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Complex regional pain syndrome

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Abstract Complex regional pain syndrome (CRPS) may develop after limb trauma and is characterized by pain, sensory-motor and autonomic symptoms. Most important for the understanding of the pathophysiology of CRPS are recent results of neurophysiological research. Major mechanism for CRPS symptoms, which might be present subsequently or in parallel during the course of CRPS, are trauma-related cytokine release, exaggerated neurogenic inflammation, sympathetically maintained pain and cortical reorganisation in response to chronic pain (neuroplasticity). The recognition of these mechanisms in individual CRPS patients is the prerequisite for a mechanism-oriented treatment.

Key words complex regional pain syndrome (CRPS) · sympathetically maintained pain (SMP) · neurogenic inflammation · neuroplasticity · physical therapy

Introduction

In the beginning of the twentieth century, Paul Sudeck, a surgeon in Hamburg, Germany, first published a paper about post traumatic bone dystrophy [56]. He described a posttraumatic pain syndrome with edema and trophic changes. As the sympathetic nervous system seems to be overactive at first glance, the term "Sympathetic Reflex Dystrophy" was used for many years [11]. Studies, which raised doubts on the role of the sympathetic nervous system in the pathophysiology of this pain syndrome, led to a new descriptive term – "Complex Regional Pain Syndrome" (CRPS), the official one in recent years [55].

Diagnosis and clinical picture

At present, the diagnosis of CRPS is based on clinical examination. According to a very recent consensus meeting of a special interest group of the International Association for the Study of Pain (IASP) [65] the diagnosis of CRPS can be made, if the following criteria are fulfilled:

- Preceding noxious event without (CRPS I) or with obvious nerve lesion (CRPS II);
- Spontaneous pain or hyperalgesia/hyperesthesia not limited to a single nerve territory and disproportionate to the inciting event;
- Edema, skin blood flow (temperature) or sudomotor abnormalities, motor symptoms or trophic changes are present on the affected limb, in particular at distal sites;
- Other diagnoses are excluded.

These criteria are easily to handle and made for clinical use. For scientific research, however, these criteria are still too sensitive and lack some specificity and therefore a more restricted definition should be used, as suggested by Bruehl and coworkers [13].

CRPS forms a typical clinical picture of sensory, motor and autonomic symptoms. In the following these symptoms will be discussed in detail. The data mainly represent the results of the examination of more than 450 CRPS patients in our department [7].

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Sensory disturbances

Pain and hyperalgesia are the most important symptoms. 75 % of patients had pain at rest with an aching, burning or pricking and sometimes shooting character. In most patients this pain is localized deep in the affected extremity. Nearly all (100 %) patients described hyperalgesia. Detailed investigation of hyperalgesia reveals hyperalgesia to mechanical impact (pinprick) stimuli [6]. Mechanical hyperalgesia explains the motion-dependent amplification of pain in all CRPS patients. According to the current basic scientific knowledge, mechanical hyperalgesia in CRPS might be due to central sensitisation. Most obvious is this for this third of patients, who suffer from allodynia (brush-evoked pain), in particular in long-lasting CRPS. A further hallmark of central sensitisation is the spreading of hyperalgesia, which mostly goes far beyond the initial site of injury. On the other hand thermal hyperalgesia, the clinical surrogate of peripheral nociceptive sensitisation, occurs less often. This is not surprising since peripheral sensitisation usually is restricted to the injury site. After a fracture, an injury deep in the tissue, there are simply no sensitised primary afferents which could be investigated by thermal testing. Hyperalgesia to cold is regarded as a symptom of sympathetically maintained pain (see below) and is significantly more frequent in CRPS II [7].

Other sensory symptoms such as numbness or paresthesias have been reported less often than pain or hyperalgesia. About 30 % of CRPS patients spontaneously reported a "foreign" feeling of their affected limb – reminiscent of some kind of cognitive neglect [19].

Motor disturbances

77% of CRPS patients have weakness of the affected site. In acute stages this might be a pain-dependent, guarding weakness. Range of motion is reduced by oedema in acute stages, in chronic stages contraction and fibrosis can occur, especially on palmar and plantar sides of hands or feet. In 50 % tremor can be seen [17]. In 30 % myoclonus or focal dystonia can occur, mainly in CRPS II after a nerve lesion [58]. About 45 % of the patients have exaggerated deep tendon reflexes on the affected extremity without pyramidal tract signs.

Autonomic disturbances

During acute stages 81 % of the patients have a distal limb edema on the affected limb. In the first months of posttraumatic CRPS the skin is usually red and hot. Later on in chronic stages, the skin turns to bluish and becomes cold. About 20 % of CRPS cases are primarily cold [61]; this type of CRPS more often occurs spontaneously or after minor injuries [8]. Regardless of whether hot or cold, the typical temperature difference between affected and unaffected side is more than 1.0 °C [63]. This temperature difference separates CRPS from other causes of painful extremities, but using it as a diagnostic tool, one has to remember that it is not static. Temperature difference may change within minutes, depending on thermoregulatory condition [62]. In 50 % of the patients increased sweating can be observed [9].

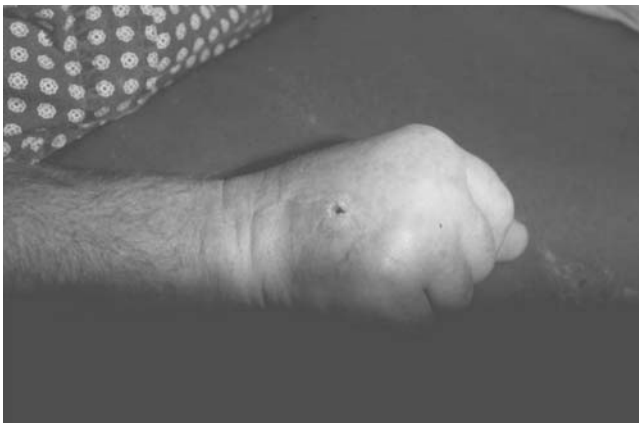

Fig. 1 Tonic posturing in chronic CRPS. This patient was unable to open his hand voluntarily for years. Investigation under general anesthesia revealed that meanwhile a contracture of finger joints was present limiting finger extension by about 50 degrees. The patient had also recurrent skin ulcers on the affected skin

Trophic changes

Further characteristic CRPS symptoms are trophic changes which occur in more than 50 % of CRPS patients. Increased hair- and nail growth appears several days after the onset of symptoms. Over time these "plus-symptoms" dwindle converting to "minus-symptoms" with reduced hair- and nail growth and atrophy of the skin. In severe cases even atrophy of the muscles with fibrosis and contracture can occur [59].

Diagnostic Tools

Beside clinical examination, several technical diagnostic tools can support the diagnosis. Nevertheless, CRPS cannot be proven by any diagnostic measure. A negative result in these tests should not question a clinically typical CRPS and should by no means delay treatment (see below).

Radiography

A conventional radiograph typically shows spotty osteoporotic changes after 4–8 weeks [61]. However, these changes only occur in 40 % of the cases.

Three phase bone scintigraphy

Three-phase-bone-scintigraphy with Technetium-99m is an important diagnostic tool, although its sensitivity might be lower than has been assumed. The increased tracer uptake in the late pictures, the "mineralization phase", is a sign of increased bone metabolism.

MRI

Sometimes MRI of the affected extremity is necessary to exclude other diseases. In CRPS, the edema in deep tissues (muscle, connective tissue) and periarticularly can be seen. After gadolinium injection a subtle enhancement is seen which points to an increased permeability of blood vessels, which is much less than in infective arthritis.

Pathophysiological considerations

Within the last few years intensive research has led to improved knowledge which helps to explain distinct symptoms.

Neurogenic inflammation, pain and hyperalgesia

Many clinical symptoms of acute CRPS resemble inflammation: pain, edema, increased skin temperature and blood flow. However, inflammation in the classical sense has not been unequivocally proven, but any inflammation has a "neurogenic component". Trauma related activation and sensitisation of primary afferents, e. g. by cytokines [23], causes neuropeptide release in the affected body region (mainly substance P (SP) and calcitonin-gene related peptide (CGRP)). Chronic release of neuropeptides might be responsible for the above mentioned peripheral CRPS symptoms. In addition, central neuropeptide release facilitates nociceptive sensitization and may contribute to motor disturbances.

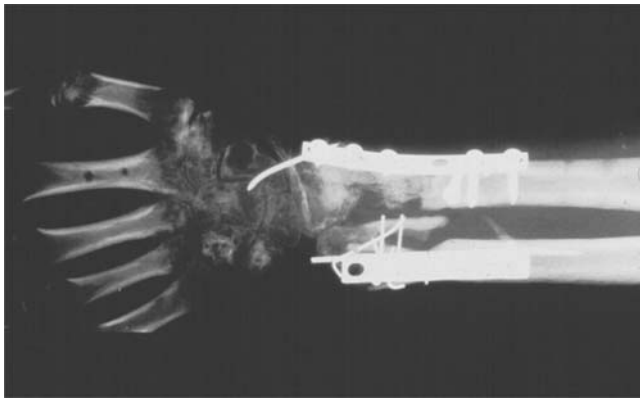

Fig. 2 This is a typical radiograph finding with spotty osteoporosis, which is pronounced in the metaphysal segments of bones

Nerve lesion experiments in rats have shown that neuropeptides contribute to pain behavior and many clinical symptoms resembling CRPS [29]. In analogy to migraine studies, we therefore measured CGRP (RIA) in serum samples from patients with acute CRPS. CGRP was significantly increased, in particular when clinical inflammatory signs were present and if there was evidence of trauma related nerve lesion [8]. In order to verify that increased CGRP indeed comes from primary nociceptive afferents, neurogenic inflammation was elicited directly in the skin by transcutaneous electrical stimulation via intradermal microdialysis capillaries. We first investigated the flare by laser-Doppler scanning on the affected and on the unaffected side in our CRPS patients. Neurogenic flare was significantly more intense in patients, surprisingly on both sides – the affected and the clinically unaffected one. Another characteristic of neurogenic inflammation in rodents is SP mediated plasma protein extravasation (PPE). In healthy humans, however, there are usually too few SP-containing C-fibers to induce PPE. In CRPS, however, significant PPE could be shown in almost all patients investigated. In contrast to the flare response this increased PPE was limited to the affected side [64]. These results so far suggest two possible pathomechanisms leading to facilitated neurogenic inflammation in CRPS – either increased release or hampered inactivation of neuropeptides. In order to further unravel these mechanisms we perfused SP in ascending concentrations through dermal microdialysis fibers. We found SP significantly more effective in inducing PPE in CRPS patients than in controls. Alike increased flare, this increased responsiveness to SP was present on both the affected and unaffected limbs [32]. That is, we found a trauma-related up-regulation of neuropeptide release from primary afferents on the affected side and in addition a constitutionally impaired inactivation of neuropeptides on both sides. This impaired inactivation of neuropeptides might predispose some subjects to develop CRPS in response to limb trauma [22].

Neurogenic inflammation in the acute stage of CRPS could explain increased skin temperature, edema and the trophic changes (increased hair- and nail growth, high turnover osteoporosis) [45]. Moreover, peripheral neuropeptide release might also contribute to hyperhidrosis [50], a clinical sign which usually has been thought to be a sympathetic failure. Furthermore, neuropeptides are released not only in the periphery, but

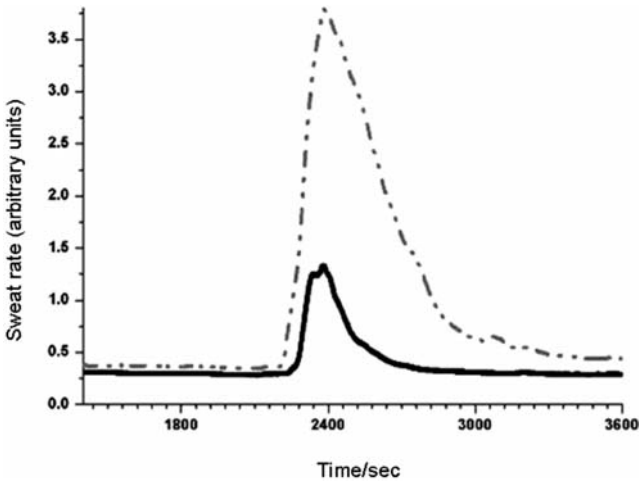

Fig. 3 This figure shows the sweat output of a healthy subject after microapplication of nicotine. The solid line indicates nicotine induced sweating alone, which was more than doubled after adding low doses (10–8M) of Calcitonin Gene Related Peptide (CGRP, dashed line)

also in the central endings of the primary afferents. After trauma and nerve lesion, the SP receptor (NK1-R) will be upregulated in dorsal horn neurons of the spinal cord, and thereby SP initiates sensitization of central pain neurons for forthcoming nociceptive input.

Impairment of the function of the sympathetic nervous system

Within the first weeks of CRPS skin temperature on the affected limb is increased – probably owing to neurogenic inflammation. In "primary cold" CRPS cases and in chronic stages skin temperature of the affected limb is decreased, often in combination with increased sweating, which is of central origin in this case [6]. These findings indicate an impairment of thermoregulatory control of the skin. Because of its pattern (vasoconstrictor hypoactivity and sudomotor hyperactivity) this sympathetic dysfunction must be located in the central nervous system [6]. As indicated above, skin vasoconstriction is reduced in acute CRPS. Beside neurogenic inflammation, there is evidence that sympathetic noradrenergic control of blood vessels is reduced [18]. In chronic CRPS, however, vasoconstriction is increased leading to cold skin. How can this be explained? There are several possibilities. 1) In contrast to sweat glands blood vessels develop an increased sensitivity to catecholamines if there is insufficient innervation [14]. For superficial hand veins an increase of noradrenaline susceptibility has been demonstrated [3]. 2) Impairment of vasoconstriction in CRPS is due to thermoregulatory CNS disturbances (see above). Even if this is at present speculation, there might be also denervation supersensitivity of central catecholaminergic neurons [40]. If these neurons are important for regulation of skin perfusion, cold extremities during chronic stages could be explained. 3) Our examination of patients a few days after acute stroke has shown [46] that the loss of sympathetic control itself could lead to cold extremities independent of catecholamine sensitivity change. In this case cold extremities are the result of blood pooling by the loss of microcirculatory control of skin blood flow. Thereby, blood flow velocity decreases and temperature in the surface layers of the skin will adapt to the ambient temperature, which is normally colder than skin temperature [16]. Which of these possibilities is the best explanation for the sympathetic disturbances certainly has to be focused on in future. However, it cannot be excluded that there are several successive mechanisms in the course of the disease which would explain the changing clinical pictures.

Is there a coupling between sympathetic efferents and nociceptive afferents?

Two facts suggest sympathetico-afferent coupling in at least some CRPS cases: The effectiveness of sympathetic nerve blocks [5], and the painfulness on injection of noradrenalin contrasts with the effects on healthy people [1]. The most likely explanation for these phenomena is that after nerve lesions functional adrenoreceptors may be present on primary nociceptive afferents [31]. However, if this were the only explanation for sympathoadrenergic coupling, blocking the adrenoreceptors should rapidly abolish the pain in all cases of SMP. This is not the case. Therefore indirect coupling has to be also considered. A long-lasting impairment of the sympathetic nervous system – or chronic neurogenic inflammation – in CRPS probably leads to a shift of blood flow in the arterioles and to a reduction of nutritive-capillary supply. This means that there is hypoxia and acidosis or at least reduced buffer capacity in the affected tissue [10]. Protons are powerful algesic substances and cause pain and mechanical hyperalgesia [24]. Furthermore, inflammatory mediators could be influenced by the sympathetic nervous system. Just the existence of peripheral sympathetic neurons is sufficient to facilitate plasmaextravasation in experimental joint inflammation [41].

Long term activation of primary afferents triggers cortical changes

CRPS patients often report striking numbness of the skin of the affected body region (about 50 %, see above), or even hemisensory impairment [47]. This cannot be explained solely by peripheral nerve lesion, particularly

in CRPS 1. Moreover, the numbness quickly resolves when CRPS pain is relieved. From recent human experimental QST studies there is evidence that pain induced by intracutaneous capsaicin injection elicits surrounding tactile hypesthesia [33]. A possible mechanism is that C-fiber-induced primary afferent depolarisation may result in presynaptic inhibition of low threshold mechanoreceptors at the spinal level [25]. Furthermore, it has been shown recently that tonic experimental pain impairs cortical processing of sensory evoked potentials [48]. Functional imaging studies in chronic pain patients have even revealed deactivation of S1 and S2 cortical areas if touch was not perceived [36]. Thus, chronic pain might effect cortical processing of touch in CRPS. This could explain why numbness usually goes beyond innervation territories of single peripheral nerves or nerve roots.

A further symptom pointing to altered cortical sensory processing is referred sensations in CRPS patients [37]. Using magnet-encephalography (MEG) we have demonstrated a significant shrinkage of the extension of the hand representation in the primary sensory cortex (postcentral gyrus) for the CRPS affected side, and a shift of hand representation towards the lip. This cortical reorganisation correlated linearly with the amount of CRPS pain [34], and reversed following pain relief [35]. These findings in CRPS indicate that ongoing pain alters somato-sensory processing in the brain. It might be that a limited ability to inhibit cortical reorganization may be a further prerequisite for CRPS, at least for very severe cases with predominant CNS symptoms [51].

Why do some patients develop CRPS and others not?

There is evidence for a susceptibility of patients to develop CRPS [32]. Further, molecular biological examination has pointed to HLA-association. Up to now an association to HLA II-Loci DR 15 and DQ 1 has been described [27]; in CRPS patients with multifocal or generalized dystonia Locus DR 13 has been shown to be over-represented [57]. Although the connection between CRPS and HLA-Loci remains unclear, these results hint at some kind of CRPS genetic mechanism, at least in patients with familiar predisposition [22].

The opinion that CPRS has psychosomatic background is popular. In some studies personality traits such as anxiety were verified [21], in other studies not [60]. In the end it is not clear if these personality traits predispose for CRPS or may be the result of it. Possibly, the antidepressant and anxiety relieving properties of antagonists of substance P (NK1)-receptors may be a connection between genetic predisposition and personality traits [4].

Treatment

The aims of CRPS therapy are the relief of pain and the maintenance or restitution of function. To achieve this, therapy has to start as soon as possible. For summary see also Table 1.

Pathophysiologically oriented therapy

Steroids

The anti-inflammatory treatment of CRPS with steroids is based on controlled studies [12,15]. Cortisone has multiple effects – it inhibits the production of inflammatory mediators, reduces the transcription rate in dorsal root ganglia cells and thereby reduces SP content of sensory neurons [30], and it facilitates degradation of neuropeptides [44]. Thus, development of neurogenic inflammation and of neuropathic pain can be prevented [28].

Sympathetic blocks

Unfortunately, there has been no reliable investigation to detect sympathetically maintained pain (SMP) in CRPS, apart from sympathetic blocks. If these blocks are successful (pain reduction of more than 50 %), repeated stellate ganglion blocks or lumbar sympathetic chain blocks with local anesthetics should be performed.

Radical scavengers

According to controlled studies topical treatment with 50 % dimethyl sulfoxide (DMSO) cream four times/day can be effective in reducing hypoxia-related production of free oxygen radicals [66].

Table 1 This table shows symptom-oriented treatment options for posttraumatic CRPS

1. All patients should receive physical therapy and symptomatic therapy for neuropathic pain Antineuropathic pain therapy should be selected according to pain characteristics and concomitant symptoms (sleeplessness, fears, secondary depression). Best evidence exists for TCA and Ca^{2+} channel blockers. If side effects are unbearable, but the drugs work: serotonin – noradrenalin re-uptake inhibitors are worth trying
2. Patients in an acute stage with edema, increased skin temperature systemic steroids + local DMSO
3. Repeated sympathetic blocks should be performed in all patients under suspicion of SMP – primary cold CRPS, cold allodynia, positive effect of single sympathetic block
4. In severe chronic stages Spinal cord stimulation

Treatment to be further evaluated

Calcitonin and diphosphonates effect the bone turnover. Although the mechanisms for pain relief may be unclear, there have been randomised controlled studies showing a beneficial effect of both substances [20].

Symptomatic treatment of neuropathic pain in CRPS

There are no randomised controlled studies for CRPS. The rationale to use drugs comes from treatment studies of other types of neuropathic pain.

Antidepressants

The most important class of substances being used for neuropathic pain are tricyclic antidepressants (TCA). The best studies have been of amitryptilline and imipramine [53]. The analgesic effect of TCAs is based on serotonine and noradrenaline re-uptake inhibition in the CNS and on the peripheral blockade of sodium channels. The major hindrance for TCAs are dose-dependent side effects. Newer substance classes like combined serotonine/noradrenaline re-uptake inhibitors may be an alternative [52].

Antiepileptic drugs

Antiepileptic drugs are also very important substances for treatment of neuropathic pain. Best evidence for analgesic properties exist for gabapentin and pregabalin, calcium-channel blocking agents [39]. There are less convincing data for carbamazepine, a sodium-channel blocker.

Opioids

A few years ago, opioids were considered to be ineffective in neuropathic pain [2]. However, our own experiences in CRPS treatment and meanwhile studies in other types of neuropathic pain suggest that opioids are effective with higher doses [49].

Non-drug therapy

Although studies on physical therapy are rare [43], such therapy is essential for CRPS treatment. The aim of physical therapy is to improve or maintain function and mobility of the affected extremity. Most important is that physiotherapy does not hurt. Pain thresholds are good indicators for individual limits of exercise. Starting passively and as soon as possible with active participation of the patient physical therapy should be beneficial in all cases. In addition, motor learning programs employing mirror images of movement of the unaffected limb have been shown to be efficacious in acute [38] and chronic CRPS [42].

Transcutaneous electrical nerve stimulation (TENS) may be used in therapy of neuropathic pain – being free of side effects [54]. Data for CRPS do not exist. Good evidence exists for electrical spinal cord stimulation (SCS), even in chronic cases after years of ineffective drug therapy [26].

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