CRPS patients and healthy controls in the human leukocyte antigen class II molecules encoded by genes of the human major histocompatibility complex on chromosome 6.^{118–120} The investigation of the innate cytokine profile in CRPS patients to determine a possible role of the immune system in the disease pathophysiology failed to show any significant results.¹²¹ The clinical relevance of these findings is not clear. The evidence of a facilitated neurogenic inflammation and an increased serum level of the neurogenic inflammatory peptide calcitonin gene-related peptide, even in the non-affected extremity, might indicate phenotypic differences between CRPS patients and controls.^{101,102}

Psychology of CRPS

Most patients with CRPS exhibit a significant amount of psychological distress symptoms, with depression and anxiety being most common. Many patients become overwhelmed by the pain and associated symptoms. Without adequate psychosocial support the patients may develop maladaptive coping skills. These observations in connection with normal neurophysiological test results in CRPS I led to the hypothesis that CRPS is primarily a psychogenic disorder.^{122,123} However, well designed studies and comprehensive reviews of the available literature have suggested that psychological symptoms are the result and not the cause of CRPS.^{124–127}

Diagnosis of CRPS and additional diagnostic tests

For the present the diagnosis of CRPS is based on the clinical criteria described above. Procedures should start with taking a detailed medical history considering an initiating trauma and any history of sensory, autonomic and motor disturbances. One should explicitly ask for the development, time course, distribution and characteristics of pain. A general neurological examination is needed. Detection of any swelling, sweating, trophic, temperature and motor abnormality in the disturbed area is important. Muscle strength of the affected limb, as well as characteristics and distribution of somatosensory abnormalities, should be investigated in detail. One should test if the pain can be elicited by movements and pressure at the joints. Such an approach, according to the

standardized diagnostic criteria for CRPS, is important in order to provide an accurate and complete description of patients' characteristics.¹²⁸

Furthermore, many tests and procedures are valuable diagnostic tools that can add information to confirm the diagnostic impression about autonomic, sensory and motor function and dysfunction.

Bone scintigraphy

Bone scintigraphy can provide information about vascular bone changes,¹²⁹ but it should be noted that bone scintigraphy is only positive for significant changes during the subacute period (up to 1 year). Especially, pathological uptake in the metacarpophalangeal joints and metacarpal bones in phase three of the three-phase bone scintigram are described as highly sensitive and specific for CRPS (Figure 5).¹³⁰ It is therefore often applied to differentiate CRPS from other pain causes after central lesion.³⁹ However, there is no known gold standard against which to compare this test.

Plain radiographs

These could be used to evaluate the status of mineralization, but are only positive in chronic stages.

Quantitative sensory testing (QST)

Psychophysical testing of thermal and thermal pain thresholds can provide information about the function or dysfunction of unmyelinated and small myelinated afferent fibers that project into the spinothalamic tracts. QST can also analyse the functional status of large myelinated fibers projecting to the dorsal columns by vibratory threshold testing.^{14,15,78,131,132} However, there seems to be no sensory profile that is characteristic for CRPS.

Figure 5 Three-phase bone scan in acute CRPS. In phase three a diffuse increase in tracer-uptake is found around the distal joints of the disturbed extremity. Adapted from ¹⁷⁰, with permission

Autonomic function

This can be tested by a variety of new and emerging methods. These are infrared thermometry, laser Doppler flowmetry,^{20,22,133} infrared thermography^{134,135} and a quantitative sudomotor axon reflex test (QSART).^{19,23,26} Skin temperature differences may be helpful for diagnosis of CRPS. These typical temperature side differences are no static descriptors but comprise dynamic changes critically depending on environmental temperature and are most prominent at a high to medium level of sympathetic vasoconstrictor activity (Figure 6).^{25,136} Under resting conditions sensitivity of skin temperature asymmetries was only 32% compared with healthy controls. However, during experimental alteration of sympathetic activity by whole-body cooling and warming with a thermal suit, temperature differences between both sides increased dynamically in CRPS patients but not in

controls, so that the sensitivity increased up to 76%. A skin temperature asymmetry of more than 2.2°C had a specificity of 93% compared with patients suffering from painful limbs of other origin (Figure 6).¹³⁶ Autonomic testing with the QSART can provide information about the function of sudomotor reflex loops. Swelling can be quantified by measuring water displacement.

Differential diagnosis of CRPS

The current CRPS diagnostic criteria are adequately sensitive (ie, rarely miss a case of actual CRPS). However, both internal and external validation research suggests that CRPS is currently overdiagnosed, despite the discrepancy that it is often recognized too late by general practitioners.^{5,36,38} Probable reasons are that there is no test available as

Figure 6 Characteristics of interside skin temperature differences during controlled alterations in sympathetic activity in CRPS. Controlled alterations of cutaneous sympathetic activity (whole-body cooling and warming) were applied by means of a thermal suit. The subject was lying in a suit supplied by tubes, in which running water of 12°C and 50°C, respectively, was used to cool (increase of sympathetic activity) or warm (inhibition of sympathetic activity) the whole body. The skin temperature of the fingers of both hands was monitored. (A) Temperature of the right and left hand in a healthy subject (C) Affected and healthy extremity in a CRPS patient. Side differences in skin temperature of the fingers of both hands in the healthy control subject (B) and in the CRPS patient (D) during controlled alterations of sympathetic activity. The arrow indicates beginning of whole-body warming. Maximal skin temperature differences during whole-body warming are indicated by the vertical dotted lines. Adapted from ¹³⁶, with permission

a gold standard and many other clinical entities are included under the umbrella of CRPS.^{8,37} Therefore, one should always search for the full picture of CRPS, including all clinical criteria and the typical medical history described above. In case of doubt other diseases that may cause neuropathic pain should be excluded. Furthermore, one should be aware of disorders causing pain and unilateral vascular changes such as inflammation or infections (eg, rheumatism, ulceration) and unilateral vascular occlusive diseases. Differential diagnostic problems might also be due to repetitive artificial occlusion of the blood supply to one limb as in a malingering or factitious disorder that needs a detailed psychological exploration.

Therapeutic options for CRPS

Lack of understanding of the underlying pathophysiological abnormalities and lack of objective diagnostic criteria resulted in inherent difficulties of conducting clinical trials with therapeutic modalities. Therefore, only few evidence-based treatment regimens for CRPS are available so far. In fact, three literature reviews of outcome studies find discouragingly little consistent information regarding the pharmacological agents and methods for treatment of CRPS.^{137,138} In the absence of more specific information about pathophysiological mechanisms and treatment of CRPS one has to rely on outcomes from treatment studies for other neuropathic pain syndromes. Furthermore, the still hypothetical mechanism-based treatment concept has to be transferred from ideas derived from animal experiments on peripheral nerve lesions to the situation in CRPS patients. Therefore, the following treatment options should be considered as a recommendation based on clinical evidence.

General rules

Treatment of CRPS requires a multidisciplinary approach including neurologists, anesthesiologists, orthopedic specialists, physiotherapists and psychologists. Treatment should be immediate, and most importantly directed toward restoration of full function of the extremity. The general principles of pharmacological treatment are the individualization of therapy and the titration of a given pharmacological agent, depending on the effect on one hand and side effects on the other. 'No-response' should not be accepted until a sufficient period of time has passed to judge the efficacy of the drug. Destructive surgery of the peripheral or central afferent nervous system in cases of CRPS always implies further deafferentation and thereby provides an increased risk for a persistent deafferentation type of pain.

Pharmacological therapy

Nonsteroidal anti-inflammatory drugs (NSAIDs) have not been demonstrated to have significant analgesic

effect in treatment of CRPS, however, NSAIDs could be used for relief of mild to moderate pain.

Opioids strongly inhibit central nociceptive neurons mainly through interaction with μ -receptors. Opioids are clearly effective in postoperative, inflammatory and cancer pain. The use of opioids in CRPS has not been studied. In other neuropathic pain syndromes intravenous morphine is clearly analgesic when compared to placebo.¹³⁹ However, there are no long-term studies of oral opioids in the treatment of neuropathic pain, CRPS included. Even without solid scientific evidence the expert opinion of pain clinicians is that opioids could be, and should be, used as a part of a comprehensive pain treatment program. Given that some patients with neuropathic pain may obtain considerable pain relief, opioids should be tested early in the course of CRPS, and a trial of opioids should not be delayed to the 'last resort' status. Administration of opioids requires specific treatment programs for patients with a history of chemical dependence and caution in patients with pulmonary disease. Prophylactic treatment of common side-effects, notably nausea or constipation, can improve patients' compliance.

Tricyclic antidepressants (TCA) are the best studied group of pharmacological agents in neuropathic pain and they have shown an analgesic effect. TCA inhibit re-uptake of monoaminergic transmitters. There is solid evidence that the re-uptake blocker of serotonin and noradrenaline amitriptyline and the selective noradrenaline blocker desipramine produce pain relief in diabetic or postherpetic neuropathy.^{140–142} The mean dose that is often sufficient for pain reduction (eg amitriptyline 75–150 mg/day) is smaller than doses necessary to achieve anti-depressant effects. Onset of the analgesic effect occurs within 1–2 weeks and peaks around 4–6 weeks.¹⁴¹ Improvement of sleep, mood and anxiety can further add to the pain relieving action.

Sodium blocking agents, the type Ib anti-arrhythmic drugs lidocaine, mexiletine and tocainide, and the anticonvulsant carbamazepine have an effect on sodium channels and potentially relieve neuropathic pain.^{139,143} Intravenous lidocaine was effective in CRPS.¹⁴⁴ Care needs to be taken when administering these compounds. Contra-indications include electrocardiac abnormalities, reduced left ventricular function and coronary heart disease.

GABA-agonists such as baclofen, valproic acid, vigabatrin and benzodiazepines interacting with GABAergic transmission have been reported to alleviate different neuropathic pain conditions. The general clinical impression is that such drugs do not provide substantial pain relief, except for baclofen in trigeminal neuralgia. Some agents may have a place in the treatment of painful muscle spasms.

The action of the drug gabapentin is not completely resolved, but probably includes an inhibition of calcium channels. In one study, gabapentin had a promising effect on CRPS.¹⁴⁵

Glucocorticoids taken orally are the category of agents that has clearly demonstrated efficacy in controlled trials.⁹⁶ There is no evidence that other immune-modulating therapies, notably intravenous immunoglobulins or immunosuppressive drugs have a place in the treatment of CRPS.

Transdermal application of the α_2 -adrenoceptor agonist clonidine, which is thought to prevent the release of catecholamines by a presynaptic action, may be helpful when small areas of hyperalgesia are present.^{146,147}

Clinically available compounds that are demonstrated to have NMDA receptor blocking properties include ketamine, dextromethorphan and memantine. They offer new options for treatment of CRPS pain, but studies which will help clinicians to fully utilize these agents are not available.

Subcutaneous calcitonin only had a mild effect on spontaneous pain.¹⁴⁸ Intravenous bisphosphonates (alendronate, clodronate), however, showed a significant improvement in pain, swelling and movements.^{149,150}

Interventional therapy at the sympathetic nervous system

Interruption of the sympathetic nerve supply to the affected extremity has been used to treat CRPS for many years. Proof of the effectiveness of sympathetic blockade, however, is scanty.^{137,151} Some authors even discard the concept that the sympathetic nervous system is actively involved in the generation of pain.^{122,152} They claim that interventions that block sympathetic activity lack specificity, and argue that the techniques and results of sympathetic blockade have rarely been adequately evaluated and are in most cases not placebo-controlled.

Currently, two therapeutical techniques to block sympathetic nerves are used: (1) injections of a local anaesthetic around sympathetic paravertebral ganglia that project to the affected body part (sympathetic ganglion blocks); and (2) regional intravenous application of guanethidine, bretylium or reserpine (which all deplete noradrenaline in the postganglionic axon) to an isolated extremity blocked with a tourniquet (intravenous regional sympatholysis, IVRS).

Although sympatholytic therapy can frequently result in substantial or even complete pain relief, blockade of the sympathetic activity is ineffective in some patients. Nonetheless, with all of the shortcomings there is a compelling historical and basic and clinical science evidence that it is important that an adequate sympatholytic trial by a qualified clinician should be performed in an attempt to differentiate between SMP and SIP. In the presence of a significant sympathetic component, treatment strategies towards the sympathetic therapy could be considered. Beside the pain, other symptoms may improve after sympathetic blocks.

There are many uncontrolled surveys in the literature reviewing the effect of sympathetic interventions in CRPS and post-traumatic neuralgias. In CRPS, about 85% of the patients report a positive acute effect, but fewer patients experience long-term relief (60% in sympathetic block and 30% in intravenous regional sympatholysis). In post-traumatic neuralgias the sympatholytic interventions are clearly less effective. One controlled study in patients with CRPS I has shown that sympathetic blockade with local anaesthetic has the same immediate effect on pain as a control injection with saline.¹⁵³ However, after 24 hours patients in the local anaesthetic group were much better, indicating that non-specific effects are important initially and that evaluating the efficacy of sympatholytic interventions is best done after one day. Interestingly, one prospective study showed that perioperative stellate ganglion blocks in patients with a history of CRPS can significantly reduce the recurrence rate of this disease.¹⁵⁴ Controlled studies using guanethidine IVRS did not show a beneficial effect.^{155–157}

In our view, there is a desperate need for controlled studies that assess the acute as well as the long-term effect of sympathetic blockade on pain and other CRPS symptoms, in particular motor function. Well performed sympathetic ganglion blocks should be performed rather than IVRS.

Stimulation techniques and spinal drugs application

Transcutaneous electrical nerve stimulation (TENS) may be effective in some cases and has minimal side effects. Epidural spinal cord stimulation (SCS) has shown efficacy in one randomized study in selected chronic CRPS patients^{158,159} and may be a promising treatment for this group of patients. Interestingly, these patients had undergone previous unsuccessful surgical sympathectomy. The pain relieving effect was not associated with peripheral vasodilatation suggesting that central disinhibition processes are involved.¹⁶⁰ Sensory detection threshold were not effected by the stimulation.¹⁶¹ Other stimulation techniques, ie peripheral nerve stimulation with implanted electrodes, and deep brain stimulation (sensory thalamus and medial lemniscus), have been reported to be effective in selected cases of CRPS.¹⁶²

Also in selected patients with severe refractory CRPS, epidural administration of clonidine or the NMDA-antagonist ketamine induced analgesia associated with marked side-effects like sedation and hypotension.^{163,164} Intrathecal baclofen demonstrated a positive outcome for CRPS patients with severe dystonia.¹⁶⁵

Physical therapy

Clinical experience and two prospective studies indicate that physiotherapy is of utmost importance to achieve recovery of function and rehabilitation.^{166–168} At the

acute stage of CRPS when the patients still suffer from severe pain, it is mostly impossible to carry out intensive active therapy. Painful interventions and in particular aggressive physical therapy at this stage leads to deterioration. Therefore, immobilization and careful contralateral physical therapy should be the acute treatment of choice. Later, when pain subsides, passive physical therapy, active isometric followed by active isotonic training should be performed in combination with sensory desensitization programs.

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