Complex Regional Pain Syndromes

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Complex regional pain syndromes (CRPS) (formerly reflex sympathetic dystrophy and causalgia) are neuropathic pain conditions that are initiated by an extremity trauma or peripheral nerve lesion. Clinical definition and scientific understanding of CRPS are still evolving; however, both the clinical picture and therapeutic options are significantly influenced by a dysfunction of the sympathetic nervous system. Recent investigations suggest functional central abnormalities and a peripheral inflammatory component in the pathophysiology of CRPS. Interdisciplinary treatment includes physical, pharmacologic, and invasive interventional therapy, as well as stimulation techniques.

Introduction

Complex regional pain syndromes (CRPS) are painful disorders that develop as a disproportionate consequence of an extremity trauma or a nerve lesion. Symptoms that occur in a distal generalized distribution include swelling, hyperalgesia, and autonomic and motor dysfunction. Newer investigations revealed somatosensory deficits in many patients, so that the whole picture of CRPS is considered to be a neurologic disorder. Formerly, these syndromes were called reflex sympathetic dystrophy (RSD) and causalgia. For many years, the term RSD has been inappropriately used to describe a much more extensive range of clinical presentations than originally intended. Moreover, because the pathophysiologic mechanisms underlying these syndromes are poorly understood, terms like ”reflex” and ”sympathetic” can be misleading. Therefore, a new terminology was introduced based entirely on elements of history, symptoms, and findings on clinical examination, with no implied pathophysiologic mechanism [1]. According to the International Association for the Study of Pain (IASP) "Classification of Chronic Pain," RSD and causalgia are now called CRPS. In CRPS type I (RSD), 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 [2].

Clinical Characteristics: Complex Regional Pain Syndromes

CRPS type I (RSD)

Paul Sudeck first described this disorder early in the century [3]. These patients develop asymmetrical distal extremity pain and swelling without presenting an overt nerve lesion (Fig. 1). Precipitating events include fracture or minor soft tissue trauma, frostbite, and burns, as well as stroke and myocardial infarction, and more rarely a low-grade tissue infection. The swelling and pain often develop at a site remote from the inciting injury, and there may be no obvious local tissue damaging process at the site of pain and swelling [4].

Patients with CRPS I often report a burning spontaneous pain felt in the distal part of the affected extremity [5]. 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 [6–8]. 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 [9•].

Autonomic abnormalities include swelling and changes of sweating and skin blood flow [10–13,14•,15]. At normal room temperature the skin temperature of the limbs shows an inconstant side difference in about 30% to 80% of the patients, *ie*, the affected extremity is 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 patients with CRPS I. Either hypohidrosis or, more frequently, hyperhidrosis is present [10,11,16,17]. The acute distal swelling of the affected limb depends very critically on aggravating stimuli. Because it often diminishes after sympathetic blocks, it is likely that it is maintained by sympathetic activity [18].

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.

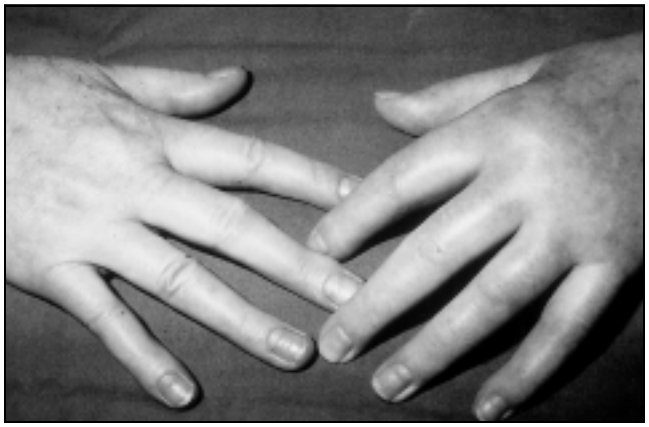

Figure 1. Patient with acute complex regional pain syndrome (CRPS). The patient developed CRPS of the left hand after a radial fracture. Marked swelling occurred 2 weeks after the initial trauma.

Weakness of all muscles of the affected distal extremity is often present. Small accurate movements are characteristically impaired [18]. 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 physiologic tremor [19]. In about 10% of cases, dystonia of the affected hand or foot develops [20,21].

CRPS type II (causalgia)

This develops in the distal extremity following traumatic partial peripheral nerve injury [22]. In addition to spontaneous pain, patients reported exquisite hypersensitivity of the skin to light mechanical stimulation. In addition, movement, loud noises, or strong emotions could 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 often occurred remote from the site of injury. Because all symptoms show many similarities to those of CRPS I, this syndrome is now called CRPS II.

In 1916, Leriche [23] reported that sympathectomy dramatically relieves causalgia. This notion was confirmed in several large clinical series, primarily in wounded soldiers. In his exhaustive 1967 centennial review, Richards [24] describes the clinical features of causalgia and the effect of sympatholytic interventions in hundreds of cases. He was emphatic about the dramatic response of causalgia to sympathetic blockade.

Post-traumatic Neuralgia

It is important to recognize that many patients with post-traumatic neuropathy have pain but do not have the full clinical picture of causalgia (CRPS II). In these cases, in contrast to patients with causalgia, the pain is located largely within the innervation territory of the injured nerve [25]. 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. The patients occasionally obtain relief with sympatholytic procedures, although much less often than those with CRPS.

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 new definition of CRPS II includes the statement that symptoms may also be limited to the territory of a single peripheral nerve [2]. 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 should be aware of other clinical entities that demonstrate a similar clinical picture to CRPS, *eg*, neuropathy [26]. 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 [27].

Pathophysiology of Blood Flow and Sweating Abnormalities

Denervation supersensitivity

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 [28]. Similar observations were recently described in the chronic nerve constriction injury model in rats [29,30]. The skin on the lesioned side was abnormally warm for about the first postoperative 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.

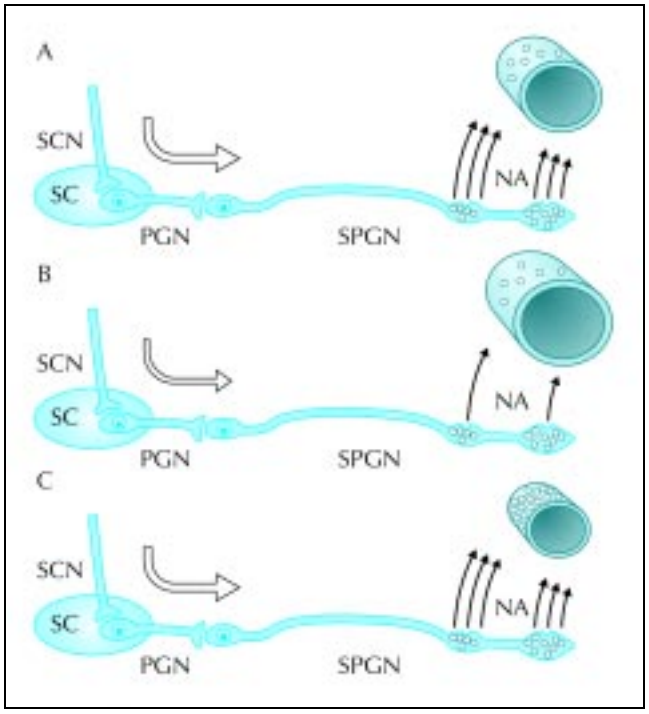

Figure 2. A, Under physiologic conditions, sympathetic central neurons (SCN) are spontaneously active (*white arrow*), leading to release of noradrenaline (NA) from sympathetic postganglionic neurons (SPGN) in the periphery via preganglionic neurons (PGN). Vasoconstriction is mediated by NA acting on α-adrenoceptors (*white dots on vessel*). **B,** In acute CRPS central sympathetic activity is functionally reduced (*white arrow*) resulting in a decreased release of NA with relative vasodilatation. **C,** In chronic CRPS central sympathetic activity has returned (*white arrow*). Due to former functional inhibition of neural activity in acute CRPS, blood vessels have developed a supersensitivity with increased α-adrenoceptor density (*white dots on the vessel*), resulting in an increased vasoconstriction. SC—spinal cord.

Central nervous system abnormalities

Sympathetic denervation and denervation hypersensitivity cannot completely account for vasomotor and sudomotor abnormalities in RSD and causalgia. First, in CRPS I there is no overt nerve lesion [31]. Second, in CRPS II the autonomic symptoms spread beyond the territory of the lesioned nerve. In fact, there is indirect evidence for a reorganization of central autonomic control in these syndromes.

Hyperhidrosis, for example, is found in many patients with RSD and causalgia. Resting sweat output, as well as thermoregulatory and axon reflex sweating, are increased in patients with RSD [10,17]. Increased sweat production cannot be explained by a peripheral mechanism because, unlike blood vessels, sweat glands do not develop denervation supersensitivity [28]. Therefore, the increased sweating in patients with RSD and causalgia probably relates to an increase of activity in sympathetic sudomotor neurons, which is of central origin.

In order to study cutaneous sympathetic vasoconstrictor innervation in patients with CRPS I, we have analyzed central sympathetic reflexes induced by thermoregulatory and respiratory stimuli [12]. Sympathetic effector organ function, *ie*, skin temperature and skin blood flow, was measured bilaterally at the extremities by infrared thermometry and laser Doppler flowmetry [32]. Under normal conditions these reflexes do not show interside differences. During the acute phase of CRPS I (< 6 months), however, all patients demonstrated a functional inhibition of cutaneous sympathetic vasoconstrictor activity in the affected extremity, leading to skin vasodilatation and warming (Fig. 2) [14•]. Consistently, direct measurements of norepinephrine levels from the venous effluent above the area of pain show a reduction in the affected extremity [14•,33,34]. In more advanced stages (> 6 months), unilateral hyperactive sympathetic reflex responses and cutaneous vasoconstriction were found in 80% of patients, whereas 20% still showed sympathetic inhibition. These data support the idea that CRPS I is associated with disturbed sympathetic reflex patterns in the affected extremity [11,13]. The locus of pathophysiologic 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 [35,36]. The few microneurographic studies of small sympathetic nerve fascicles that have been performed so far in patients with CRPS, however, have not confirmed the presence of reflex abnormalities; the average skin sympathetic activity, *ie*, a combination of vasoconstrictor and sudomotor activity, was not different on the two sides, at least in chronic CRPS [37,38].

A continuous functional inhibition of vasoconstrictor activity induced by central mechanisms might also lead to secondary end-organ supersensitivity (decentralization supersensitivity) in the absence of structural damage to sympathetic fibers (Fig. 2) [28,31,39]. Such supersensitivity could lead to apparent sympathetic overfunction, even though sympathetic postganglionic neuron activity is reduced. In fact, α-adrenoceptor density has been reported to be increased in skin biopsies of patients with RSD [40,41].

Inflammation

Some of the features of CRPS that have been attributed to sympathetic dysfunction, *ie*, vasomotor abnormalities, swelling, and pain, could be explained by inflammation without the requirement for a sympathetic contribution. It is very likely that there is an inflammatory component to CRPS I [42,43], particularly in its early phase [44,45]. Consistent with this idea, corticosteroids may be beneficial [46]. In addition, scintigraphic investigations with radiolabeled immunoglobulins show extensive plasma extravasation in patients with acute CRPS I [47]. Analysis of joint fluid and synovial biopsies in patients with CRPS have shown an increase in protein concentration, synovial hypervascularity, and neutrophil infiltration [48–50].

Thus, the weight of evidence indicates that inflammatory processes are involved in the pathogenesis of early

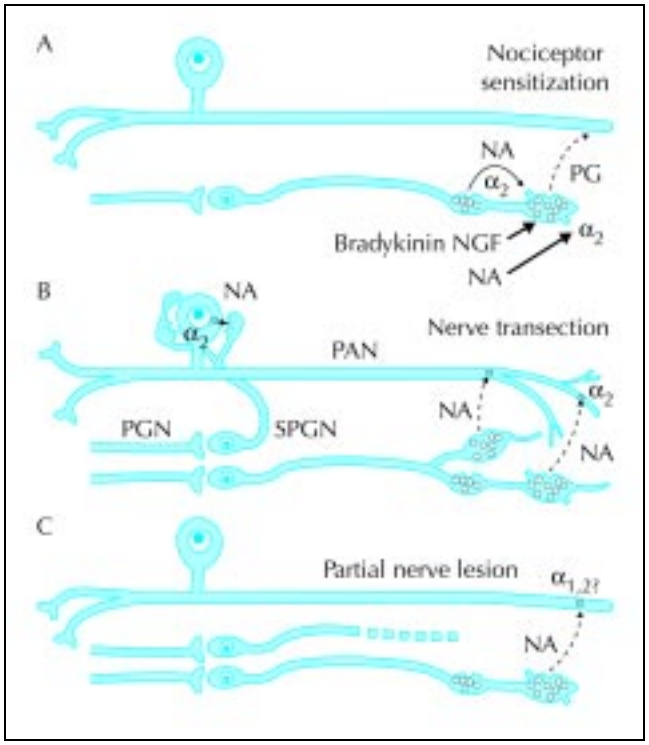

Figure 3. A, Tissue inflammation. Norepinephrine (NA) induces the release of prostaglandins (PG) from sympathetic terminals that sensitize the afferents. In accordance, bradykinin and nerve growth factor (NGF)-induced nociceptor sensitization is also mediated by the release of prostaglandins from sympathetic postganglionic neurons. **B,** Nerve transection. The sympathetic-afferent interaction is located in the neuroma and in the dorsal root ganglion. It is mediated by NA released from sympathetic postganglionic neurons (SPGN) and α-adrenoreceptors expressed at the plasma membrane of afferent neurons. **C,** Partial nerve injury is followed by a decrease of the sympathetic innervation density (stippled sympathetic postganglionic neuron). This induces an upregulation of functional α-adrenoceptors at the membrane of intact afferent fibers. PAN—primary afferent neuron; PGN—preganglionic neuron.

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 [51,52], and studies indicate that sympatholytic procedures can ameliorate both pain and inflammation in humans (Fig. 3) [53]. However, this concept has yet to be proven in patients with CRPS.

Sympathetically Maintained Pain

Definition

On the basis of experience and recent clinical studies the term sympathetically maintained pain was redefined: Patients with neuropathic pain presenting with similar clinical signs and symptoms, can clearly be divided into two groups by the negative or positive effect of selective sympathetic blockade or antagonism of α-adrenoceptor mechanisms [54,55]. 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. Conversely, the only possibility to differentiate between SMP and "sympathetically independent pain" (SIP) is the efficacy of a correctly applied sympatholytic intervention [1].

Currently, two therapeutical techniques to block sympathetic nerves are used: 1) injections of a local anesthetic 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).

The experimental basis for a pathologic interaction of sympathetic and afferent neurons

Under physiologic conditions there is no interaction between the sympathetic and the afferent system; stimulation of the sympathetic trunk does not induce any activity in afferent neurons [56••,57]. Under pathophysiologic conditions the situation dramatically changes [58]. Neurophysiologic and neuroanatomic 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. The interaction is chemically via noradrenaline from sympathetic endings and adrenoreceptors that are expressed on afferent neurons under pathophysiologic conditions (Fig. 3). Accordingly, mRNA for α_{2A}-adrenoceptors is upregulated in DRG neurons after nerve lesion [59].

Clinical studies in humans support the idea that nociceptors develop catecholamine sensitivity after complete or partial nerve lesions (Fig. 3). After limb amputation, injection of epinephrine around a stump neuroma is reported to be intensely painful [60,61]. In addition, intraoperative stimulation of the sympathetic chain induces an increase of spontaneous pain in patients with causalgia (CRPS II) but not in patients with hyperhidrosis [62,63].

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 that noradrenergic sensitivity of human nociceptors is present after partial nerve lesion [64]. Also in postherpetic neuralgia, spontaneous pain and mechanical hyperalgesia are enhanced after injection of epinephrine or phenylephrine [65]. A potential criticism of

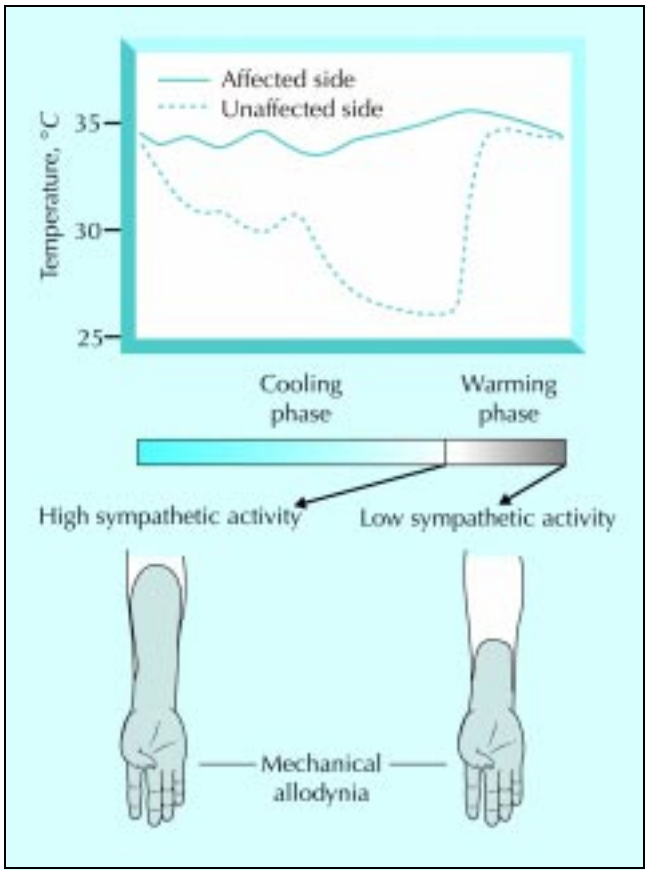

Figure 4. Whole body warming and cooling was performed to alter sympathetic skin nerve activity. Cooling induces a massive tonic activation of sympathetic vasoconstrictor neurons; warming leads to a considerable decrease of activity. High sympathetic activity during cooling induces a decrease of skin temperature due to vasoconstriction (unaffected side). On the affected side forearm temperature was clamped at 35°C by a feed-back-controlled heat lamp to exclude temperature effects on the sensory receptor level. Activation of sympathetic neurons leads to a considerable increase of the area of allodynia in patients with sympathetically maintained pain, indicating that in some complex regional pain syndrome (CRPS) a pathologic coupling between sympathetic and nociceptive neurons in the skin does exist.

the previously mentioned studies in which pain was rekindled with exogenous adrenergic agonists is that the doses of norepinephrine used were much higher than are likely to exist in vivo. Therefore, the algesic effects of peripheral administration of norepinephrine in physiologically relevant doses were compared in patients with SMP and normal subjects [66]. Intradermal norepinephrine, 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, it could be clearly demonstrated in patients with CRPS that spontaneous pain and dynamic as well as punctate mechanical hyperalgesia was augmented when sympathetic cutaneous vasoconstrictor neurons were activated physiologically by thermoregulatory stress (Fig. 4) (Baron, Unpublished data). Interestingly, this applies also to patients with acute CRPS who demonstrate a functional inhibition of cutaneous sympathetic vasoconstrictor activity in the effected extremity. 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 upregulated acutely. In addition, animal experiments have demonstrated that the sympathetic influence on inflammatory processes does not depend on sympathetic activity itself, but on the anatomic integrity of postganglionic fibers (Fig. 3A) [67].

Sympathetic interruption for the treatment of SMP: the clinical evidence

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 [68]. Many authors even discard the concept that the sympathetic nervous system is actively involved in the generation of pain [69,70]. 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.

There are several uncontrolled surveys in the literature reviewing the effect of sympathetic interventions, *eg*, sympathetic blocks, surgical sympathectomies, and intravenous regional sympathetic blocks (IVRS) in CRPS and post-traumatic neuralgias. In CRPS, about 85% of the patients report a positive acute effect of sympathectomies, sympathetic blocks, and IVRS, but fewer patients experience long-term relief (60% in sympathetic blocks and 30% in IVRS). In post-traumatic neuralgias the sympatholytic interventions are clearly less effective.

One recent controlled study in patients with CRPS I has shown that sympathetic blocks with local anesthetic have the same immediate effect on pain as a control injection with saline [71••]. However, after 24 hours patients in the local anesthetic group were much better, indicating that nonspecific effects are important initially and that evaluating the efficacy of sympatholytic interventions is best done after 24 hours. With these data in mind, the uncontrolled studies mentioned previously must be interpreted cautiously. Only 10 out of the 24 studies we reviewed assessed long-term effects.

Bonelli *et al.* [72] compared sympathetic blocks and guanethidine IVRS in a two-arm controlled study (no placebo arm) and could not find a difference between them, in either acute or long-term periods. Five placebo-controlled studies using guanethidine IVRS have been performed [73–77]. Only one demonstrated a significantly better acute effect (1 hour after the block) [73]. One potential criticism of these guanethidine data is that four studies used only one IVRS, but multiple blocks may be necessary for treatment of CRPS [78]. In addition, the follow-up periods after the block were only 30 to 60

minutes in three studies and up to 6 months in two studies. One study demonstrated that IVRS bretylium and lidocaine produce significantly longer pain relief than lidocaine alone [79]. Two studies showed that IVRS reserpine was ineffective [74,76].

Local application of opioids at sympathetic ganglia reduces pain in refractory trigeminal neuralgia [80] and might have an effect in CRPS [81]. However, there are no placebo-controlled studies and the underlying mechanism is unclear, because sympathetic activity does not change during ganglionic local opioid analgesia.

Practical Suggestions for the Diagnosis of CRPS and Additional Diagnostic Tests

For the present, the diagnosis of CRPS is based on the clinical criteria described previously. 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 neurologic 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. 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 can provide information about vascular bone changes [82], but it should be noted that bone scintigraphy is only positive for significant changes during the subacute period (up to 1 year). Pathologic uptake in the metacarpophalangeal joints and metacarpal bones in phase three of the three-phase bone scintigram are especially described as highly sensitive and specific for CRPS [83•]. However, as with any other test there is no known gold standard against which to compare this test. Plain radiographs could be used to evaluate the status of mineralization, but these are only positive in chronic stages.

Quantitative sensory testing can provide information about the function or dysfunction of unmyelinated and small myelinated afferent fibers that project into the spinothalamic tracts by using psychophysical testing of thermal and thermal pain thresholds. It can also analyze the functional status of large myelinated fibers projecting the dorsal columns by testing vibratory threshold testing [6,7,84–86].

Autonomic function can be tested by a variety of new and emerging methods. These are infrared thermometry, laser Doppler flowmetry [11,13,87], infrared thermography [88,89], and quantitative sudomotor axon reflex testing (QSART) [10,16,17]. Skin temperature differences may be helpful for diagnosis of CRPS; however, these typical temperature side differences are not static descriptors but comprise dynamic changes critically depending on environmental temperature [32]. They are profound at room temperature or in colder environments and possibly under emotional stress. After sufficient body warming and emotional relaxation, however, very often no side differences can be measured [11]. However, the maximal skin temperature difference that occurs during the thermoregulatory cycle reliably distinguishes CRPS from other unilateral extremity pain syndromes. Autonomic testing with the QSART can provide information about the function of sudomotor reflex loops. Swelling can be quantified by measuring water displacement.

Therapy for CRPS

Lack of understanding of the underlying pathophysiologic abnormalities and lack of specific diagnostic criteria resulted in inherent difficulties of conducting clinical trials with therapeutic modalities. Two large and comprehensive literature reviews of outcome studies find discouragingly little consistent information regarding the pharmacologic agents and methods for treatment of CRPS [68,90]. For that reason one has to rely on basic principles of pain management: pain and symptom relief, supportive care, and rehabilitation. In addition, in the absence of more specific information regarding treatment of CRPS, one has to rely on outcomes from treatment studies for other neuropathic pain syndromes.

General rules

The most important general principle in the treatment of CRPS is to organize a multidisciplinary approach after the onset of the disease. The pain specialists should include neurologists, anesthesiologists, orthopedics, physiotherapists, and psychologists. The general principles of pharmacologic treatment are the individualization of therapy and the titration of a given pharmacologic agent, depending on 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 on the peripheral or central afferent nervous system in cases of CRPS always implicates further deafferentation, and thereby provides an increased risk for persistent deafferentation type of pain.

Pharmacologic therapy

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) have not been demonstrated to have significant analgesic effect in the treatment of CRPS; however, NSAIDs could be used for relief of mild to moderate pain.

Opioids

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 with placebo [91]. However, there are no long-term studies of oral opioids use for 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 part of a comprehensive pain treatment program. Because 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 patient compliance.

Tricyclic antidepressants

Tricyclic antidepressants (TCAs) are the best studied group of pharmacologic agents in neuropathic pain. They have shown analgesic effect, although modest and in a limited group of patients. TCAs 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 [92–94]. Selective 5-HT re-uptake blockers are no more effective than placebo, suggesting that TCA efficacy for neuropathic pain depends mainly on the noradrenergic component [94–96]. The mean dose that is often sufficient for pain reduction (*eg*, amitriptyline 75 to 150 mg/d) is smaller than doses necessary to achieve antidepressant effects. Onset of the analgesic effect occurs within 1 to 2 weeks and peaks around 4 to 6 weeks [93]. Improvement of sleep, mood, and anxiety can further add to the pain-relieving action.

Sodium blocking agents

Sodium blocking agents, as the type Ib antiarrhythmic drugs lidocaine, mexiletine, and tocainide, and the anticonvulsant carbamazepine have effects on sodium channels and potentially could relieve pain. Systemically administered lidocaine has clearly demonstrated analgesic efficacy for control of neuropathic pain, and its oral congener mexiletine have been shown to alleviate pain in diabetic or postherpetic neuropathy [91,97]. Although these drugs have successfully been used for the treatment of neuropathic pain, there are no well studied and accepted standards for their administration of these agents, and therefore care needs to be taken when administering these compounds. Contraindications include electrocardiac abnormalities, reduced left ventricular function, and coronary heart disease.

GABA-agonists

GABA-agonists, such as baclofen, valproic acid, vigabatrine, 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. There is recent evidence that intrathecal baclofen improves dystonia in CRPS [98••]. The action of the drug gabapentin is not completely resolved, but probably includes an inhibition of calcium channels. In a recent study gabapentin had a promising effect on CRPS [99].

Glucocorticoids

Glucocorticoids taken orally are the category of agents that has clearly demonstrated efficacy in a controlled trial [46]. There is no evidence that other immune-modulating therapies, notably intravenous immunoglobulins or immunosuppressive drugs, have a place in the treatment of CRPS or of any other pain condition.

Adrenoceptor antagonists

Transdermal application of the 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 [100,101].

NMDA-receptor antagonists

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

Interventional therapy at the sympathetic nervous system

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 compelling historical and basic scientific evidence that it is important that an adequate sympatholytic trial by a qualified clinician be performed in an attempt to differentiate between SMP and SIP. In the presence of a significant sympathetic component, treatment strategies toward the sympathetic therapy could be considered. Besides the pain, other symptoms may also improve after sympathetic blocks.

Physical therapy

At this point it should be stressed that clinical experience clearly indicates that physiotherapy is of the utmost importance to achieve recovery of function and rehabilitation. It is impossible to carry out intensive active therapy at the acute stage, when the patients still suffer from severe pain. Aggressive physical therapy can lead to deterioration. Therefore, immobilization and contralateral therapy should be the acute treatment of choice. Later passive physical therapy, and active isometric followed by active isotonic training, should be performed in combination with sensory desensitization programs. Few clinical studies could demonstrate a signif-

icant improvement of CRPS after physical therapy [86,102, 103•]. However, more investigations are needed to demonstrate the efficacy of physical therapy and the establishment of a standardized approach in CRPS.

Stimulation techniques

Transcutaneous electrical nerve stimulation may be effective in some cases and has minimal side effects. More invasive stimulation techniques, *ie*, peripheral nerve stimulation with implanted electrodes, epidural spinal cord stimulation, and deep brain stimulation (sensory thalamus and medial lemniscus), have been reported to be effective in selected cases of CRPS [104,105].

Conclusions

Complex regional pain syndrome is a neuropathic pain condition that is clinically characterized by sensory, autonomic, and motor disturbances. Centrally mediated dysfunction of the sympathetic nervous system and peripheral inflammatory processes seem to be involved in the pathophysiology of the disease. An early diagnosis and an interdisciplinary approach are important for optimal and successful treatment.

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- • Of importance
- •• Of major importance

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