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Regional pain syndrome: clinical characteristics, mechanisms and management

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SUMMARY

Regional soft-tissue complaints are commonplace, and they usually relate to a disease process, such as strain, inflammation or degeneration of a muscle, tendon or related muscle–tendon unit. The clinical features and investigations of the causative processes of these complaints are characteristic, and outcomes to treatments are usually predictable and satisfactory. Regional pain syndromes are different: these syndromes present with regional pain and tenderness, and other sensory symptoms unaccounted for by a simple musculoskeletal mechanistic explanation. Approved classification criteria for regional pain syndromes are lacking, and these syndromes are poorly understood and frequently misdiagnosed. Regional pain syndromes often occur after injury and overlap extensively with other musculoskeletal pain syndromes, in terms of clinical signs and symptoms. The clinician and patient are often confused about the nature of the problem and routine treatments directed to putative tissue damage will fail. Review of the epidemiology of regional pain syndromes combined with knowledge of other similar pain syndromes has enabled an evolving understanding of the condition. The musculoskeletal and central nervous systems both contribute to regional pain syndromes, through spine-related pain mechanisms and central sensitization, respectively. The patient's emotional state, particularly the effect on pain modulation, links these two systems.

KEYWORDS complex regional pain syndrome, fibromyalgia, regional pain syndrome

REVIEW CRITERIA

I searched for articles focusing on regional pain syndrome, fibromyalgia, complex regional pain syndrome, whiplash, spinal dysfunction and muscle–tendon injury in PubMed between 1960 and 2007. The search word was "regional pain", either separately or in combination with "syndrome". The full text of articles that were deemed relevant was obtained and reviewed. Cited references in these articles were searched for further articles.

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INTRODUCTION

The term 'regional pain syndrome' denotes a characteristic set of clinical features that are localized to one region of the musculoskeletal system, most commonly the low neck or back, or the upper or lower quadrant. This discussion considers regional pain syndromes involving one body region only—if multiple regions are involved, there is a less clear distinction between regional and generalized pain syndromes. Regional pain syndrome falls within a spectrum of disorders that includes complex regional pain syndrome and fibromyalgia syndrome (FMS). The syndrome is often triggered by musculoskeletal injury that occurs in the context of defined third-party safety-net schemes, such as workers' compensation, rather than in individuals who are privately employed. Similar to other pain syndromes in this setting, it is subject to much debate and controversy. Important mechanisms contributing to the clinical features of regional pain syndrome include central sensitization, referred pain, regional brain neurobiological dysfunction and emotional distress. The syndrome is common, but its clinical severity and subsequent impact on daily life varies considerably from patient to patient. Important interventions include prevention, early identification and treatment according to the management principles of chronic pain syndromes. This review focuses on upper quadrant and cervical regional pain syndrome, to examine important characteristics of the disorder.

NOMENCLATURE AND DESCRIPTORS

A pain syndrome is a predictable and characteristic collection of symptoms and clinical signs, with pain predominating, for which there is no identifiable primary nociceptive cause. In other words, there is no identifiable local or proximal tissue pathology that causes the ongoing pain. Regionalized musculoskeletal disorders that have a defined mechanism or pathophysiology, such as injury, strain, inflammation or degeneration, are not pain syndromes. The term 'regional pain

Box 1 A selection of inappropriate nomenclature used for regional pain syndromes, by region.

Upper quadrant
Repetitive strain injury or syndrome
Cumulative trauma disorder
Work-related upper limb pain
Diffuse upper limb disorder

Cervical
Whiplash-associated disorder

Lumbar
Low back pain

Box 2 Operational diagnostic criteria for regional pain syndrome.[a]

Essential features
Regional pain and allodynia:
- includes tender points within the region

Clinical features are non-neuroanatomic
Significant emotional distress

Common features
Sensory dysfunction:
- dysesthesia

Muscle dysfunction:
- tightness
- trigger points

Spine dysfunction:
- stiff
- referred sensory symptoms

Region in which signs or symptoms occur consistently links to spine

[a]Symptoms or signs occur in a regionalized body area.

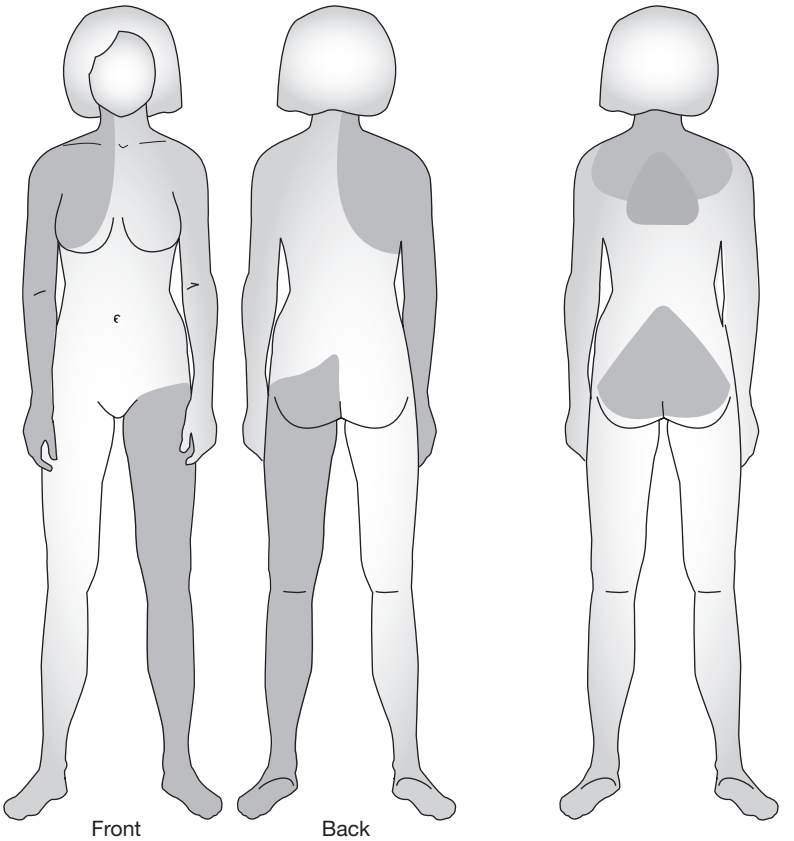

Figure 1 Common regions involved in regional pain syndromes include upper and lower quadrants, low neck and back and the interscapular region.

syndrome' is descriptive only and preferred to other evocative nomenclature that attempts to link the syndrome to a putative cause (Box 1). There is no validated classification or set of diagnostic criteria for regional pain syndrome, but operational classification criteria can be used to help diagnose this disorder (Box 2). Although many criteria for chronic pain syndromes require a symptom duration of 3 months to ensure that tissue-damage contributions are minimized, for regional pain syndrome the presence of the defined clinical features denotes the syndrome as being present. Early identification is essential for optimum management.

The pain in regional pain syndrome is regionalized rather than widespread, as in FMS, and involves a body area that links, at least in part, to the spine (Figure 1). The pain is accompanied by the key clinical sign of abnormal sensitivity to low-level stimulation, such as gentle pressure (allodynia) within the symptomatic region. These two features are essential for diagnosis.[1] A combination of other features might occur within the involved region, including segmental non-neuroanatomic dysesthesia, joint and muscle stiffness, peripheral swelling and, at times, skin-color change or sweating. The individual with the problem often feels fatigued and invariably has symptoms or signs of emotional distress. Similar to other pain syndromes, not all accompanying clinical features are present in all patients who are diagnosed with regional pain syndrome.

CLINICAL FEATURES

The clinical features of regional pain syndrome overlap with those of complex regional pain syndrome[2,3] and FMS.[4,5] Complex regional

Table 1 Similarities in clinical features of patients with common musculoskeletal pain syndromes (typical presentations).

	Pain	Allodynia	Sensory symptoms	Motor dysfunction	Emotional distress
Fibromyalgia	+	+	+	+	+
Regional pain syndrome	++	++	++	++	++
Complex regional pain syndrome	+++	+++	+++	+++	++

Abbreviations: +, mild; ++, moderate; +++, severe.

pain syndrome is arbitrarily subdivided into two types: type I, for which reflex sympathetic dystrophy syndrome was the previous descriptor among other names, and type II, which was previously described as causalgia and in which nerve damage is present. Regional pain syndrome, complex regional pain syndrome and FMS all have contributions from sensory, vasomotor, sudomotor and motor inputs, suggesting common neurophysiologic mechanisms for these disorders (Table 1).

Although there are no definitive prospective studies, it is thought that trauma or injury to a component of the muscle–tendon unit (MTU) precedes regional pain syndrome in most cases.[6–8] Typical examples include acute injury to a MTU in the neck following a motor vehicle accident[9,10]or subacute or chronic injury to an upper limb MTU component during work activity.[11] In both settings, the clinical features of regional pain syndrome are present even though there might be no evidence of ongoing tissue damage from the original trauma. The original injury heals, but regional pain persists. The mechanism of the pain in regional pain syndrome is different from the mechanism of the nociceptive pain in the original tissue damage, and this pain also has different characteristics to nociceptive pain: it is clinically out of proportion to the usual injury pain; it presents in a segmental manner, involving a wide region that has its apex at the spine and can include the whole of a limb; it is easily aggravated by activity, weather change or emotional distress; and it is often described as dull, aching, burning and distressing but can also include episodes of spontaneous sharp pain. In many cases, patients with regional pain syndrome develop widespread pain,[11,12] although the link between regional pain syndrome and FMS is still debated.[13] The area of complaint is abnormally tender to palpation from the spine to the distal part of the region, despite the common report of 'numbness' in the region.[14]

In addition to the dominant pain complaint, other common abnormal sensory phenomena include non-neuroanatomic dysesthesia and heaviness. The patient usually complains of subjective swelling, muscle tightness and vasomotor changes, including Raynaud's phenomenon, and livedo and dermatographia are common.[15,16] Emotional distress is common and psychological factors associated with distress are usually embedded in the syndrome; they are seen as triggering factors by some individuals and resultant from the predicament of regional pain syndrome by others.[17] Depression might follow and needs independent assessment.

DIFFERENTIAL DIAGNOSIS

If there is regional pain, particularly after injury, it is important to identify and treat ongoing or secondary conditions that might mimic or coexist with regional pain syndrome. The most common conditions in this setting are myofascial pain syndrome, spinal dysfunction (also known by many other names) and specific soft-tissue injuries. Although definitions of these disorders will vary with different disciplines, a standardized system of classification is used in this discussion.

Myofascial pain syndrome

Myofascial pain syndrome results from pain generated by localized areas of muscle and is identified clinically by the presence of exquisitely sensitive palpable thickening in a muscle belly, which causes both local and referred pain *sequelae* on stimulation.[18] This syndrome is commonly induced by physical activities that might cause strain or injury to a muscle group. Myofascial pain syndrome can also accompany other MTU

injuries and is commonly seen in patients with regional pain syndrome, complex regional pain syndrome and FMS. Treatment of myofascial pain syndrome focuses on physical therapy.

Spinal dysfunction

Spinal dysfunction can result from a functional abnormality of a spinal joint, disc or related MTU structure, which can cause referred spinal pain. The relevant pain-generating structure is usually a result of a minor mechanical injury, particularly postural strain. The pain is necessarily referred, in a segmental fashion, to a limb or chest wall area and hence resultant symptoms comprise non-neuroanatomic segmental pain and dysesthesia, in addition to regional tenderness. Diagnosis is determined by clinical examination, particularly palpation-elicited spinal restriction, pain and tenderness.[19] To identify a specific structural spinal abnormality, such as facet arthritis, disc prolapse or neural tissue injury, imaging is required. In typical spinal dysfunction, whereby the symptoms are the result of changes in neuromuscular function and not structure, imaging shows only the normal anatomy expected for the age of the patient. Spinal dysfunction is common in patients with regional pain syndrome and FMS, and referred spinal pain mechanisms probably contribute to the clinical features of both these syndromes.[15] Indeed, many of the clinical features of regional pain syndrome seem to be basically an exaggerated form of 'referred' spinal pain. Treatment of simple spinal dysfunction is directed to the cause, with emphasis on physical therapy.

Specific muscle–tendon unit injuries

Specific injuries to MTUs that might have precipitated the regional pain syndrome require careful clinical and imaging evaluation, to appropriately treat any unresolved tissue damage separate to the management of the pain syndrome. In the setting of regional pain syndrome, it is extremely important to avoid overinterpretation of images of soft-tissue or joint changes that relate to noninjury factors, such as age or constitution.

EPIDEMIOLOGY AND PSYCHOSOCIAL FACTORS

Epidemics of upper quadrant regional pain syndrome, for instance the Australian 'repetitive strain injury' experience of the 1980s, have highlighted the significant input of psychosocial factors, over and above the background ergonomic factors, as contributors to the pain syndrome.[11] For example, workers in the same company with higher ergonomic demand did not have higher rates of regional pain syndrome, those using the same ergonomic techniques in different locations in the same country had considerable differences in the incidence of regional pain syndrome, and those using the same work techniques in the same industry in different countries had similar symptoms, but marked differences, in disability.[20–22]

Numerous observations of regional pain syndrome have highlighted the disconnection between ergonomic factors, tissue-damage factors and syndromic pain features.[23] In a prospective study of 1,953 workers who were followed up over a period of 2 years, 8.3% developed forearm pain. Associations between pain and emotional distress or psychological factors were higher than associations between pain and ergonomic mechanical factors; the level of satisfaction with support, the influence of supervisors and colleagues and decision-making were particularly important.[24] Other studies also found that nonspecific forearm pain, as distinct from defined conditions of MTUs, is associated with high psychosocial distress, but less so than mechanical factors.[23,25–28] Similar observations relate to other regional pain syndromes.[22,29,30] Regional pain syndrome clearly shares many generic epidemiologic, clinical and psychosocial features with other chronic pain syndromes.

MECHANISMS

The exact mechanisms that result in the clinical presentation of regional pain syndrome remain uncertain; however, it is clear that they involve intertwined changes in peripheral and central pain-related neurophysiologic functions, the most important of which is central sensitization.

Central sensitization

Sensory peripheral nerves are linked to deeply placed pain-transmission neurons located in the dorsal horn. In regional pain syndrome, there is increased spontaneous activity of these neurons, which is called 'central sensitization'.[31] As a result of this process, the large myelinated afferent A-β fibers, which can also access these neurons, translate sensory mechanoreceptor function inputs into pain sensation. Thus, movement and touch, which otherwise would be innocuous, activate pain and also account for the regional pain syndrome that is a key feature of allodynia.

Referred spinal pain

As mentioned previously, many of the clinical characteristics of regional pain syndrome seem to be identical to, but are of a more intense and persistent nature than, those of simple referred spinal pain. The physical mechanisms responsible for the development of regional pain syndrome involve spinal postural inputs, such as sustained abnormal posture[32] or injury.[33] Inputs generated from deeply placed MTU spinal structures, such as ligaments or muscles, initiate the process of referred pain. If there is central sensitization, the referred pain and associated tenderness, dysesthesia and other syndromic features, such as muscle dysfunction and vascular changes, are markedly exaggerated.[34] Regional referred pain then develops in relation to the location of the involved spinal structure, whether it is placed centrally or to the right or left. This mechanism might also be relevant for abnormal physiologic sensory findings in upper limb regional pain syndrome, such as altered capsaicin-induced flare response,[35] induced dysesthesia,[36] autonomic dysfunction[37] and vibration-perception thresholds.[38] These mechanisms probably share features with those of complex regional pain syndrome and continue to be evaluated.[39]

Peripheral changes

Key peripheral abnormalities in patients with regional pain syndrome result from changes in the function of sensory, autonomic and motor nerves in the symptomatic region. Increased activity of the two afferent nociceptor fiber types (the small-diameter nonmyelinated C fibers and myelinated A-δ fibers), proprioception afferents (the large myelinated A-β fibers) and sympathetic efferents seem to result in many of the peripheral features. For example, release of proinflammatory neuropeptides, such as substance P, by activated C fibers is likely to contribute to regional neurogenic inflammation, leading to increased blood flow, edema and other features.[40]

Dorsal horn inputs

In patients with FMS, it has been proposed that inputs from injured tissue nociceptors, for example in the neck or periphery, to the dorsal horn might initiate central sensitization.[41–43] Many injuries that are associated with the onset of regional pain syndrome, however, are seemingly trivial and unlikely to cause clinically significant central sensitization by themselves, and, in addition, other patients with more severe trauma do not develop the syndrome.[42] This apparent paradox is explained by the fact that the dorsal horn pain-transmission neurons are modulated by more potent inputs than those from the periphery; these include descending brain-derived pathways that involve the neurotransmitters norepinephrine and serotonin.

The brain

These antinociceptive brain-derived pathways descend from the limbic forebrain and midbrain—the emotional part of the brain.[44] The emotional response to pain and injury might not only increase sympathetic tone, but also impact on sensitization of the spinal cord through a change in its pain modulation.[45,46] Brain changes in regional pain syndrome are likely to be similar to those seen in complex regional pain syndrome, which include expansion of pain-related limb areas that implies significant functional changes within the cerebral cortex.[47,48]

A mixture of peripheral and central interactions, of differing degrees in different patients, therefore, contributes to sensitization of the spinal cord. A central link between these processes is psychological stress. The resultant cascade of downstream events leads to the typical clinical features. Thus, although from a superficial clinical perspective the regional pain syndrome might seem to be driven from a bottom-up process (i.e. resulting from ongoing tissue damage), from a neurophysiologic perspective it is dominated by a top-down process (i.e. resulting from altered pain modulation in the brain).[44]

MEDICOLEGAL AND SOCIETAL CONSIDERATIONS

As previously mentioned, regional pain syndrome commonly occurs in the context of an injury or event associated with third-party safety-net deliberations. The prevalence of regional pain syndrome in countries in which such safety-nets are absent is unknown. The legal processes involved in compensation, disability or litigation determinations are often protracted and adversarial, and medical management can be equally inappropriate. These medicolegal aspects are central to the syndrome in many patients, result in significant stress to the individual and further aggravate the situation.[49] Approaches to this societal input vary considerably between countries and jurisdictions and cannot be easily

summarized. Each aspect of medical understanding is subject to legal interpretation in this setting, with resultant effects on outcomes. Despite this, early clinical diagnosis and better understanding of regional pain syndrome, in addition to identification of disease mechanisms, will lead to more effective management strategies and better outcomes. Importantly, known societal risk factors for regional pain syndrome must be translated into everyday preventive healthcare practices.[50]

MANAGEMENT

Once established, regional pain syndrome can be difficult to manage. There is limited evidence-based literature on therapy for regional pain syndrome. Accurate diagnosis, a label specifically incorporating the term 'pain syndrome' and careful education are essential for effective management. Of utmost importance is the need to exclude or treat other conditions that might coexist with or mimic the features of the regional pain syndrome.[51] The principles of management of regional pain syndrome are essentially the same as those of other similar pain syndromes, particularly FMS.[52] Regional pain syndrome differs, however, in that an initial triggering injury might be taken by the healthcare professional and patient alike to be the continuing source of the pain, which can result in expensive, frustrating and illogical management, with poor outcomes.[53] These predicaments often lead to emphasis on medicolegal deliberations rather than effective self-management-derived outcomes. Common management strategies are based on the four principles of education, exercise, mechanism-targeted drug therapy and psychological treatments (Box 3).[54] The patient must know that they have a potentially reversible problem; they must understand the concept of sensitization as a mechanism of their pain and recognize the input of societal constraints and personal reactions to their significant life predicament as potent stressors and amplifiers of pain-related mechanisms. The positive effect of activity, particularly aerobic fitness, on sensitization, muscle stretch and regional muscle symptoms must be emphasized. Medications shown to modulate pain in this setting include tricyclic antidepressants and related dual serotonin–norepinephrine reuptake inhibitors, in addition to drugs modulating α2–δ ligands, such as pregabalin. Opioid medication can interfere with positive psychological drive and its use must be carefully considered in this disorder. Psychological treatments are the mainstay of management and will range from commonsense explanations and pragmatic strategies, usually delivered using a team approach, through to complex cognitive-behavior programs in the minority of cases.

Box 3 Management principles for patients with regional pain syndrome.

Diagnosis and education

Consider regional pain syndrome as a possible diagnosis in high-risk situations (i.e. work or motor vehicle injury)

Ensure accurate diagnosis

Identify any unresolved nociceptive stimulus but unnecessary investigations to be avoided

Provide careful explanation of pain syndrome and indicate expected good outcome

Pharmacologic treatment

Neuroactive medication (low-dose tricyclic antidepressants, serotonin–norepinephrine re-uptake inhibitors and α2–δ ligands)

Provide analgesia: simple (e.g. acetaminophen, which might be ineffective) or complex (e.g. opioids, which are often unhelpful for sensitization pain)

Physical management

Encourage activity and involve a physical therapist

Avoid passive physical therapies

Plan resumption of normal activities

Psychological strategies

Identify and manage psychosocial stressors

Address social predicaments and involve a psychological therapist

Use a patient-centered approach

CONCLUSION

Regional pain syndrome shares many features with FMS. The significant input of spine-related pain mechanisms to clinical features in regional pain syndrome and the epidemiologic observations linking personal distress to clinical symptoms emphasize the importance of these mechanisms in FMS. Regional pain syndrome is also similar to complex regional pain syndrome: the current revised classification criteria of complex regional pain syndrome incorporate many types of regional pain syndrome.[3] Mechanistically, the role of central sensitization in these syndrome variants and the association with emotion-related brain modulatory centers suggest that there should be a shift away from peripheral interventions to psychological and self-management treatment strategies in all of these disorders. Management thus must emphasize the early identification of the syndrome, to obviate secondary pain behaviors that are often associated

with decreased function and increased symptoms, especially pain. Early intervention is associated with better outcomes. This approach will be facilitated by ongoing discussion of the classification criteria, disease mechanisms and management strategies of regional pain syndrome.

KEY POINTS

- Regional pain syndrome is characterized by regional pain and tenderness, which has a non-neuroanatomic distribution, with the symptomatic area involving the spine
- Regional pain syndrome shares clinical features with both fibromyalgia syndrome and complex regional pain syndrome
- Epidemiologic studies implicate a more significant role for psychosocial factors than ergonomic factors in these syndromes
- Central sensitization and spine-associated pain mechanisms are probably major contributors to the syndrome
- Regional pain syndrome is managed using similar approaches to those used for fibromyalgia syndrome, which address sensitization through education, neuroactive drugs, exercise and psychological techniques

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The author declared no competing interests.