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Topical review

Complex regional pain syndrome: how to resolve the complexity?

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1. CRPS history: the development of a clinically defined syndrome

About 150 years ago Sir Weir Mitchell reported about 'Gunshot wounds and other injuries of peripheral nerves' (Mitchell et al., 1864), probably the first detailed description of complex regional pain syndrome (CRPS, more precisely CRPS II). Since then, many attempts were made to explain the clinical features: in particular pain and sympathetic disturbances, to define diagnostic criteria and to find an adequate name for this disease. Still the most familiar names (among a variety of others) are 'sympathetic reflex dystrophy' and 'causalgia' (Bonica, 1979), the use of the latter term depending on the apparent presence of peripheral nerve damage. The term 'sympathetic reflex dystrophy' was chosen since the sympathetic nervous system seemed to be overactive and therefore, on superficial examination, responsible for the pains. 'Causalgia' describes the burning character of spontaneous pain. At least as numerous as the names were the hypotheses put forward to explain pathophysiology. All of them focussed on sympathetic disturbances: Reverberating circuits in the spinal cord (Livingston, 1943), the ephaptic crosstalk between peripheral sympathetic efferents and nociceptive afferents (Nathan, 1947) and the 'turbulence' theory (Sunderland, 1976). However, none of these theories has ever been proven to explain CRPS comprehensively and newer studies have cast doubts on sympathetic nervous system overactivity: thereby on its exclusive role in CRPS pathophysiology. Finally, a consensus conference, held 1993 in Orlando, Florida, rejected the prejudicing term 'reflex sympathetic dystrophy' and introduced the purely descriptive 'Complex Regional Pain Syndrome' (CRPS), now the official name for several years.

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2. Definition of CRPS

According to the consensus paper (Stanton-Hicks et al., 1998) the diagnosis of CRPS is based on the following criteria:

1. Preceding noxious event without (CRPS I) or with apparent nerve lesion (CRPS II);
2. Spontaneous pain or hyperalgesia not limited to a single nerve territory and disproportionate to the inciting event;
3. Present or reported edema, skin blood flow (temperature) or sudomotor abnormality in the distal part of the affected limb;
4. Exclusion of other diagnoses.

These criteria are easy to handle and sufficient for clinical use. For scientific research, however, they are too circumstantial and lack specificity. Therefore a more restricted definition, which requires the presence of a combination of symptoms should be used for scientific studies, as suggested by Bruehl and coworkers (Bruehl et al., 1999). These symptoms include mechanical hyperalgesia, skin color or temperature changes, sudomotor abnormalities or edema, and motor or trophic symptoms.

The incidence of CRPS I is obviously higher than CRPS II. Despite a significant overlap in clinical symptomatology, there is one important difference between both syndromes (Jänig, 2001): The presence of an apparent peripheral nerve lesion. While lesions of peripheral nerve branches by trauma may occur in CRPS I deep in the somatic tissue, in CRPS II it is part of the definition and usually involves cutaneous nerves. That means, changes of functional properties of peripheral nerves, like possible receptor up- or down-regulation, sensitization and changes of neurosecretory properties, which all have been demonstrated in peripheral nerve injury in different animal models, probably are important in CRPS II, but its presence in CRPS I is doubtful. The same reservation applies to the origin of pain: it has to be classified as neuropathic in CRPS II, but not necessarily in CRPS I. However, most cases of CRPS I develop after

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limb trauma, in particular after bone fractures. Evidence from animal studies suggest that after fractures the density of periostal nerves is regularly reduced: indicating nerve damage (Hukkanen et al., 1993). Therefore, the trigger initiating CRPS I and II might be similar, after all – at least in the majority of patients. Of course, this cannot apply to those rare cases of CRPS, which develop after visceral trauma. However, CRPS occurring after brain damage is very often triggered by an additional peripheral trauma (Braus et al., 1994).

3. How to diagnose CRPS?

3.1. Clinical symptoms

It is most important to recognize CRPS and to be aware of its existence. It typically presents as a constellation of sensory, motor and autonomic symptoms together with trophic changes (Birklein et al., 2000c). Physicians have to recognize that symptoms of CRPS are not static, and with increasing chronicity, they will change, probably as pathophysiology does (see below).

Intense spontaneous pain and hyperalgesia are the most pertinent symptoms. In most patients the maximum pain of aching, burning, pricking or shooting character is localized deep in the somatic tissue. All patients suffer from hyperalgesia, predominantly to mechanical stimuli or on joint movement. One third (higher incidence in chronic stages) suffer from severe allodynia (brush-evoked pain), a hallmark of central nociceptive sensitization. Cold allodynia, which is regarded as a clinical symptom of sympathetically maintained pain (see below), is significantly more frequent in CRPS II (60 vs. 30%)(Birklein et al., 2000c). Almost all of the patients simultaneously have sensory deficits; with a glove and stocking like distribution on the affected limb, or spreading beyond the affected skin. This coincidence of sensory plus- and minus- symptoms strongly suggests that the basis of the symptoms might be functional rather than structural, at least in acute CRPS.

Other indicators for CRPS are motor symptoms: weakness, tremor, exaggerated tendon reflexes, dystonic posturing and myoclonic jerks. In acute stages weakness might be explained by pain – a ‘giving-way’ weakness. In chronic stages, however, impaired nutrition of affected muscles (Heerschap et al., 1993) and abnormalities of central motor processing may be the causes of motor symptoms. Tremor has been classified as an enhanced physiological form, myoclonic jerks and focal dystonia occur particularly in CRPS II. Range of motion is reduced: by joint effusion in acute stages and by contraction and fibrosis in chronic stages. About 45% of the patients have exaggerated tendon reflexes on the affected side. Since there are no pyramidal tract signs but a good correlation to the presence of pain, this reflex exaggeration could be regarded as pain facilitation of tendon reflexes.

The autonomic (sympathetic) symptoms are distal limb edema, skin color and temperature changes, and sweating abnormalities. In the beginning, the affected skin commonly is red, in the chronic stages mainly bluish. Typically, skin temperature difference between affected and unaffected side exceeds 1.0°C and during the development of the disease the temperature shifts from warmer affected extremities in acute stages to colder in chronic stages. However, skin temperature difference also depends on acute thermoregulatory state (Wasner et al., 2001). In 50% of the patients increased sweating can be observed in the affected limb (Birklein et al., 1997a).

A description of CRPS symptomatology should not neglect some typical trophic changes, which occur in more than 50% of the cases. Increased hair and nail growth appears a few weeks after trauma. Over time these ‘plus-symptoms’ increasingly dwindle changing to ‘minus-symptoms’ with decreased hair and nail growth and atrophy of the skin. In severe cases even skin ulcers might develop.

Sometimes, it may be difficult to distinguish between ‘normal’ trauma related symptoms and early CRPS. A recent study of our group showed that motor signs, trophic changes and increased sweating are most suitable to recognize early CRPS (Birklein et al., 2001). This could help to facilitate correct diagnosis and thereby to improve therapy. Edema, skin temperature difference and even pain could be clinically indistinguishable between trauma related symptoms and acute CRPS.

3.2. Diagnostic tools

Beside clinical examination, some specific tests can support diagnosis.

Measurement of skin temperature differences during controlled alterations of sympathetic vasoconstrictor activity by exposition to cold or warmth revealed a sensitive and specific diagnostic tool for CRPS (Wasner et al., 2001). However, these controlled alterations of sympathetic activity are cumbersome. More simple are repeated measurements of skin temperature at different times, which should also demonstrate typical dynamic temperature changes of the affected limb. Quantitative measurements of sudomotor activity may prove an enhanced sweat production at the affected extremity in the acute and chronic stages of the disease in many CRPS patients (Birklein et al., 1997a).

On the side-comparing X-rays typically spotty osteoporotic changes can be found after 4–8 weeks. However, these changes only occur in 40% of the cases. Although sensitivity and specificity of 3-phase-bone-szintigraphy with Technetium-99m is not as good as previously assumed, the typically increased tracer uptake in the late pictures is a sign of increased bone metabolism. Sometimes MRI-scans of the affected extremity may be required to exclude other diseases. In CRPS, the typical edema in deep tissues (muscle, periarticular connective tissue) can be seen in MRI. After gadolinium a subtle enhancement occurs, which indicates an increased permeability of blood vessels. However, this is much less dramatic than seen in arthritis or infections.

Diagnostic blocks of sympathetic nerves are not helpful to diagnose CRPS. However, it is to date the only possibility to recognize sympathetically maintained pain (SMP) in a subgroup of patients suffering from CRPS.

4. Pathophysiological considerations

Within the last few years intensive research led to improved knowledge, which helps to explain distinct symptoms. Nevertheless there is still no unquestioned pathophysiological explanation for the whole disease.

4.1. Neurogenic inflammation, pain and hyperalgesia

Paul Sudeck described an acute bone dystrophy and his description takes into account that the clinical symptoms of CRPS are similar to inflammation: pain, edema, redness and impaired function (Sudeck, 1942). A real humoral inflammation could never be proved. However, the coincidence of signs of inflammation with trophic changes and mechanical hyperalgesia in CRPS strongly resembles neurogenic inflammation. Activation of primary afferents leads to the release of calcitonin gene-related peptide (CGRP) and substance P (SP) from nerve endings. Release of CGRP leads to an increase in peripheral blood flow (vasodilation) by an action on the arterioles, whereas release of substance P, in addition, induces plasma protein extravasation from venules. In CRPS we were able to show that the excitability of primary afferents and thereby the release of neuropeptides is increased (Weber et al., 2001). In the acute stage this may explain increased skin temperature, edema and trophic changes (increased hair- and nail growth). It has been assumed that neuropeptides are mainly released from the so called 'sleeping' mechano-insensitive nociceptors, which might be sensitized by the initial trauma and the resulting processes of regeneration. Recruitment of 'sleeping' nociceptors predominantly leads to mechanical hyperalgesia, another marked sign in CRPS (Sieweke et al., 1999). However, one has to bear in mind that neuropeptides are released not only in the periphery, but also from the central endings of the primary afferents. After nerve trauma, the SP receptor (NK1-R) will be up-regulated in dorsal horn neurons of the spinal cord, and thereby SP will initiate sensitization of central pain transmission neurons, a distinctive mechanism leading to pain chronicity.

Acutely after trauma, in inflammatory processes or triggered by ischemia and reperfusion, oxygen-derived free radicals occur in the affected tissues. Animal models with intra-arterial infusion of tert-butylhydroperoxide, a free radical donor, strongly resemble clinical symptoms of acute CRPS: edema, increased skin temperature, impaired function and pain behavior (van-der-Laan et al., 1998a). On the other hand, prophylactic administration of vitamin C, a free radical scavenger, reduces the incidence of CRPS after wrist fractures (Zollinger et al., 1999). Both studies support a pro-inflammatory role of free radicals in CRPS I.

4.2. Impairment of sympathetic function

Within the first weeks of CRPS, skin temperature on the affected limb is increased in nearly all patients, with the exception of some 'primary cold' cases (Veldman et al., 1993). As indicated by this increased skin temperature, in acute CRPS the sympathetic noradrenergic control of blood vessels of the skin is reduced, and not enhanced, as assumed until some years ago. In combination with an increased sweating observed throughout all stages of the disease, several investigations point to an impairment of thermoregulatory outflow to the skin. Due to its pattern (vasoconstrictor hypo-activity and sudomotor hyper-activity) this impaired sympathetic output function must be due to functional alterations in the central nervous system which might be reversible, in principle (Wasner et al., 2001).

In chronic stages the skin temperature of the affected limb is almost always decreased on the affected side. The most likely explanation for this temperature shift with chronicity is, that due to the reduced sympathetic outflow in acute stages (see previous paragraph) the skin vessels in the affected extremity develop an increased sensitivity to catecholamines, similar to denervation supersensitivity. Multiple mechanisms may contribute to this supersensitivity, including a decrease in neurotransmitter re-uptake or enzymatic degradation, an increase in post-junctional receptor density, an increase in the binding affinity of agonists to receptors, reduced efficiency of the sodium-potassium pump, and an up-regulation of second messenger signaling systems. In a pilot study comprising five chronic CRPS I patients the density of specific alpha-adrenoreceptors was slightly greater in biopsies from the symptomatic skin of patients than in controls (Drummond et al., 1996). For superficial hand veins functional evidence for a catecholaminergic supersensitivity has been demonstrated in CRPS I (Arnold et al., 1993). However, for arterioles in the same region we were not able to demonstrate supersensitivity (Birklein et al., 1997b).

Since it is still unclear whether impairment of vasoconstriction at the CNS level in acute CRPS (see above) really could lead to denervation supersensitivity of peripheral blood vessels, alternative explanations for cold skin in chronic CRPS should also be considered. Like peripheral target tissues, central catecholaminergic neurons could develop supersensitivity (Menkes et al., 1983). If these neurons are important for the regulation of skin perfusion, cold extremities during chronic stages could be explained by a central rather than a peripheral alteration. Alternatively, the loss of sympathetic control itself could lead to cold extremities independent of any catecholamine supersensitivity, as an examination of patients a few days after stroke has shown (Riedl et al., 2001). In these patients, sympathetic failure leads to edema and blood pooling in the paretic limb. Thereby, blood flow velocity decreases and surface skin temperature adapts to the ambient temperature, which is normally colder than the core temperature. The decreased skin temperature could then selectively potentiate adrenergic vasoconstriction in superficial veins, but not in arterioles (Vanhoutte and Flavahan, 1986) and this might explain the divergent results described above. Which of these theories provide the best explanation for the cold limb in chronic CRPS will be a key issue for future research. It cannot be excluded that several mechanisms work together.

4.3. Is there a coupling between sympathetic efferents and nociceptive afferents?

In a subgroup of CRPS patients: those with sympathetically maintained pain (SMP), sympatho-afferent coupling apparently is pertinent. Two observations support this claim: (1) The effectiveness of sympathetic nerve blocks, and (2) the painfulness of intracutaneous injections of noradrenalin. After nerve lesions, functional alpha- adrenoreceptors may be present on primary nociceptive afferents, either at the injury site, peripherally on surviving axons or proximally in the dorsal horn (Sato and Perl, 1991). From these findings in animal studies one has to extrapolate that receptor mediated coupling should be important for CRPS II. Obviously, these patients may be treated successfully with repeated sympathetic blocks. In CRPS I major nerve lesions are excluded. However, subclinical traumatic nerve lesions in the deep somatic tissues (see above) and axonal degeneration in peripheral nerves in chronic cases (van-der-Laan et al., 1998b) may also occur in CRPS I and hence some of these patients may develop SMP.

If receptor-mediated sympatho-afferent interaction would be the only mechanism of pain induction, blocking of adreno-receptors should always abolish pain at once, which often is not the case. Therefore, in addition a more indirect form of coupling has to be considered. Long -lasting impairment of microcirculatory control in CRPS could lead to an impairment of nutritive-capillary blood flow and on this basis hypoxia and consecutively acidosis finally will develop which indeed has been demonstrated in CRPS limbs (Birklein et al., 2000b). Protons are among the most important nociceptor stimulants and cause an increase of pain in skin and muscles in CRPS patients (Birklein et al., 2000a).

The action of inflammatory mediators may also be influenced by the sympathetic nervous system. Just the existence of peripheral sympathetic neurons is sufficient to facilitate plasma extravasation in experimental inflammation. It has been discussed that this is due to the release of prostaglandines from sympathetic nerve endings (Levine et al., 1986).

Noradrenaline in the sympathetic nerves is co-localized with neuropeptide Y (NPY). In CRPS, NPY plasma concentration is diminished on the affected side (Drummond et al., 1994). As NPY is a mediator of opioid-independent pain reduction, this is yet another mechanism of possible indirect sympatho-afferent coupling.

5. Why do some patients develop CRPS and others not?

Only a small minority of patients develop CRPS after peripheral trauma. We have evidence that there are at least some families with multiple occurrences of CRPS. Recently, molecular biological examination has pointed to an association with HLA II- Loci DR 15 and DQ 1 (Kemler et al., 1999). In CRPS patients with multifocal or generalized dystonia Locus DR 13 has been shown to be overrepresented (van de Beek et al., 2000). These results may be the first hints to CRPS genetics.

6. Principles of therapy

The most important principle is to start therapy as soon as possible before irreversible changes in the affected limbs occur.

6.1. Oriented to pathophysiology

The anti-inflammatory treatment of CRPS with steroids is based on controlled studies (Braus et al., 1994). Steroids have multiple effects; they inhibit the production of inflammatory mediators, reduce the transcription rate in dorsal root ganglia cells and thereby reduce neuropeptide content of sensory neurons and they facilitate degradation of neuropeptides. Thus, development of neurogenic inflammation and of neuropathic pain could be successfully prevented.

Dimethyl sulfoxide (DMSO) 50% in a fatty cream applied four times daily is effective to reduce free oxygen-derived radicals in CRPS limbs (Zuurmond et al., 1996).

As to the treatment of SMP, there is no method of safely predicting the effectiveness of sympathetic blocks – besides sympathetic blocks themselves. If first blocks are successful (pain reduction of more than 50%), repeated blocks should follow (Price et al., 1998).

6.2. Symptom oriented treatment of neuropathic pain

The most important class of substances being used for the treatment of neuropathic pain are tricyclic antidepressants (TCA). The analgesic effect of TCAs is based on serotonin and noradrenaline re-uptake inhibition, on peripheral blockade of sodium channels, which accumulate on injured axons, and on blockade of NMDA: receptors on spinal cord dorsal horn neurons. In addition, a sympatholytic activity has also been discussed. Although controlled studies on CRPS pain don't exist, TCAs should be considered in particular in cases with spontaneous burning pain or if symptoms of central nociceptive sensitization are present: pinprick hyperalgesia or allodynia (brush-evoked pain).

Antiepileptic drugs have also been employed for treatment of neuropathic pain. In particular shooting pain may be an indication for these drugs. Evidence for analgesic properties in CRPS exists for gabapentin with few side effects (Mellick and Mellick, 1997). There are few convincing data for other antiepileptic drugs.

No significant data exist for other antineuropathics: NMDA-receptor antagonists, opioids or non-steroidal anti-inflammatory agents.

6.3. Treatment to be further evaluated

Calcitonin and diphosphonates effect the bone turnover. There are first studies showing a beneficial effect of both substances (Gobelet et al., 1992; Varenna et al., 2000). However, the mechanism for pain relief of both substances has first to be elucidated before they can be generally recommended.

6.4. Non-drug therapy

Although controlled studies on physical therapy in general are rare for obvious reasons, it certainly must be applied in CRPS therapy. The aim of physical therapy is to improve or maintain function and mobility of the affected extremity. Notwithstanding, it is of extreme importance that physiotherapy doesn't hurt, in order to avoid further pain stimuli. If all non-invasive therapy fails, electrical spinal cord stimulation (SCS) may be effective, even in chronic cases (Kemler et al., 2000).

7. Future perspectives

In the next years knowledge about the pathophysiology of CRPS will certainly increase; leading to a more individualized therapy. Hopefully, there will be tests to safely distinguish between the major pathophysiological mechanisms in individual patients. Most urgent we need a reliable test to discriminate between sympathetically maintained and sympathetically independent pain. Ongoing research will reveal mechanisms of neurogenic inflammation, its initiation by trauma, its contribution to post-traumatic tissue reactions, and its termination during normal wound healing. This future knowledge should help to develop targeted therapy regimes.

The presence of patients with a family history of CRPS should trigger research on one, or a group of 'CRPS genes'. If we could recognize, which patients are prone be develop CRPS, preventive treatment can be intensified after trauma.

For neuropathic pain, mechanism-oriented treatment should improve drug therapy. There are distinct mechanisms; accumulation of sodium channels, NMDA derived central sensitization, disinhibition of pain perception, which need to be explored in individual patients and then precisely treated.

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