Muscle-Related Temporomandibular Disorders

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Rapid developments in laboratory-based research in the past decade have provided important new insight into the cellular and molecular mechanisms of nociception. However, the integration of the new understanding into clinical practice is hampered by our inability to combine discrete and often disparate bodies of knowledge and to translate new facts into a perspective of disease-specific significance and case-specific relevance. This process is also inhibited by the current classification systems, which focus heavily on the peripheral anatomy and provide little room to incorporate new understanding of the central nervous system (CNS) in the pathogenesis of disease. If central targets become the object of treatment, crude and often invalid measures of CNS, neuroendocrine, and autonomic processes are used as justification. With the widening gap between bench top–derived research data and clinical practice, an effort needs to be made to translate the basic science frontier into meaning for patients.

The muscle-related conditions constitute the most enigmatic subset among the temporomandibular disorders (TMD). These conditions also represent the most prevalent presentations among the TMD, with at least 50% of cases falling into this category. Intense research in the past 10 years has resulted in *(1)* an improved epidemiologic and clinical description of the phenomenon; *(2)* new understanding of the molecular, neurophysiologic, and psychophysiologic mechanisms of nociception; and *(3)* the emergence of metabolic, neuroendocrinologic, and genetic findings.

Rather than focusing on the dismissal of previous etiologic constructs, this paper attempts to define what the muscle-related TMD are rather than what they are not. Special consideration is given to the large spectrum of case presentations and the fact that the more severe and persistent forms occur in women more often than in men. With this perspective in mind, the intent of this project was to develop a conceptual framework of the pathogenesis and clinical phenomenology of the muscle-related TMD.

Conceptual Framework

Although the initiating sequence of events that leads to the development of muscle-related TMD remains unknown, key attributes,

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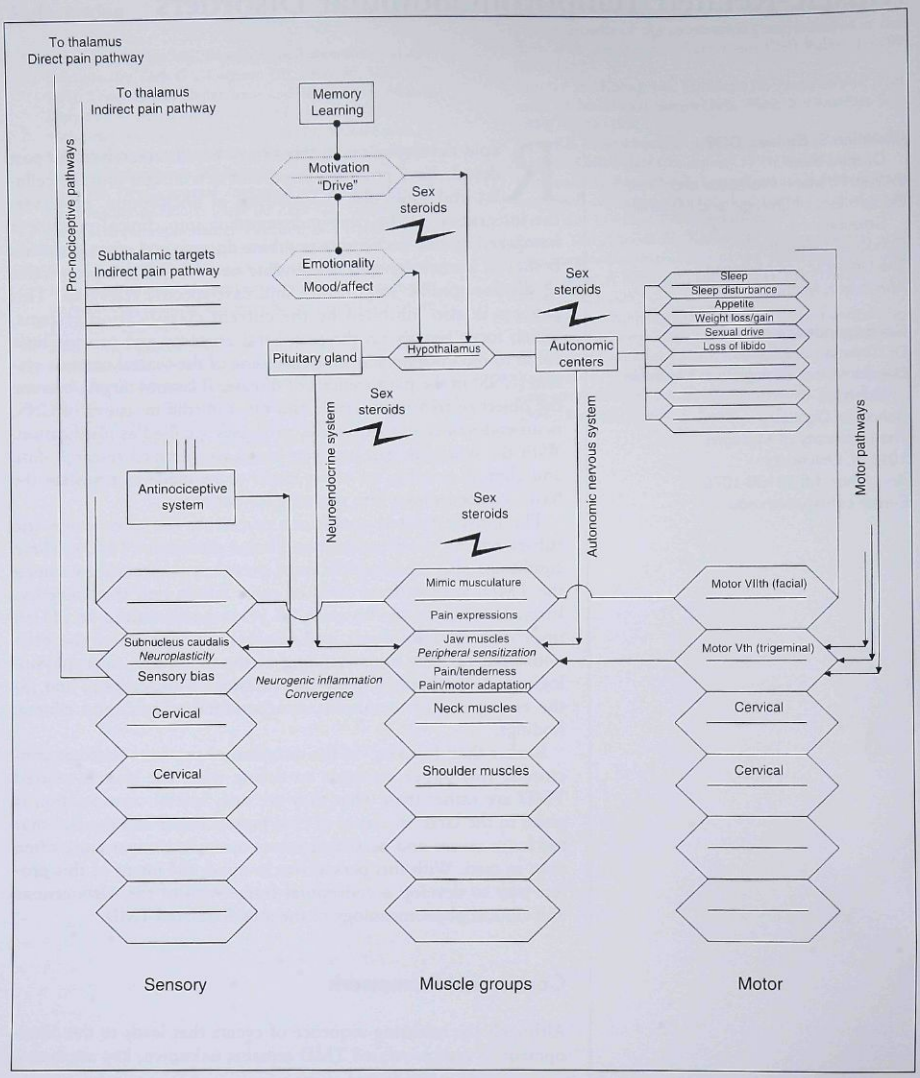

Fig 1 Explanatory model of the pathogenesis of muscle-related TMD symptoms and signs. See text for details.

such as tenderness to palpation of muscle, limitation in mandibular range of motion, perceived alteration in the dental occlusion, and changes in mood, are conceptualized as consequences of pain. Mechanisms that underlie the generation of symptoms and signs include the sensitization of peripheral tissue, central neuroplasticity and sensitization in pro-nociceptive and anti-nociceptive systems, neuroendocrine and autonomic stress effects, and the consequences of pain on motor function, emotional state, and cognition. The wide range of clinical presentations is explained by variations in the overall response or its components among individual patients. Attributes encountered in the more serious cases include sleep disturbances, weight loss or weight gain, loss of libido or drive, and memory effects. Answers to explain the vulnerability of women to, on average, greater severity and persistence of pain must be found in the modulatory effect of female hormones in peripheral and central targets, such as neuroendocrine, autonomic, and emotional centers (Fig 1).

Clinical Phenomenology

Case Definition

The muscle-related TMD should not be understood as a single, discrete disease entity. Instead, a number of related and often overlapping conditions are included under this umbrella term, with pain being the main symptom. Most muscle-related pain conditions are identified on the basis of clinical attributes; there are no biomarkers of exposure or effect that would permit both valid and reliable case ascertainment. Prevalence figures depend to a large extent on the case definition employed. As a consequence, prevalence data vary considerably from investigation to investigation. This inconsistency frequently creates confusion, particularly in discussions of treatment need.

To standardize diagnosis, the National Institute of Dental and Craniofacial Research (NIDCR), assisted by the Pain Research Group at the University of Washington, has sponsored the development of a diagnostic system for the TMD (RDC/TMD). This dual-axial system requires on Axis I a report of pain or ache in the jaw, temples, face, preauricular area, or inside the ear at rest or during function, in combination with tenderness to palpation of 3 or more of 20 palpation sites, with at least 1 of the sites being on the same side as the complaint of pain. Applicable palpation sites include the posterior temporalis, middle temporalis, anterior temporalis, origin of masseter, body of masseter, insertion point of masseter, posterior mandibular region, submandibular region, lateral pterygoid area, and tendon of the temporalis, with the right side and left side counting as separate sites. Axis II criteria serve to assess pain intensity, pain-related disability, and the presence of depression and non-specific physical symptoms.[1]

Observational Setting

Information on the muscle-related TMD is context-bound. To appreciate the breadth of the clinical spectrum, community cases and patients in primary or even tertiary care settings need to be distinguished. These broad categories of care settings would be irrelevant if there were no meaningful variation in case characteristics among subjects encountered under these different conditions. However, the occurrence of pain; its severity, spread, and impact; and the presence of comorbid conditions vary considerably among cases identified in these settings. While infrequent masticatory muscle pain, comparable to an occasional headache, represents a nuisance rather than a reason to seek care, longer-lasting pains are less likely to be neglected. Previous treatment failure and the continued persistence of pain and dysfunction characterize tertiary care cases. It is also important to recognize that the proportion of women among cases increases from community-based observations to primary and tertiary care settings, with women comprising 90% or more of patient populations in academic research centers.

Time-Varying Characteristics

Data on the time-varying nature of muscle-related TMD are limited. Only a small percentage of cases continue to be labeled as muscle conditions according to the RDC/TMD at the 1-year (23%), 3-year (13.3%), and 5-year (6.7%) follow-up examinations. Aside from the fact that more than half the cases resolve with time, only rarely do muscle-related TMD seem to persist over a period of 5 years without clinical indicators being suggestive of the involvement of the temporomandibular joint.[2]

Pain Involvement

Muscle pain conditions are often not limited to a single topographic domain. Subjects who seek advice in a dental setting may experience pain in parts of the body other than the trigeminal system; however, they are not likely to report pain outside

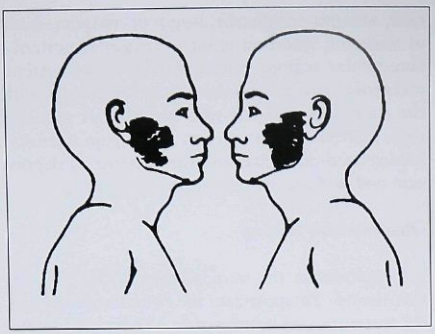

Fig 2 Pain drawing of a patient with muscle-related TMD.

the head and face to a dentist. In their chief complaint, only 29% of adult TMD patients acknowledged the presence of pain outside the head/face region.[3] Among cases encountered in academic research centers, widespread pain involvement is anything but rare. In a series of 200 consecutive female patients, only 18.5% of subjects exhibited pain that was limited to the trigeminal system. Between 55 and 60% of cases showed involvement of any or all of the cervical dermatomes C2 to C6. As far as thoracic dermatomes are concerned, spontaneous pain was noted in as many as 15 to 34% of cases. In the overwhelming majority of cases, pain was bilateral.[4]

Overlapping Pain Conditions

Because patients with 2 diseases have a greater likelihood of being referred than subjects with only 1 disease, the resulting bias produced by such differential referral to research centers could result in an overestimation of the problem of disease overlap.

Pain conditions that are often observed in combination with muscle-related TMD include headache, regional myofascial pain involving the neck and shoulders, and fibromyalgia syndrome (FMS). Myofascial pain is understood as a local-regional pain disorder, with the muscle-related TMD being a form of myofascial pain that is focused on the muscles of mastication (Fig 2). Regional pain involvement extends to the muscles of the neck and shoulder.[4] The classic text on myofascial pain associates the condition with so-called trigger points, which when "active" have been described to refer pain to specific body locations.[5] Unfortunately, most observations on the subject of trigger points are uncontrolled and subject to clinician bias. Consequently, the phenomenon of myofascial pain, despite its high prevalence and clinical significance, remains insufficiently understood.

In contrast to this local-regional muscle pain disorder, FMS is a clinical disorder that is characterized by persistent widespread pain and tenderness to 4 kg of pressure at 11 of 18 predefined anatomic sites. Pain is considered widespread when all of the following criteria are met: *(1)* left side body pain, *(2)* right side body pain, *(3)* pain above the waist, and *(4)* pain below the waist. Widespread pain must have been present for at least 3 months.[6] Emotional distress; fatigue; sleep disturbance (restlessness, insomnia, and early awakening); headache; and irritable bowel syndrome often occur in combination with the widespread pain and tenderness. About 2% of the general population, 3.5% of females (often around the onset of menopause), and 0.5% of males fulfill the criteria of FMS of the American College of Rheumatology.[7]

As in the case of TMD, community FMS patients distinguish themselves from those who seek care. Treatment-seeking FMS patients are more likely to exhibit elevated rates of psychiatric illness when compared with non–treatment-seeking subjects.[8] In fact, the disabling nature of FMS is responsible for 9% of all long-term disability claims of a major Canadian life insurance company, with annual payments of about $200 million (Canadian) about 10 years ago.[9] As far as the relationship of FMS to muscle-related TMD is concerned, recent studies performed in academic research centers have shown significant overlap of the 2 conditions.[10–12] According to Plesh and coworkers,[10] 75% of FMS patients had TMD, while on the other hand, 18% of cases with TMD met the diagnostic criteria for FMS.

The diagnostic system of the International Headache Society classifies headaches based on the clinical features of individual episodes.[13] To be classified as a tension-type headache, a minimum of 10 headaches of mild to moderate intensity and bilateral pain distribution, lasting from 30 minutes to 7 days, is required. The key diagnostic feature of migraine consists of the experience of at least 5 unilateral headache attacks that last between 4 and 72 hours. Population-based and clinic-based studies indicate that women are more often affected than men for these types of headache in terms of frequency, duration, and severity (for review, see Unruh[14]).

Many epidemiologic studies report a high association between the TMD and the 2 most common types of headache, tension-type and migraine.[15] Because of this association, some authors go as far as considering headache part of the symptom complex of TMD.[16] As far as overlapping signs between the TMD and these types of headache are concerned, there is a greater chance for a subject to exhibit pericranial muscle tenderness when affected by tension-type headache than by migraine headache.[17,18] With tenderness to palpation being another essential diagnostic feature of the muscle-related TMD, it becomes obvious that the boundary between these types of headache and the muscle-related TMD is indistinct.

Susceptibility Risk

Variations in prevalence rates of muscle-related TMD among different populations often provide insight into their etiopathogenesis. Unlike most chronic pain conditions, for which the relative importance of chronic illnesses and their impact on functional limitation increases as subjects age, the muscle-related TMD represent an exception. Prevalence rates are lower among older subjects, and the initial onset in both males and females is more likely to occur before age 50 than later in life. However, this does not mean that severe symptoms cannot occur later in life.[19]

More recent studies that focus on TMD types rather than individual signs and symptoms indicate that more women than men are affected by facial pain. Among women, prevalence rates are higher for subjects of reproductive age than subjects in postmenopausal years.[20,21] Chances of seeking treatment increase by 77% with the use of supplemental estrogen in the postmenopausal years, or by 19% in subjects using oral contraceptives.[22] Pain on palpation of masticatory muscles is significantly more prevalent among women than men.[23] In children and young adults, gender differences are not clear.[24,25] With respect to gender effects observed in persistent pain conditions involving tissues adjacent to the face, women also have higher prevalence rates for chronic tension headache and neck pain (for review, see Unruh[14]).

Aside from age, sex, and the use of estrogen supplements there are no other factors consistently reported as increasing the susceptibility risk for the muscle-related TMD and any of the related pain conditions. Cross-culturally, no differences appear to exist: the muscle-related TMD represent about 50% of both United States and Swedish TMD cases.[26] Thus far, race and socioeconomic status do not appear to be an issue. According to the 1989 National Health Interview Survey in the United States, prevalence rates for facial and jaw pain were 7% for whites and 5% for blacks (not of Hispanic origin).[27]

Increasing awareness of the genetic contribution to disease has stimulated discussion about the potential role of genes. The underlying concept states that in a genetically predisposed individual, *(1)* susceptibility to the disease itself, *(2)* susceptibility to follow a particular clinical course, or *(3)* susceptibility to a varying response to treatment is determined by polymorphism affecting DNA sequences of (mostly several) genes. It is estimated that about 30% of enzyme loci exhibit polymorphism, with subtle differences forming the basis of altered enzymatic activity when compared to the standard enzyme. However, the genetic contribution to susceptibility to muscle-related TMD has not been subject to systematic research by genetic epidemiologists, and data on the related pain conditions are limited as well. Whether the observed familial aggregation in FMS patients is due to genetic influence or a common family environment cannot be resolved with certainty at this time.[28]

Although the role of genetic factors is in question, one recent finding is worth mentioning because it points to the possibility of genetic susceptibility at the target site of a variety of drugs that exhibit modest pain relief in conditions of persistent muscle pain. Polymorphism in the serotonin transporter gene regulatory promoter region has been linked to anxiety-related traits.[29] The serotonin transporter is responsible for the inactivation of the serotonin release in the synaptic cleft. Drug-induced enhancement of the serotonergic transmission, on the other hand, has been associated with the amelioration of depression, anxiety, and pain. Whether this finding has any relevance in the muscle-related TMD remains to be seen.

Causation and Pathogenesis

Causation Models

Biologic, familial, chemical, physical, occupational, and psychosocial factors have been considered as potential causes of muscle-related TMD; however, no necessary or sufficient cause has been identified. The possibility that muscle-related TMD are composed of subtypes that are etiologically distinct cannot be excluded. There is also no reason to assume a common etiology for muscle-related TMD and other related pain conditions,

even though these conditions may share common downstream effects.

Proposed causation models range from simple unifactorial to complex biopsychosocial models of stressors and predisposition. Popular unifactorial models assume that serotonin deficiency is pivotal to these muscle pain conditions, or that muscle hyperactivity due to structural or psychologic abnormality initiates a vicious circle of persistent pain and dysfunction. Many assumptions underlying popular causal models are missing either the key evidence in their support or oversimplify the role of the CNS to an extent that the construct no longer gives justice to the biologic substrate. More realistic constructs that are based on the deficient modulation of nociceptive and anti-nociceptive information or the dysfunction of the hypothalamic-pituitary-adrenal system (HPA) are based on circumstantial evidence in support of the assumption of cause and effect. No single model of the causation of muscle-related TMD has emerged as being the most valid at this time.

Peripheral Sensitization

There is a lowered response threshold of nociceptors to mechanical and thermal stimuli in the state of inflammation or tissue damage. This so-called peripheral sensitization of nociceptive afferents[30] is in contrast to the adaptive changes that occur in other somatosensory systems with continued stimulus presentation. The altered response characteristic is attributed to a range of chemical mediators that are released from damaged tissue cells, mast cells, platelets, or the nociceptors themselves, and can either activate (eg, histamine, bradykinin, serotonin, potassium) or sensitize (eg, substance P, prostaglandins, leukotrienes) free nerve endings.[30,31] Nociceptors can also be activated by sympathetic stimulation following sensitization by an injury or inflammation.[32] Increasing the complexity of possible interactions, newer data suggest that endogenous opioid peptides are synthesized by inflammatory cells, which may be a mechanism by which anti-nociception is exerted in peripheral tissues.[33,34]

In the context of peripheral sensitization, increasing interest focuses on nerve growth factor (NGF) as a mediator in persistent muscle pain.[35] Besides the role of NGF as a target-derived trophic factor in early ontogeny, it was shown that small adult primary sensory neurons, particularly those that contain calcitonin gene-related peptide, express the high-affinity NGF receptor trkA. Systemic application of NGF causes hyperalgesia in both neonatal and adult rats.[36] Pretreatment with NGF antibody reduces or prevents carrageenan-induced arthritis in rats.[37] Because healthy volunteers developed pain in the bulbar, jaw, and truncal musculature following intravenous injection of NGF, this secretory protein appears to be important in the pathogenesis of muscle-related TMD. Human volunteers injected with NGF described the experience as "muscle overuse pain," and women seemed to experience pain for a longer time than men.[38] Indeed, estrogen has been shown to up-regulate trkA messenger RNA and thereby to affect the efficiency of NGF binding.[39] This could be one of a number of reasons for the increased persistence and severity of muscle pain conditions among women.

Nerve growth factor has also been shown to stimulate the production of substance P, somatostatin, and vasoactive intestinal polypeptide in sensory neurons and affects inflammatory cells that express the trkA receptor, such as mast cells. Because mast cells are known to exist in the perimysium of muscle, and mast cell degranulation has been shown to occur in muscle soreness following strenuous muscle work, there is a real possibility that NGF-related peripheral effects contribute to clinical muscle pain conditions.

Central Neuroplasticity and Sensitization

There is great benefit to be gained from conceptualizing the clinical muscle pain conditions in the context of neuroplasticity and central sensitization.[30] Regarding neuroplasticity, a distinction is made between neural and behavioral plasticity. Neuroplasticity refers to the reorganization of the nervous system based on mechanisms that influence synaptic efficacy and connectivity at all levels of the brain. Both short-term (lasting minutes) and long-term (lasting for hours and longer) changes are distinguished. Examples of behavioral plasticity include sensitization, habituation, and rehabilitation. Sensitization describes the phenomenon of an enhanced behavioral response; habituation, on the other hand, refers to the decrease in the behavioral response with repeated stimulus applications. At the level of cellular networks, a decrease in the synaptic strength forms the basis of habituation, whereas sensitization involves the greater availability of excitatory neurotransmitter in the synaptic cleft. Neuroplasticity and sensitization provide the basis for matching the response to the local condition in terms of injury detection, pain avoidance, pain escape, and the need for rest of the injured body part to promote recuperation.[40] Although

neuroplasticity and sensitization have a sense of purpose in the context of survival function, the very same mechanisms seem to be involved in the generation of symptoms and signs that dominate the clinical picture of muscle-related TMD.

With their first synapse, nociceptive afferents arising from the jaw and neck musculature connect to projection neurons and inhibitory or excitatory interneurons. The significant convergence of afferent input at this level explains the spread and referral of pain.[30,41] In addition to nociceptive input, non-nociceptive afferents and descending anti-nociceptive systems may influence the excitability of these neurons as well. Different neurotransmitters (eg, glutamate, aspartate, and substance P) are implicated in evoking both fast and slow synaptic potentials by acting on NMDA, AMPA, and neurokinin-1 receptors.[30] Among the excitatory neurotransmitters, substance P, an 11-amino-acid neuropeptide, has been receiving most attention because of its perceived relevance in conditions of persistent muscle pain. Studies in humans have shown that substance P levels in the cerebrospinal fluid are elevated in FMS patients when compared with controls.[42] Allodynia (see below), which is a key feature of muscle-related TMD, is associated with increased excitability of rat dorsal horn neurons during spinal cord superfusion with substance P.[43] The increased excitability that is paralleled by enlargement of mechanoreceptive fields of the second-order neurons is an expression of the inflammation-induced neuroplasticity.[30,44–46]

Pro-Nociceptive Pathways

Nociceptive information arising from the muscles of the head and neck is relayed via the spinal cord and corresponding structures of the trigeminal brain stem complex to subcortical and cortical centers.[30] A direct pathway, which connects with nuclei in the lateral part of the thalamus, is primarily made up of ascending input from spinal or trigeminal laminae I and V. Deeper layers (laminae VI, VII, and VIII) contribute to an indirect pain pathway, which targets the reticular formation before establishing a connection with nuclei in the medial portion of the thalamus. The latter system is implicated in influencing hormone release from the hypothalamus and pituitary gland and is known to affect supraspinal autonomic reflexes. It is increasingly clear that the neurosecretory function of a particular cell type is not regulated by a single neurotransmitter. Instead, the response of hypothalamic neurosecretory cells is dependent on a combination of neurotransmitters, with hormones acting as modulators. Evidence further suggests that the lateral or direct pathway carries predominantly the sensory-discriminative information of pain, while the indirect or medial pain pathway is associated with more affective-motivational aspects of pain. At the cortical level, the primary somatosensory cortex is the target of the sensory-discriminative information content of pain, and there is evidence that the frontal lobe is linked to pain and unpleasantness. All this is relevant because certain therapies have been shown to exert differential effects in these 2 systems.[47]

Anti-Nociceptive Pathways

Descending inhibitory influences are exerted from the cortex, diencephalon, areas such as the periaqueductal gray and periventricular gray in the midbrain, and the medulla on nociceptive neurons in the subnucleus caudalis or spinal dorsal horn.[30] Nociceptive neurons with input predominantly from deep tissues appear to be especially influenced by such descending control, with the evidence further suggesting that the anti-nociceptive influences are greater in tonic pain than in acute pain.[48,49] Endogenous opioid peptides and serotonin are implicated in mediating these inhibitory, anti-nociceptive effects. High levels of substance P in the spinal cord are associated with low brain serotonin levels in rats.[50,51] In humans, low concentrations of endogenous opioids in the cerebrospinal fluid have been reported in persistent painful neuropathy.[52] Antidepressants that demonstrate an analgesic effect when compared with placebo are believed to exert this influence by facilitating pain-inhibiting pathways.

Neuroendocrine and Autonomic Stress Response

Because abnormality in neuroendocrine function exists in depressed persons, it has been suggested that stress-induced dysfunction of the HPA system is a factor in FMS and possibly other related pain conditions in which depressive symptoms are prevalent. As far as stress is concerned, 2 major response patterns are distinguished. The acute response supports the defense reaction; the chronic response pattern elicits a vigilance reaction. Complex neuroendocrine and autonomic mechanisms are in effect to influence any stress-induced deviation from homeostasis, with the hypothalamus forming the major link between the CNS, the HPA axis, and the supraspinal autonomic reflex centers.

Environmental stimuli and emotional and cognitive factors influence the hypothalamic neurosecretory cells that regulate the release of neurohormones (eg, corticotropin-releasing hormone), which in turn affect the synthesis of hormones by the pituitary gland. Synthesis of peripheral hormones, such as cortisol from the adrenal cortex, is under pituitary control by way of adrenocorticotropin. To increase complexity, hypothalamic and pituitary neurohormones have not only peripheral but also central targets, which include altering the expression of neurotransmitter receptors and thereby affecting the neural regulation of autonomic reflexes, behavior, and emotional states. For example, corticotropin-releasing hormone is implicated in increasing arousal and emotionality, and adrenocorticotropin facilitates attention. On the other hand, inputs from the cerebrospinal fluid and circulatory system (hormones, neuropeptides, etc) function as feedback signals that affect the release of neurotransmitters and adjust the hypothalamic release of neurohormones.

In view of stress being a poorly defined construct and the highly interactive nature of the neuroendocrine system, cause-effect questions are difficult to resolve in clinical cases of muscle pain. Insight into the role of the HPA axis is further complicated by the fact that cortisol is secreted in a circadian rhythm, with the lowest levels occurring at midnight and the highest levels at about 8 in the morning, calling for hourly sampling to track levels in serum. Because newer findings also suggest that the nature of the HPA system response is specific for a particular type of stressor, greater care is applicable in the synthesis of the literature. If the current stress construct, which is based on the assumption of non-specificity in the response to a wide range of stressors, is no longer valid, many generalizations about catecholaminergic activation are no longer appropriate. Although neuroendocrine functions appear to be highly relevant in muscle-related TMD, detailed studies of the nature of their contribution to the pathogenesis of symptoms and signs in the TMD are not yet available.

Diagnostic Criteria and Classification

Classification

Layzer[53] proposes a diagnostic system that is applicable to the broad range of medical muscle pain presentations and that divides the painful muscle conditions into focal and generalized manifestations. Focal presentations of muscle pain are further divided into 2 categories, based on whether muscle enlargement or induration is present. Focal muscle pain with swelling includes conditions such as neoplasm, trauma (hematoma), thrombophlebitis, infection (eg, streptococcal myositis, painful leg in children with influenza), inflammation (eg, eosinophilic fascitis), ischemia, toxic and metabolic disorders, and motor unit hyperactivity states (eg, stiff-man syndrome, tetanus). These relatively rare conditions need to be distinguished from myofascial pain in general, or specifically the muscle-related TMD that do not exhibit clear evidence of swelling. The RDC/TMD, which deal with the most common painful masticatory muscle conditions, require the user to rule out muscle spasm, myositis, and contracture from conditions covered under the umbrella term of TMD.

Current classification systems categorize clinical TMD entities and subtypes, such as muscle-related TMD, according to the presence or absence of clinical features. Pain or ache in the jaw, temples, face, preauricular area, or inside the ear at rest or during function, in combination with tenderness to palpation of 3 or more of 20 palpation sites with at least 1 of the sites being on the same side as the complaint of pain, must be present to be diagnosed as TMD. Although a categorical classification system works well if discrete clinical features are available, limitations become apparent for symptoms and signs that recur in more than 1 class or subset.

The need for additional axes for the classification of muscle-related TMD arises from the fact that pain is a multidimensional experience. In this respect, pain intensity, affect, and pain-related disability are captured on a second axis in the RDC/TMD, which happens to be a controversial feature because, based on the line of questions, patients often assume that the provider thinks that the problem is in the patient's head. However, information on the affective-motivational meaning of pain and its impact provides information on the central state and offers valuable data for the management of selected features. It should also prevent the unsuccessfully managed case from being treated with methods that are more appropriate for acute pain than persistent pain.

Muscle Pain

Terms such as *analgesia, referred pain, allodynia,* and *hyperalgesia* are often used in the context of clinical descriptions of deep somatic and visceral

pain states. *Analgesia* refers to the absence or reduced pain experience of a normally painful stimulus. *Referred pain* represents pain that is either adjacent to, or at a distance from, the site of its cause. According to the International Association for the Study of Pain, *hyperalgesia* refers to the state of increased pain responsivity to a stimulus that is normally perceived as painful, while *allodynia* describes the state in which pain is perceived in response to a stimulus that is normally not painful.[54] Hyperalgesia and allodynia often coexist, and in the context of acute pain they are understood to have survival value by amplifying protective reflexes and promoting immobilization after injury.[55] Pain referral, allodynia, and hyperalgesia also constitute the dominant clinical features of persistent muscle pain states; however, their purpose is unclear.

With respect to muscle pain, temporal and spatial aspects of pain need to be distinguished. Persistent forms are more likely encountered in a clinical context because of their obvious impact on patients. Chronic (muscle) pain contains an element of permanency, as reflected in the explanatory expressions used by many authors, eg, "for a long period," "prolonged period," "a long time course," or "ongoing/never-ending." In this respect, chronic muscle pain, by implication and by its very nature, is either extremely resistant to treatment or never completely relieved. Pain is often described as "aching," "tight," "throbbing," "tender," "exhausting," or "nagging" and is known to fluctuate in intensity over time. However, the sensory and affective meaning of persistent muscle-related TMD pain does not require months to develop. Experimentally induced and maintained bilateral masseter muscle pain exhibits indistinguishable sensory and affective properties from the clinical correlate of chronic pain.[56] With the unclear boundaries between acute and persistent pain and the understanding that different treatment approaches are required for the 2 conditions, it is left to the clinician to make a guess without a validated approach in place that facilitates reliable and useful decision-making.

As far as the spatial distribution of pain is concerned, there is a wide range that satisfies the RDC/TMD. Local forms exhibit muscle pain limited to trigeminal dermatomes, while regional presentations demonstrate the additional involvement of cervical dermatomes. Patients with widespread pain report additional muscle pain in locations other than the head, neck, and shoulder, and a portion of these patients fulfill the diagnostic criteria of FMS. Comparisons between groups of patients with FMS, widespread myalgia, or regional myalgia show that unspecific symptoms, such as sleep disturbance, subjective swelling, intolerance to cold and exercise, and self-report of a worsening physical condition, are more prevalent in FMS than in the others.[57]

Regional pain distributions can be conceptualized by mechanisms responsible for the radiation and spread of pain, such as *(1)* branching of primary afferent neurons in the periphery, *(2)* the convergence of superficial and deep inputs onto the same projection neurons, and *(3)* central neuroplastic changes that occur with continued nociceptive barrage. For heterotopic pain, most authors assume that dysregulation of anti-nociceptive systems is responsible for a generalized heightened pain experience. However, the heterotopic pain presentations are not easily explained by the distribution of terminations of the anti-nociceptive system at trigeminal and spinal levels. Peripheral sensitizing mechanisms must likely be contributory to the pathogenesis of heterotopic pain distributions, given the strong predilection of particular muscle groups.

Tenderness to Palpation

If pain on palpation is a key component in the assessment of muscle-related TMD and related muscle pain conditions, it is essential to follow protocol to ensure reproducible and reliable measurement. The examiner should keep in mind that diagnostic assignment is probabilistic and based on counts of pressure-pain reports at specified sites of measurement. As far as the TMD are concerned, palpation sites are clearly specified in the RDC/TMD. For FMS, the American College of Rheumatology criteria describe the examination sites as well. Examiners are instructed in the RDC/TMD to use the fingertips of the index and third fingers (or the spade-like pad of the distal phalanx of the index finger only) to press on specific muscle sites with 2 lbs. of pressure and with the muscle in a relaxed state. The patient is requested to indicate whether the palpation hurts or whether he or she simply feels pressure. If it hurts, he or she is asked to report whether the pressure-pain is mild, moderate, or severe. During palpation, the opposite hand should brace the head to provide stability.

The examiner should be reminded that a more general lowering of thresholds at non-painful sites parallels pressure allodynia observed at sites of spontaneous pain in FMS.[58] Lowered pressure-

pain thresholds do not seem to be limited to muscle, at least in FMS. Skin-fold tenderness and pressure-pain thresholds over bone are lower in FMS patients than in controls, and the phenomenon is observed irrespective of whether or not spontaneous pain is felt at the examination site.[59] Unfortunately, data on myofascial pain conditions, including the muscle-related TMD, are inconclusive on this subject. However, it appears that generalized pressure-pain sensitivity extending beyond the site of painful involvement is not present.

Changes in Motor Function

Pain has general effects on motor function, including changes in facial expression and body posture and a tendency to avoid movements or to perform them more slowly. Pain also lowers the ability to work against heavy loads and makes it difficult to move quickly. The biologic advantages are obvious. The inability to contract muscles forcefully and rapidly limits further damage to the body, while the typical facial expressions and gestures of pain are signals to others that the person is in pain, is suffering, and is in need of help and sympathy.[60]

The control of muscles of the painful body part is affected in specific ways that are probably not dependent on the type of tissue in which pain arises. The activity of the agonist muscles is diminished, while the antagonist become slightly more active.[60] Heavy pressure on the periosteum of the zygoma reduces the frequency, amplitude, and velocity of mastication caused by electrical stimulation of the corticobulbar tracts of decerebrate rabbits.[61] Pain-induced changes in mandibular posture form the basis for the patient's perception of being disturbed by teeth not fitting together properly.[62]

Changes in Mood

The sustained mood change constitutes the symptom; affect describes the observable sign associated with a particular state of mood. Cognitive and motivational changes are reflected in the patient's thoughts; a change in the overall emotional state is expressed in the subject's mood. By the very nature of chronic conditions to be of long and continuous duration, and because current treatments leave much to be desired, interruption in lifestyle is often unavoidable.[63] Changes in mood are not surprising, given the fact that patients with persistent pain recognize that their current quality of life is much lower than it was. Anger, frustration, fear, sadness, tension, worry, and irritability constitute the most prevalent negative mood types in persistent and severe pain.[64,65] Symptoms of depression are numerous and include changes in appetite, sleep disturbances, weight variations, decreased sexual drive, anxiety, loss of interest, and/or decreased ability to concentrate.

Women are much more vulnerable to mood disorders and are twice as likely as men to develop depression. The significance of sex differences in terms of emotionality and neuroendocrine and autonomic function becomes clear when examining the distribution of estrogen receptors in the brain. The highest densities of estrogen receptors are observed in areas that are involved in shaping the pain response, such as the amygdala, pituitary gland, and hippocampus.[66] The vulnerability of women to greater severity and persistence of pain needs to be better understood in the context of the modulatory effect of female hormones exerting their effect at various levels of the CNS, as well as in peripheral tissues.

Conclusions

The clinical features of the muscle-related TMD, such as tenderness to pressure applied to muscle, limited range of mandibular motion, perceived changes in the dental occlusion, and mood alterations, can be explained as direct consequences of pain. The mechanisms underlying the pathogenesis of these symptoms and signs include *(1)* sensitization of peripheral tissues, *(2)* neuroplasticity in pro-nociceptive and anti-nociceptive circuits, and *(3)* the behavioral sensitization associated with increased emotionality and with pain-specific neuroendocrine and autonomic responsivity. It is the differential contribution of these mechanisms that can explain the significant variation in individual case presentations. The increased vulnerability of women in terms of prevalence, and the severity and persistence of muscle-related TMD pain, could be accounted for by the modulatory effects of female hormones acting on these pain response systems.

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