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Disturbances of Pain Perception in Temporomandibular Pain Syndrome

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INTRODUCTION

Musculoskeletal pain affecting the orofacial region is quite prevalent and has frequently been reported throughout the developed world (Dworkin and Ohrbach 2001). Common TMD symptoms include spontaneous pain in the area of the ear, the temporomandibular joint, or the muscles of mastication, physical limitations or irregularities in jaw movement, and clicking and popping noises in the temporomandibular joint during jaw function. Referred head and neck pain and tooth wear may also occur.

Disorders involving the temporomandibular joint and/or the muscles involved in mastication have been called by such terms as temporomandibular pain and dysfunction syndrome, myofascial pain dysfunction syndrome, temporomandibular joint dysfunction, and craniomandibular disorder. However, because each of these disorders involves similar clinical signs and symptoms, the American Dental Association, in1983, recommended that the more general term, temporomandibular disorders (TMD), be utilized to describe disturbances of the masticatory system. TMD is an all encompassing term and is preferred by many researchers because it is neutral in regards to the potential etiology and pathology of the disorder (Dworkin 1999).

EPIDEMIOLOGY

Temporomandibular disorders are frequently seen in nonpatient samples. Although Sharav and Benoliel (Sharav and Benoliel 1993) estimated that as much as 60–70% of the population

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displays individual symptoms of TMD, significantly fewer individuals require treatment. As such, the prevalence rate of TMD is estimated at approximately 12% in the adult population (Von Korff et al. 1988a). Longitudinal studies indicate that over time, there is significant fluctuation in TMD signs and symptoms (Magnusson 1986), and studies specifically examining elderly populations have indicated that reports of the signs and symptoms associated with TMD tend to decrease with age (Ow et al. 1995).

Epidemiological studies indicate that females demonstrate a much higher prevalence of the disorder. In fact, TMD has been estimated to be approximately two to three times more common in women than men (LeResche 1997b). TMD appears to be most prevalent among women in their childbearing years (LeResche et al. 1997d), although gender differences are present in epidemiological studies with pediatric populations as well. Potential explanations offered to account for the over-representation of females in TMD patient samples include increased treatment seeking by women and their greater pain sensitivity and monitoring of bodily symptoms (Dworkin et al. 1990). Endogenous female reproductive hormones have also been implicated as potential contributors to the etiology of TMD (LeResche et al. 1997c).

CLASSIFICATION

The Research Diagnostic Criteria for TMD (RDC/TMD) (Dworkin and LeResche 1992) has become the standard system for the classification of TMD. It is a multiaxial system that assesses both physical and psychological characteristics of individuals with the disorder. Axis I examines the physical domain and allows for differential diagnosis of the numerous physical characteristics of TMD. Assessment of this axis involves examining the site of pain, range of mandibular motion, temporomandibular joint sounds, temporomandibular joint imaging, and pain or tenderness of the muscle and joint upon palpation. The RDC/TMD Axis I diagnostic groups include muscle disorders, disc displacements, and other joint conditions (arthralgia, arthritis, arthrosis).

The second axis of the RDC/TMD examines patients' pain-related disability, psychological status, and level of psychosocial adaptation. This axis is assessed through a self-report questionnaire, with particular attention being paid to levels of pain, disability, depression, anxiety, somatization, and the psychosocial impact of TMD.

The RDC/TMD has demonstrated reliability and validity in both adult and pediatric populations (Turk and Rudy 1995; Wahlund et al. 1998). Its value as a comprehensive assessment and diagnostic tool for orofacial pain disorders (Dworkin and Ohrbach 2001), suggests that it should serve as a model for the assessment of other pain conditions.

CONTRASTING CONCEPTS

Despite the large number of studies that have been conducted on TMD, we are still at a very early stage in understanding the biological and psychosocial factors that underlie the disorder. There are many reasons for this: lack of theoretical models, heterogeneity of symptoms, overlap with other disorders, poor understanding of individual differences, inadequate communication between clinical and academic researchers, restricted funding for dental care, and limited access to newer neuroimaging and other diagnostic instruments.

REGIONAL OR WIDESPREAD DISORDER

Woolf et al. (Woolf et al. 1998) called for a move away from the traditional organ or system based classification system for pain to one established on the basis of the underlying biological mechanisms. By its very name, TMD has been considered to be localized to the face, but there are important reasons to question whether the pathophysiology is centered in that region. If TMD reflects a general pain disorder (whose nature is still to be established) rather than simply a regional one, we would expect to see increased responsiveness to noxious stimuli throughout the body. A number of studies have examined this issue.

Malow, Grimm, and Olson (Malow et al. 1980) examined the sensitivity and response bias of individuals presenting with TMD. Using a focal pressure stimulator on the arm, they found that, compared to normal control subjects, TMD patients had significantly lower pain thresholds and were more likely to report the experimental stimuli as painful. Testing at the forearm, Maixner et al. (Maixner et al. 1995) found that TMD patients had lower thermal pain and tolerance thresholds, as well as markedly shorter latencies before ischemic pain onset and tolerance. This group (Fillingim et al. 1996) subsequently found that those TMD patients who exhibited the highest sensitivity to the ischemic pain task also had greater levels of clinical pain. While they favored the notion of an impaired central inhibitory system, the finding that the more pain sensitive patients also rated innocuous visual stimuli as more intense indicated that a style of hypervigilance (Rollman and Lautenbacher 1993; McDermid et al. 1996a; Naliboff et al. 1997b), influencing attention and amplification of perceptual stimuli could also account for the data.

Maixner et al. (Maixner et al. 1998) compared TMD patients and matched controls for the intensity and time course of pain evoked on the face and forearm by a series of noxious thermal pulses. As well, they tested the temporal summation of C-fiber-mediated pain by applying brief trains of noxious heat pulses to the palm. In all tests, the patients showed heightened reactivity, leading the authors to conclude that there may be alterations in central nervous system processes underlying the enhanced pain sensitivity observed in TMD patients.

Not all studies, however, have found that TMD patients are more sensitive or reactive to experimentally-induced pain presented at sites other than the face. Numerous studies reported no group differences (Sharav et al. 1982; Davidson and Gale 1983; Moss and Adams 1984; Xie and Hampf 1994), although they typically had very small samples. Interestingly each of these investigations assessed pain perception utilizing electrical, ischemic, or thermal stimulation, rather than pressure pain. Svensson et al. (Svensson et al. 2001) suggested that most investigations which failed to find differences between TMD patients and controls for pain threshold determinations outside the trigeminal region presented phasic stimuli and that a longer lasting tonic stimulus, which more closely mimics clinical pain, might provide a better test of altered pain processing.

Accordingly, Svensson et al. utilized both phasic and tonic experimental pain stimuli to test pain reactivity of TMD patients and controls within and outside the craniofacial region. Two forms of phasic pain were utilized, pressure and heat, each applied to the masseter muscle of the face and the anterior tibialis muscle of the lower leg. The tonic pain was induced by injections of hypertonic saline into these same regions. The outcome was not straightforward. TMD patients were more responsive than control subjects to pressure stimulation at both regions, but there were no group differences in response to noxious heat. Likewise, the TMD patients found that the hypertonic saline infusion at the face created more pain than did controls, but there were no

group differences for tonic stimulation of the anterior tibialis. The data appear to suggest that TMD patients are more responsive to muscle stimulation, whether by pressure or hypertonic saline, especially in the face. The increased response by patients to phasic pressure stimulation of the deep tissue on the leg is compatible with the notion that they show a broad zone of heightened pain reaction, but the absence of a similar effect for heat or tonic stimulation of the leg restricts that conclusion.

It should be added, however, that the clinical complaints of TMD patients are not necessarily limited to the craniofacial region. When asked where on the body they have persistent pain, the patients in Svensson et al.'s sample were much more likely than the controls to report pain at the neck, shoulders, arms, chest, back, and legs, in addition to the face and head. Turp et al. (Turp et al. 1997; Turp et al. 1998) described similar findings. Such pervasive pain (and the considerable overlap between TMD and fibromyalgia) suggests that although TMD is generally labeled a regional pain syndrome, it should be considered a widespread pain disorder with particular discomfort in the orofacial region.

There is some disagreement about whether pressure pain thresholds are lower on the side of the face which the patient finds more painful or whether it is bilaterally lower than that of control subjects. Ohrbach and Gale (Ohrbach and Gale 1989) and Reid et al. (Reid et al. 1994) reported low pain thresholds on both sides, findings which support a theory that TMD involves a centrally-mediated pain disturbance. Conversely, Farella et al. (Farella et al. 2000) found that the threshold was lower on the more painful site, an outcome more in line with a localized inflammatory state. However, the side of face difference was quite small compared to the difference between the patients and controls; while there may be both central and peripheral mechanisms which distinguish them, the first of these seems much the more important one.

Additional evidence for dual modes of pain modulation in TMD comes from a recent study by Romaniello et al. (Romaniello et al. 2002). They induced two forms of pain in healthy volunteers: tonic muscle pain in the left masseter muscle by infusion of hypertonic saline or topical skin pain at the left cheek by the application of capsaicin. CO_2-laser stimulators delivered heat pulses to the perioral region on both the painful and non-painful side. The magnitudes of cortical evoked potentials to stimulation on either side were reduced by both forms of unilateral pain. Likewise, the experimentally-induced pain from either muscle or skin caused diminished suppression of brainstem reflex responses, measured by bilateral electromyographic activity over the masseter region. The findings suggest that there are both segmental and suprasegmental regulatory mechanisms of facial pain which may function interdependently.

The results of a study of stimulus-response curves for varying levels of pressure over the masseter muscle and the index finger emphasize that local factors should not be underplayed. Svensson et al. (Svensson et al. 1995) noted that the slopes of such curves obtained on the face of TMD patients were markedly steeper than those for matched control subjects, while there were no differences between the groups for pressure at the finger. Injection of 5% saline into the masseter muscles of controls caused the slopes of their curves to become significantly steeper. These findings could point to a peripheral disturbance in TMD or to a more central effect initiated by the induction of experimental hyperalgesia.

RESPONSE TO NON-NOXIOUS STIMULI

A number of recent reports have examined the relationship between muscle pain and tactile perception in patients with TMD and in participants exposed to experimental models of

craniofacial pain. Stohler et al. (Stohler et al. 2001c), working with healthy volunteers, discovered that muscle pain induced by hypertonic saline infused into the masseter muscle increased tactile threshold at the site of pain and, to a lesser degree, at the mirror site in the contralateral face. Ongoing stimulation of intramuscular nociceptors may excite brainstem neurons that suppress trigemino-thalamic transmission from touch receptors on either side of the face. Since the effect far outlasted the local pain sensation, the local neural activation may trigger strong levels of central sensitization.

Hollins et al. (Hollins et al. 1996), also noting that experimental pain can elevate the threshold for vibrotactile stimuli (a "touch gate"), found that threshold for a 25 Hz vibratory stimulus presented on the cheek was significantly elevated in a group of TMD patients, compared to a matched control group. Moreover, those with greater levels of muscle tenderness had significantly higher thresholds than those with lower levels of palpation pain. Such data also support a hypothesis of a disturbance in sensory processing.

Hollins and Sigurdsson (Hollins and Sigurdsson 1998) extended this work into the suprathreshold range by asking TMD patients and control subjects to discriminate changes in the amplitude and frequency of vibratory stimuli delivered to the face. The TMD group was significantly impaired with respect to frequency discrimination, but not amplitude discrimination, pointing to a selective impairment of cortical processing of tactile signals in TMD patients.

Interestingly, Fillingim et al. (Fillingim et al. 1998) described a female TMD patient who showed marked allodynia, described as an intense burning pain, to low levels of vibrotactile stimulation of both the face and the usually pain-free volar forearm. This finding is in the opposite direction of the more usually seen diminished tactile response. Administration of the N-methyl-D-aspartate (NMDA) receptor antagonist dextromethorphan diminished the vibration-induced pain at both the face and arm, raising the possibility that the patient was in a tonic state of central sensitization. Other TMD patients, clinically indistinguishable from this woman, did not show similar vibrotactile allodynia.

HYPERVIGILANCE

Biopsychosocial models of chronic pain emphasize the interaction between biological predispositions and reactions to stressful events. Pain-related beliefs and other cognitions, coping responses, and environmental factors are critical in understanding and managing complex disorders such as TMD. Ferrari (Ferrari 1999) summarized an important feature of the biopsychosocial approach:

> Such a model means that psychosocial factors do not in themselves generate the symptoms ... Instead, psychosocial factors modify the patient's recognition of these symptoms, their severity, the response and attribution to a specific cause, and further effects on behavior. The origin of the symptoms is still physical, but their severity and attribution, along with the patient's behavior, are otherwise dependent on psychosocial factors (p. 498).

The major characteristics of TMD, orofacial pain, restricted jaw opening, and noise in the jaw, are very common symptoms. Von Korff et al. (Von Korff et al. 1988b), in an epidemiological comparison of pain complaints, found that the prevalence of facial pain in the past six months was about 12% and that about 20% of the population suffer from these symptoms. However, only about 5% of people in the community seek medical or dental treatment for their

problem (Dimitroulis 1998). These data suggest that most published studies, which describe the characteristics of persons who sought treatment at dental clinics, might be reporting the biological and psychosocial characteristics of a special subset of people experiencing facial pain. Those individuals may pay particular attention to bodily symptoms, many of which are widely experienced, attribute them to somatic dysfunctions, become anxious about their presence, and catastrophize about their meaning and consequences (Rollman and Lautenbacher 1993; Lautenbacher and Rollman 1999).

McDermid and Rollman (McDermid and Rollman 1999) found that TMD patients scored significantly higher than matched controls on the Somatosensory Amplification Scale (Barsky et al. 1988). Their scores were similar to those of both FM and RA patients. They also scored higher than control subjects on bodily monitoring and catastrophizing. Raphael et al. (Raphael et al. 2000) also discovered a small but significant elevation in somatosensory amplification in patients with TMD, particularly so for those whose pain was currently active. These findings could indicate that somatosensory amplification and maladaptive affective and coping responses are secondary to clinical pain states, but it is also possible that a pattern of hypervigilance is a risk factor for various pain conditions such as TMD, fibromyalgia, and IBS. Whitehead et al. (Whitehead et al. 2002), proposed that patients who have these disorders share a common factor that is most likely psychological and involves "stress reactivity and/or a tendency to selectively attend to somatic sensations and to amplify their intensity and significance."

A recent prospective study on nearly 250 pain-free females (Bhalang et al. 2002b) provided some important information about the pathophysiology of TMD. Baseline data were obtained on measures of anxiety and somatization. Thirty months later, 13 of these women met the established Research Diagnosis Criteria for TMD. Their baseline scores on the psychological distress and dysfunction scales were significantly higher than those of the women who remained pain-free, indicating that psychosocial factors are important predictors of later TMD. So, too, are perceptual factors. The same group (Bhalang et al. 2002a) found that the women who later showed clinical signs of TMD had significantly lower baseline pressure pain threshold at the wrist. Their data also suggest that there was a progressive change in pain sensitivity during that several year period, since for the women who became patients, pain thresholds at the temporalis muscles, masseter muscles, and temporomandibular joints, which were already lower than the control subjects, showed a further significant decline. Moreover, another study by these investigators (Slade et al. 2002) found that among 253 subjects free of TMD, 53% had muscle palpation tenderness of head and neck muscles at one or more RDC sites. These subclinical signs of TMD were accompanied by markedly lower ischemic pain tolerance on the upper arm. All these findings point to a preexisting impairment of central pain regulatory mechanisms.

Some evidence suggests that pain sensitivity changes as a function of treatment. After a treatment period, subjective pain decreased somewhat and the PPT tended to increase in patients with both muscle and capsule pain but to decline in those with pure myogenous pain. These findings need to be replicated after a longer treatment period, but if they are confirmed, they suggest possibly different mechanisms for muscle and joint pain in the face. Malow and Olson (Malow and Olson 1981) determined that TMD patients who improved after treatment showed an increase in pain threshold and Scudds et al. (Scudds et al. 1989) found a change in the same direction for FM patients whose pain was improved after management with amitriptyline. These findings are in the direction predicted by both the hypervigilance model (Rollman and Lautenbacher 1993; McDermid et al. 1996b; Naliboff et al. 1997a) and models of modified

central pain regulation. A decrease in pain threshold (sensations earlier described as pressure are now labeled painful), despite a reduction of clinical pain, is more in line with the resetting of the anchor or comparison point described by the adaptation model of pain (Rollman 1979; Rollman 1992).

EXPERIMENTAL MODELS OF TMD

Zhang et al. (Zhang et al. 1993) developed an experimental model of tonic muscle pain that approximates the sensory and affective distress described by TMD patients. A hypertonic saline solution is infused into the masseter muscle of pain-free volunteers by a computer-controlled pump at a rate that maintains tonic pain for 18 minutes at a VAS level between 40 and 60 on a 100-point scale. On the McGill Pain Questionnaire, participants described the pain as aching, throbbing, and cramping on the sensory subscale, tiring, sickening, and wretched on the affective list, and radiating, numb, and nagging among miscellaneous descriptors. Stohler et al. (Stohler et al. 2001a) tested low-threshold mechanosensitivity with calibrated monofilaments, and found that the muscle pain caused a significant increase in threshold at the site of the pain and, to a smaller degree, at the mirror image site on the contralateral face. Moreover, the hypoesthesia effect was still present up to half an hour after the saline infusion, even though the pain only lasted about seven minutes. The authors suggested that the muscle nociceptors activated by the hypertonic saline excite brainstem neurons that, in turn, suppress transmission from the touch receptors on both sides of the face. This central sensitization appears to be powerful enough to outlast the pain itself.

There is a contradiction between these data and those of Svensson et al. (Svensson et al. 1998). Stohler et al. (Stohler et al. 2001b) reported hypoesthesia, an abnormally high detection threshold, whereas Svensson et al. found that tonic noxious stimulation of jaw muscles causes mechanical hyperesthesia on the face (lowered threshold for touch). The discrepancy may result from differences in the characteristics of the mechanical probe and a dual effect of deep muscle pain: an increase in threshold to innocuous mechanical stimulation and a decrease in threshold for noxious intensity levels.

STUDIES OF NEUROTRANSMITTERS

Alterations in neurotransmitter function may be associated with TMD. For instance, Ernberg et al. (Ernberg et al. 1999) found high levels of serotonin in the masseter muscle of both TMD and fibromyalgia patients and pain-free controls immediately following insertion of a microdialysis probe and after a steady state period. The patients, whose pain scores were already high before the muscle puncture, had higher levels of 5-HT in the muscle tissue, possibly indicating that serotonin may excite already sensitized nociceptors in these disorders, provoking further pain.

Kashima et al. (Kashima et al. 1999) recruited TMD patients and controls to participate in a study of endogenous pain modulation involving the diffuse noxious inhibitory controls (DNIC) paradigm (Le Bars et al. 1979; Le Bars et al. 1992a). Pressure pain threshold was measured on a finger of the nondominant hand before and after induction of ischemic pain in the dominant arm by the submaximal effort tourniquet procedure. As is normally the case in DNIC, the

pressure pain threshold increased in the control subjects following the tonic contralateral pain, but for the TMD patients there was no change in threshold for the phasic pain. Since it has been established that DNIC is at least partially mediated by opioid mechanisms (Le Bars et al. 1992b), these findings suggest that the TMD patients may have an impairment of an endogenous opioid system which regulates pain. Fibromyalgia patients have shown similar deficiencies in DNIC modulation (Lautenbacher and Rollman 1997; Kosek and Hansson 1997).

RESPONSE TO STRESS

Several studies have indicated that TMD patients have significantly higher levels of stress-related hormones than control subjects (Evaskus and Laskin 1972; Geissler 1985). The high association of TMD and other "stress-associated syndromes" (Korszun et al. 1998) has led to the suggestion that patients may have a dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis. Jones et al. (Jones et al. 1997) showed that TMD patients undergoing a stressful public speaking task show a considerably higher salivary cortisol response than control subjects. The data were noteworthy in demonstrating two subgroups of patients, those who exhibit hypersecretion of cortisol (more than twice as much as controls) and others who seem to show a hyposecretory pattern (although it could be that long-standing stress has diminished their earlier ability to mount an adaptive stress response).

Other evidence has been found for dual response patterns. Korszun et al. (Korszun et al. 2002) observed that TMD patients have much larger levels of daytime plasma cortisol levels compared to controls, while Costello et al. (Costello et al. 2002) found evidence that TMD patients undergoing stress may show a blunted secretion of interleukin-6 (IL-6), a proinflammatory cytokine which influences the HPA axis. Interestingly, in a study of rheumatoid arthritis (RA) and osteoarthritis (OA) patients about to undergo surgery, Hirano et al. (Hirano et al. 2001) found that the former reacted to mental stress with significant increases of both IL-6 and cortisol in the peripheral blood, but the OA patients showed no alterations. Clearly, the state of the stress-immune and stress-endocrine systems in TMD patients appears to be perturbed, but the patterns are diffuse and likely reflect several underlying subgroups.

OVERVIEW

This review points to both the excitement and frustration of research on TMD. Large numbers of individuals find themselves with a disturbing and disabling disorder whose basis is poorly understood and for which treatment options are limited. Nonetheless, there are many avenues of research which have been productive and promise considerable success in the next decade.

It appears that a multiplicity of biological and psychosocial mechanisms is fundamentally disturbed in TMD. We should not expect that the explanations for the etiology (why) and the pathophysiology (how) will be common in all TMD patients (Greene 2001). Patients may have a biological predisposition (Tenenbaum et al. 2001) to developing a chronic pain facial syndrome following local injury, ongoing stress, possibly nocturnal bruxism (Lobbezoo and Lavigne 1997; Dao and Lavigne 1998), and other factors. Likewise, their premorbid patterns of coping with stress, monitoring bodily reactions, coping with unexplained episodes of

pain, and seeking medical and dental treatment may all show some relationship to later pain chronicity.

It also seems clear that TMD patients have dysfunctions, particularly central ones, in the regulation of noxious signals (Svensson and Graven-Nielsen 2001). It is still not certain whether these problems are important in the initiation of TMD, but certainly they are critical in the maintenance of the disorder. As such, the data suggest that future interventions, both psychological and pharmacological, which can act to increase patients' ability to manage their pain (Greco et al. 1997; Dworkin et al. 2002) and to restrict sensitization of peripheral afferents, cortical plasticity and central hyperexcitability, and dysfunction of descending pain modulatory systems following injury (Zimmermann 2001; Scholz and Woolf 2002; Bolay and Moskowitz 2002), can markedly attenuate the progression to a chronic temporomandibular disorder.

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