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The focus article by Drs Dao and LeResche¹ addresses the timely topic of sex differences in pain perception. Although the specific emphasis is on pain from the orofacial region, the authors have dealt at length with general aspects and factors responsible for diversities between the sexes in this field, making considerations that can also be applied to painful disorders of other body locations. The article is very well written, easy to follow, and able to draw the attention of the reader to crucial aspects of an important issue in pain research.

The existence of sex differences in pain and the possible role played by sex hormones in pain perception have been much debated in the scientific literature for quite some time. In my opinion, however, this subject has too often been approached in a rather anecdotal manner, especially in past clinical studies.² It is only in recent years that a number of important articles have appeared that address the topic with a systematic approach,³⁻⁵ and the article by Dao and LeResche follows this line.

The authors critically review the available literature on sex differences in pain perception, analyzing separately the issues of clinical pain and experimental pain and then dealing extensively with the possible factors underlying the observed sex differences: biologic, hormonal, and psychosocial. Finally, they make specific considerations of additional factors contributing to men's and women's differences in orofacial pain.

Clinical Pain

In their analysis of the clinical pain literature, the authors have taken into account factors such as epidemiology, symptom expression, and methodologic issues.¹ Epidemiologic studies suggest that several conditions in which chronic pain is a prominent component are associated with a

higher female prevalence, and that women and men may also display different arrays of symptoms for the same algogenic pathology. As the authors point out, however, many of these studies lack adequate methodology; it is therefore difficult to draw definite conclusions about gender differences in spontaneous pain exclusively on their basis. The authors' criticism in this respect appears undoubtedly appropriate. First, they underline the descriptive nature of most epidemiologic literature to date, with reports of gender differences having often been presented as secondary findings in studies not originally designed to address the gender issue. Second, they point out how most data in these studies appear to be collected from clinical samples rather than from general population samples, an aspect that renders them more prone to bias since they are more influenced by factors that are specific to the nature of the sample. In their opinion, this consideration is particularly important in light of the claimed greater frequency of women seeking medical care.⁶ With specific regard to orofacial pain, the authors point out that "overrepresentation of women with chronic orofacial pain in clinical samples does not necessarily reflect the true gender ratio of these pain conditions, but may instead reflect the possibility that female patients more readily seek treatment." As a matter of fact, several studies report that women with orofacial pain, particularly those with temporomandibular disorders (TMD), seek treatment much more frequently than men.⁷

More epidemiologic studies are undoubtedly needed that are population-based rather than patient-based; this would certainly help eliminate bias due to the specific nature of the sample examined. However, I would be careful in generalizing the assumption that women report more medical visits than do men. While this appears to be true for a number of painful conditions (and those

affecting the orofacial region are definitely included), there are examples of an opposite tendency, for instance, with cardiac pain. Chest pain apparently alarms men more frequently than women, as this symptom is regarded as more predictive of coronary artery disease in men than in women.⁸⁻¹⁰ Foster and Mallik,¹¹ for instance, report that among patients who had experienced cardiac-related chest pain, men were admitted to the hospital more quickly than women. Men were more ready than women to believe that they might be having a heart attack and thus sought treatment more promptly.¹²

Experimental Pain

Controversial data on gender differences in pain perception also emerge from experimental investigation. Although the general trend is for females to exhibit greater sensitivity than males to laboratory pain, Dao and LeResche point out the highly variable findings of the different studies in the field, mostly as a result, again, of methodologic issues.¹ The authors stress the great variability across the various protocols regarding the nature of stimulus employed, the modality of application (single vs. repetitive), and the body tissue/location tested. They also emphasize that many studies in humans have been performed on small samples and that, in addition, the chosen subjects were most often healthy individuals rather than patients. Based on these considerations, in their opinion the clinical relevance of these studies is at least limited.

The critical analysis of experimental protocols in the field is undeniably correct; it is my feeling, however, that Dao and LeResche tend to underestimate the potential clinical utility of laboratory investigation. As Fillingim points out, "it is possible that females' greater responsivity to experimental pain is a risk factor for the development of certain clinical pain conditions."⁵ Personally, I am convinced that experimental studies designed specifically to address the issue of gender differences in algogenic perception are an indispensable step toward a better understanding of the diversities observed in clinical reality, although I entirely agree with the authors that such studies should in the future be performed at least on larger populations and include evaluation of male and female patients along with normal subjects.

Possible Mechanisms

In their analysis of possible mechanisms underlying sex differences in pain, the authors stress the importance of biologic factors.¹ With this in mind, they report Berkley's view, with which it is difficult to disagree: "... females and males do differ virtually absolutely and unarguably in three aspects of their reproductive biology. Their pelvic reproductive organs differ and their hormonal conditions differ chronobiologically and compositionally."³ In my opinion, however, the different impact of pain from the reproductive area in the 2 sexes is not given enough emphasis by the authors. Also, the possible consequences that this may have on the general capacity of pain perception in females versus males do not appear to be sufficiently analyzed.

It is undeniable that the number of potentially painful pathophysiologic events that affect the female reproductive organs, at least during the fertile phase of life, exceeds that occurring in the equivalent male region, for obvious reasons linked to females' more complex reproductive function.² Menstrual pain, labor, and postpartum pain, as well as chronic pelvic pain resulting from ascending infections, are just a few demonstrative examples of this assumption.^{13,14} Women are thus more likely than men to experience pain from their sex-specific visceral organs. As a consequence, since visceral pain is known to be referred to somatic areas neurally related to the viscera in question, where hyperalgesia of deep parietal layers (ie, muscle) takes place and persists for a long time,^{15,16} the higher impact of pain from the pelvic area in women results in a more frequent condition of muscle hypersensitivity of the lower abdominal quadrants, which also renders women more prone to develop somatic pain conditions at the same level.¹⁷ In addition, as suggested by increasing clinical evidence, algogenic phenomena of the female reproductive organs would predispose women to an increased perception of pain from other visceral organs with partially overlapping innervation, such as the urinary tract (common segments: T10-L1) (viscero-visceral hyperalgesia, a phenomenon probably sustained by a process of central sensitization involving viscerovisceral convergent neurons).¹⁶ The more frequent pain experience from the reproductive area in women would thus entail an increased susceptibility to other forms of pain.

The possible consequences of pelvic pathophysiology on pain perception in women have also been recently analyzed by Berkley,³ who put forward an interesting hypothesis. In Berkley's opinion, a

possible contributing factor to sex differences in pain perception derives from the fact that the vagina and cervix provide ready access to internal pelvic structures, and thus (in addition to physiologic functions linked to reproduction) ready access to a number of infectious agents (viruses, bacteria, etc). This entails a greater propensity to develop a number of pelvic inflammatory conditions that deeply affect the visceral pain reactivity of the pelvic domain in the area. In Berkley's opinion, the vaginal canal and cervix increase the vulnerability in women of the T10-L1 (innervating uterus and cervix) and S2-S4 (innervating vagina and cervix) segments to morbidity. The consequences of a persistent input from the periphery can be very important and long-lasting. Animal experiments have, in fact, documented persisting changes in the activity of spinal cord neurons (central sensitization) subsequent to chronic infection, inflammation, and peripheral injury. This central increase in excitability of neurons is probably the mechanism at the origin of some forms of chronic pain, the organic cause of which is difficult to identify.¹⁸⁻²⁰ Berkley's hypothesis is thus that some forms of diffuse, widespread pain that are much more common in women than in men and have no clearly detectable underlying mechanism have their starting point in a persistent noxious stimulation via the vaginal/cervical canal; in addition, input from C-fibers, the predominant type of fiber innervating the vaginal canal and cervix, is particularly efficient in producing such states of central hyperexcitability.³ It would be interesting to know Dao and LeResche's comments on this hypothesis, especially as they themselves emphasize in their article that many clinical pain conditions prevalent in women appear to be of unknown origin.

Surprisingly, in their report of these conditions, the authors never mention fibromyalgia, an important chronic pain state that is manifested almost exclusively in women.^{21,22} Fibromyalgia is not taken into consideration, even when the authors raise the interesting point of the interaction between neuroactive agents and gonadal hormones and the consequence of this interaction on pain perception. They analyze the relationship between serotonin and female sex hormones (serotonin levels vary positively with plasma estradiol, estrone, and estrogen) and correctly highlight the importance of serotonin in the pathophysiology of headache (especially migraine), a form of chronic pain that is highly prevalent in women. They fail to mention, however, that serotonin is also likely to play a crucial role in the genesis of fibromyalgia, as more studies show that serotonin

metabolism is substantially impaired in fibromyalgia.²³ Interestingly, the incidence of headache is higher amongst fibromyalgia patients than in the normal population. Also (and this is particularly relevant to the field of orofacial pain), TMD pain seems to partly overlap with fibromyalgia, as well as other musculoskeletal pain conditions.²⁴ As reported by Svensson and Arendt-Nielsen,²⁴ pain drawings administered on a systematic basis to patients with pain complaints in the craniofacial region have revealed that only about 19% have pain confined to this region, whereas 66% have widespread pain outside the craniofacial and cervical regions. According to these authors, information on these concomitant sites of pain in other parts of the body is important because it could indicate the involvement of more widespread pathophysiological mechanisms in some patients with TMD pain.

Further in their analysis of mechanisms underlying sex differences in pain, Dao and LeResche raise an interesting point regarding the possible role of the sympathetic nervous system. They underline a concept already stressed by Berkley, ie, that differences in afferent input from internal organs to the central nervous system may not only produce different visceral pain in females and males but may also result in different emotional consequences of pain experiences. I would add that the role of the sympathetic system is probably also crucial in determining differences in the way hyperalgesia develops in somatic tissues (especially superficial) in areas of referred pain—from viscera as well as from other somatic structures—in women vs. men. In fact, it has been hypothesized, based on the results of clinical studies,²⁵ that along with phenomena of central sensitization, secondary hyperalgesia in skin and subcutaneous tissue could also develop as a consequence of the activation of a reflex arc, with an afferent branch represented by afferent fibers from the primary affected structure, and an efferent branch by sympathetic efferents supplying the somatic tissues of the area of referral.²⁵

Orofacial Pain

Following their analysis of factors that may account for general differences in pain perception between the sexes, the authors consider factors unique to the craniofacial system. Their position is that the higher prevalence of chronic orofacial pain in women than in men reflects on the one hand, a generic difference in pain mechanisms between the 2 sexes, and on the other, specific

factors unique to the craniofacial system. However, as emerges from their own analysis of available data, there is still scarce support for the hypothesis of specific regional factors accounting for sex differences in this area. Some of the reported differences, in fact, such as the effects of the reproductive hormones on the temporomandibular joint complex, are mostly experimental observations, the clinical significance of which remains to be proven.

Whatever the relevance of general versus specific factors in the determination of sex differences in pain perception at the orofacial level, the authors underline how the reported higher predisposition of women toward this kind of pain contrasts with substantial undertreatment of their symptoms with respect to men. This is in line with what is reported for pain conditions of other body locations, perhaps for the still deeply rooted idea among pain clinicians that women tend to overemphasize their symptoms.² We are not here to say that women should systematically be paid more attention than men with regard to their pain. However, sex should not be a prejudicial factor in the evaluation of a patient's symptoms and, consequently, in the treatment.

I believe that the general conclusion of this focus article is very appropriate. The authors state that gender is not the major issue when diagnosing and treating a patient with pain, but should be just one of the factors to be taken into consideration. The last sentence is very important: here, the authors emphasize that each patient is unique and deserves attention, regardless of age, sex, and social status. Each of these factors only contributes to the general diversity of an individual in his or her pain experience.

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