A Unified Concept of Idiopathic Orofacial Pain: Pathophysiologic Features

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Atypical facial pain, stomatodynia, atypical odontalgia, and some forms of masticatory muscle and temporomandibular joint disorders all seem to belong to the same group of idiopathic orofacial pain illnesses. The many common clinical features they display have been discussed in a preceding paper. Some of their common pathophysiologic mechanisms are reviewed in this article. The role of female hormones is suggested as a risk factor by the strong female prevalence and by the effects of physiologic and therapeutic modification of estrogen levels in patients with these pain conditions. Osteoporosis, which appears with menopause, and neuralgia-inducing cavitational osteonecrosis have been linked to atypical facial pain. Similar clinical features have also prompted a comparison between atypical facial pain and complex regional pain syndrome of the limbs. The presence of psychosocial factors is also a common feature, but it is not known whether these are causal or whether the pain induces the psychosocial problem. Local inflammatory, infectious, or mechanical irritation as well as minor nerve trauma are frequently reported in these conditions and can also be considered as risk factors. However, none of the above factors can currently be considered as the sole etiologic factor, and instead the following hypothesis is proposed: the idiopathic pain entities depend on one or several neuropathic mechanisms, the development of which is triggered or favored by one or several events or risk factors. Different neuropathic mechanisms may be at work: nociceptor sensitization, phenotypic changes and ectopic activity from the nociceptors, central sensitization possibly maintained by ongoing activity from initially damaged peripheral tissues, sympathetic abnormal activity, alteration of segmental inhibitory control, and hyper- or hypoactivity of descending controls. Research directions that are suggested include epidemiologic approaches to improve the clinical definition of these conditions, studies to test for the factors and mechanisms proposed, and definition of mechanism-based diagnostic and treatment strategies.
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A recent concept of idiopathic orofacial pain[1,2] groups together several types of head and neck pain (atypical facial pain, atypical odontalgia, stomatodynia, and some of the chronic and painful forms of the masticatory and temporomandibular joint disorders). These illnesses display many common features (see for review Woda and Pionchon[3]). They are restricted to tissues or organs of the face or oral cavity or tissues directly related to them, such as the temporomandibular joint (TMJ) and the muscles of mastication. In all cases, the pain is of a continuous

type, has been present for at least the previous 4 months (although it may be recurrent), has no paroxysmal character, and disappears during sleep. All studies have noted a strong predominance in women. There is a higher prevalence of psychosocial disturbance than in the general population, and certain personality traits, difficult social circumstances (family problems, problems at work, or sociocultural disharmony), or psychologic problems (depression, anxiety, or continuous or episodic emotional instability) are often reported in direct association with idiopathic orofacial pain. Whether the chronic pain state or the psychosocial element is the causal factor is unclear. None of the idiopathic orofacial pain entities stated above has an obvious clinically detectable organic cause, and accordingly the pain is the main motive (if not the only motive) for consultation.

It is usual to divide these pain entities into 4 or 5 different groups. This classification is implicit in the type of tissue affected: mucosa for stomatodynia, bone for atypical facial pain, teeth for atypical odontalgia, muscles for myofascial pain, and the TMJ for capsular and disc disorders. However, in addition to their shared clinical characteristics, there are several other reasons for grouping these different disorders. They commonly occur simultaneously or consecutively in the same patient.[1,4] Also, the treatments for all these disorders were, until recently, often non-specific, and the reasons for success or failure of treatment were poorly understood. As the term "idiopathic" indicates, the etiology of these illnesses is unknown. Many different hypotheses explaining their pathophysiology have been proposed, and the better-documented ones will be reviewed here. Hormonal influences and degenerative tissue phenomena will be presented first, followed by neuropathic factors that could result from local trauma, inflammation, mechanical irritation, or minor nerve trauma. The involvement of the sympathetic nervous system will then be discussed, together with a possible relationship with complex regional pain syndromes (CRPS). Finally, the impact of psychologic and emotional factors and life events will be considered. Following the description of these different types of pathophysiology, the following hypothesis will be proposed: the idiopathic orofacial pain entities depend on the presence of one or several neuropathic mechanisms, the development of which is triggered or favored by one or several events or risk factors. Finally, perspectives for further research will be presented.

Hormonal Influences

Correlation Between Female Sex Hormones and Idiopathic Orofacial Pain

The possibility that the female sex hormones may be implicated in idiopathic orofacial pain is suggested by the fact that all these illnesses have a strong female predominance.[4–13] There is also a link between their prevalence and the female patient's fertility status. Menopausal or postmenopausal women are more prone to atypical orofacial pain,[10,14] atypical odontalgia,[6] and stomatodynia,[15] whereas the prevalence of orofacial musculo-articular pain is highest during the period of fertility, between puberty and menopause.[16] This suggests that female sex hormones may predispose women to musculo-articular facial pain, while their absence may favor the development of atypical orofacial pain, atypical odontalgia, and stomatodynia. One retrospective study showed that in a large sample of menopausal women, those who took estrogen supplements were 30% more likely to consult for TMJ or masticatory muscle pathology than control subjects. The difference was non-significant for subjects supplemented with progesterone.[16] Similarly, non-menopausal women taking an oral contraceptive were 20% more likely than controls to consult for musculo-articular pain of the masticatory apparatus. This increase was statistically significant.[16] Depressed levels of female sex hormones are found not only in menopausal women but also in young women after ovariectomy. Such a population was 18% more likely to complain of oral burning sensations than a control population.[17] There is also a correlation between stomatodynia and the presence of marked menopausal symptoms.[18] The effects of hormone replacement therapy are becoming more fully documented. Although some studies have reported that oral pain symptoms are not appreciably modified by hormonal supplements,[17] most studies have shown an alleviation of symptoms of oral burning sensation or discomfort in approximately two-thirds of patients.[15,19,20] Unfortunately, these studies used no control group. One recent study demonstrated a link between the daily pattern of myofascial pain of the masticatory muscles and both the stage of the menstrual cycle and whether an oral contraceptive is used.[21]

Gender Differences in Pain Sensitivity with Respect to Idiopathic Orofacial Pain

The role of the female sex hormones in idiopathic orofacial pain is related to the more general question of a possible difference in pain sensitivity between genders. Several recent reviews have suggested that women are more sensitive to pain than men[22–24] and that this is a result of differences in biochemistry and physiology. Epidemiologic data suggest that this increased sensitivity is particularly evident for idiopathic orofacial pain.[4–14] A difference in sensitivity seems to exist for the pain, but not for the associated signs. In a pain-free group, the prevalence of mechanical signs of facial musculo-articular dysfunction (deviation and limitation of opening, clicking of the joint, etc) and occlusal disharmony (pathway of retrusion, non-working contacts, and molar contacts on lateralization, etc) was identical regardless of gender.[25]

Peripheral or Central Mechanisms Related to Female Sex Hormones

The link between pain activity and hormonal balance may be due to gender-dependent estrogen receptor density in the orofacial tissues. The possible existence of these receptors in physiologic and pathologic conditions is currently being explored.[16] A direct influence of the female sex hormones on the mucosa[26] and oral environment[27] has been proposed, but also challenged.[17] Local application of estrogen to the mucosa of women suffering from stomatodynia relieved symptoms no more than a placebo.[26]

Data are available that help to explain why the female sex hormones may have a particular influence over the orofacial region. It has been demonstrated experimentally that sex hormones interact with the trigeminal sensory complex, the area of the brain stem that is concerned with the transmission and modulation of nociceptive and non-nociceptive signals from the orofacial region. For example, the estrogens appear to cause variation in the surface area of the peripheral receptive field of trigeminal neurons[28] according to the stage of the menstrual cycle. The sexual steroids also seem to control the central level of neurokinins at CI, a region of the spinal cord dominated by the trigeminal nerve.[29] In addition, the substantia gelatinosa of the trigeminal sensory complex contains many enkephalinergic neurons that manifest estrogen receptors. These may enable the sex hormones to modify the response of nociceptive neurons to nociceptive signals.[30]

However, the link between women and orofacial pain may be independent of female sex hormones. For example, a very recent study examined the bacteriologic content of nose and vaginal swabs taken from 2 groups of young women. The swabs from the subjects suffering from chronic orofacial muscular pain were more likely to be infected with certain types of *Staphylococcus* than were those from the control group. The authors suggested a possible causal link, considering that the bacteria in question "although clinically non-infective, may exhibit subclinical pathogenicity at the cellular level, resulting in reversible damage."[31]

Sex Steroids, Osteoporosis, and Neuralgia-Inducing Cavitational Osteonecrosis

The action of the female steroids on bone is well documented and has been reviewed recently.[32–35] Some of the main conclusions are relevant to atypical facial pain. Menopause is often accompanied by osteoporosis, and one of the primary aims of hormone replacement therapy is the prevention of this disease. One treatment for atypical facial pain proposed more than 20 years ago may be related to the role of the female sex hormones in bony metabolism, particularly in lesions found in bone that has become osteoporotic as a result of menopause. Its rationale was based on the presence of areas of non-dense bone within the jawbones. Although these findings have been strongly contested, certain aspects of the theory justify its description here. Two studies had connected the presence of intrabony cavities in the jaws with the occurrence of trigeminal neuralgia or atypical facial pain in the same patients.[36,37] These bony deficiencies apparently corresponded to areas of bone that had previously undergone trauma, usually a tooth extraction. They were not visible radiographically[38] and were suspected only after injection of a local anesthetic had successfully calmed the pain. Diagnosis was confirmed by surgical curettage of the lesion within the edentulous portion of the alveolus. This afforded a 100% success rate for cure (although many successive interventions were often required). Antibiotics were prescribed after a positive bacterial culture had been obtained; the presence of infection also prompted the authors to use the term *chronic osteomyelitis*. Other groups subsequently confirmed all or part of these findings.[39–41] Later on, the concept evolved that atypical facial pain, or at least certain forms of it, were identified as *neuralgia-inducing cavitational osteonecrosis* (NICO).[42,43] The NICO lesions were considered to arise from avascular, aseptic necrosis of the bone

that was atraumatic and ischemic and that led to pain similar to that experienced in atypical facial pain. Several authors expressed serious doubts about the efficacy of the therapeutic approaches and solutions suggested by the original authors.[44–46]

The problem with this piece of "therapeutic history" is that, 25 years later, certain practitioners are still convinced of its efficacy, despite the lack of conclusive proof. The functioning of the modern scientific and medical world may have helped these techniques to persist, in that it is difficult to report negative results, particularly in humans, if only because controlled experiments aimed at demonstrating the ineffectiveness of a surgical technique are ethically unacceptable. It may be, as in our own group, that a certain number of practitioners have simply abandoned the technique after failure in a number of patients, and that this decision has gone unrecorded in the literature. Our group undertook this therapeutic protocol in 12 patients. Our results agreed with those of Ratner et al[36] concerning the presence of abnormal bony cavities associated with the edentulous sites, at which local anesthesia was successful in alleviating pain. However, bacteriologic and anatomo-pathologic examinations did not confirm chronic osteomyelitis. The procedure was abandoned following recurrence of pain in all the patients after a period of a few days to 6 months. In conclusion, it would seem to be essential to separate the legitimate premise of bony cavities within the jaws (which has also been confirmed from autopsy data[47]) from the therapeutic intervention that has been associated with it. These bony lesions may constitute a pathophysiologic element of atypical facial pain and/or may be a type of painful osteoporotic lesion.[48] In fact, examination of non-painful jaws in control subjects would be necessary to document that these bony defects are connected with the pain condition.

Neuropathic Mechanisms

The involvement of a neuropathic mechanism in idiopathic orofacial pain is suggested by the modification of psychophysical thresholds,[49,50] by the modification of some neurophysiologic characteristics of trigeminal reflexes,[51,52] by the successful result of sympathetic block[53,54] in the treatment of some forms of the condition, and by the result of topical treatments acting on high-threshold receptors in the oral tissues.[4,55,56] It has recently been emphasized that the term *neuropathic pain* is a global item that gives no indication of the actual mechanisms involved. It only indicates that the pain arises from a lesion or a dysfunction of nervous tissue.[57]

One important point is that there are many different neuropathic mechanisms.[58–60] In the idiopathic orofacial pain entities that have been considered, the nature of the mechanisms involved is not completely known. It is likely that, in most instances, several related mechanisms may be involved that differ depending on both the tissue and the factors that have facilitated the appearance of the condition. In addition, while it has been shown that the condition of post-herpetic neuralgia appears clinically to be a single disorder, it may actually result from several neuropathic mechanisms. These mechanisms may be present simultaneously or alone in distinct and different forms of the condition.[61] Alternatively, an identical neuropathic mechanism can be induced by different causes.[58] The possibility that this applies to idiopathic orofacial pain must be considered. Indeed, it is of the greatest importance to diagnose the kind(s) of neuropathic mechanisms involved, since this is necessary to decide which treatment strategy should be adopted. However, it is clear that the identification of a particular neuropathic mechanism involved in a particular case of idiopathic orofacial pain can only be inferred by interview and by tests and/or clinical examination that have not yet been validated. It is not within the scope of this review to describe all the possible neuropathic mechanisms, and so only some of those that appear to be the most likely involved in idiopathic orofacial pain will be discussed here.

Local Factors and Abnormal Activity in Primary Afferent C-Fibers

The influence of local factors in idiopathic orofacial pain has been discussed repeatedly. Unsuitable removable dentures or inflammatory, infectious, or mechanical irritation have been suggested as causative factors for stomatodynia.[15,62–64] It has been stressed, however, that in most cases, these studies did not include control groups.[65] Mechanical factors created by an unsuitable occlusion or excessive muscle forces have long been said to represent the main etiologic factor for masticatory muscle and TMJ disorders. Although there are some strong arguments against the role of occlusal factors in temporomandibular disorders,[66,67] a recent review of the efficacy of occlusal therapy (occlusal splinting and occlusal adjustment) concluded that it was not possible to exclude completely the possibility of occlusal factors at present.[68]

Input from the periphery could be involved in the etiology of idiopathic orofacial pain in several ways. Indeed, there are frequent clinical situations in which some chronic inflammatory, infectious, or mechanical irritation exists in the oral cavity that is in itself insufficient to explain the pain symptoms but that could induce peripheral sensitization, probably of C-fiber nociceptors. Another important explanation relies on phenotypic changes occurring in C-fiber nociceptors. Fields et al[59] have suggested that in some patients with post-herpetic neuralgia, intact but abnormally hyperactive primary afferent nociceptors, termed *irritable nociceptors,* are responsible for spontaneous pain. This concept of irritable nociceptors is reminiscent of evidence presented in a case report of reflex sympathetic dystrophy: after healing of the irritation lesion, which was a light-induced skin rash, C-fiber nociceptors were shown to be sensitized without evidence of ongoing inflammation.[69] It is probable that in this patient, phenotypic changes in the primary afferent neurons were triggered by the initial nerve fiber lesion. It is possible that in other situations, other trigger factors (hormonal, degenerative, traumatic, or psychologic) may also work to induce phenotypic changes. Whether such phenomena occur in C-fiber nociceptors during idiopathic orofacial pain is unknown but is worthy of exploration and, if substantiated, would help to explain the lack of signs presented by these conditions. Peripheral nerve lesions may also trigger other neuropathic mechanisms that may activate the ascending pain pathways.[60] These include the initiation of ectopic impulses, which may arise from injured nerve fibers that may appear following axon sprouting at the peripheral end or following neuroma.[70–72] Initiation of ectopic impulses may also arise from ephapse formation, reverberating impulse phenomenon, or following a discrete lesion of nervi nervorum, the specific innervation of the nerve sheath.[73]

Involvement of Minor Nerve Lesions in Idiopathic Orofacial Pain and Trigeminal Traumatic Neuralgia

The most common cause of trigeminal traumatic neuralgia is the lesion of a large nerve trunk due to trauma, although occasionally systemic[74] or local disease such as shingles[75,76] may be responsible. The traumatic lesions are not the primary concern of this review, as they are not idiopathic. However, it is essential to understand their symptomatology if the part played by traumatic nerve lesions in the induction of neuropathic mechanisms in the idiopathic pain disorders is to be considered. The symptoms of surgical or traumatic lesions of the trigeminal nerve are well recognized and fully described.[71,75,77,78] The first characteristic is a direct link with a traumatic incident,[79] a surgical intervention, or the development of an infection or tumor. Certain dental treatments, such as extraction of impacted third molars or extrusion of endodontic material into the lower dental canal, are frequently implicated. Orthognathic surgery[75,80] and surgery of the mid-third of the face[71,77] have also been blamed. The painful area is directly related to the pathway of the severed or damaged nerve. Pain is usually intense and is characterized by a background level interspersed with paroxysmal episodes. It may be associated with neurologic signs, hyperesthesia, allodynia, hyperalgesia, and/or hyperpathia. Dysesthesia, particularly anesthesia dolorosa, and sympathetic disturbances are frequently noted.

It has long been suspected that one cause of idiopathic orofacial pain might be the presence of subtle traumatic lesions of primary afferent fibers. This is reflected in a number of terms such as "phantom tooth pain"[81,82] and "phantom orofacial pain,"[83] which are analogous to "phantom pain" of limbs[81,82,84] and have been coined as synonyms for atypical odontalgia and atypical facial pain. Apart from the pain characteristics, a traumatic origin for the different types of atypical facial pain is suggested by the fact that the patient often connects the onset of pain with a local traumatic event.[6,54,81,83] Certain interventions, such as the placement of an implant, endodontic treatment, or tooth extraction, are frequently considered as factors liable to trigger a deafferentation-involved neuropathic mechanism that may in turn lead to idiopathic pain.[53,77] In a few cases, pulpectomy associated with apical inflammation allows the transformation of elements of the periapical nervous plexus into a neuroma-type formation.[70] The term *posttraumatic dysesthesia* has been used to describe certain types of persistent pain that follow pulpectomy performed on a tooth that has previously been symptom-free.[72] For these reasons, a role for minor nerve lesions must be considered. The nerve injury may trigger different neuropathic mechanisms.[60] Ectopic activity, possibly triggered by phenotypic changes, may occur and has already been noted above. There also could be either a loss of segmental inhibitory control by impairment of large nerve fibers or a loss of inhibitory interneurons of the dorsal horn of the medulla oblongata (ie, trigeminal subnucleus

caudalis). Reorganization of central terminals of primary afferents due to central sprouting may also be implicated.

It must be emphasized, however, that pulpectomy and tooth extraction involve severing a small nerve, and in the great majority of cases, the consequent deafferentation has no clinical effect. In addition, the symptomatology of idiopathic orofacial pain syndromes is very different from that of a characteristic lesion-induced neuropathic pain of the trigeminal nerve. The pain is often bilateral[14] and does not follow the area covered by one particular nerve trunk. Paroxysmal exacerbation is rare, and neurologic signs are much less frequent.[3,4,53] In particular, the lesion of a nerve should trigger anesthesia of its corresponding area for a variable period of time, which is not described. These considerations do not rule out a deafferentation-related neuropathic mechanism induced by a small nerve lesion, but they indicate that the idiopathic orofacial pain entities do not correspond to trigeminal traumatic neuralgia.

Central Sensitization

Central sensitization of the neurons of the trigeminal sensory complex is another important mechanism likely to occur following abnormal activity of the primary afferents.[4,6,81,83] This interpretation draws on the fact that an abnormally high level of afferent impulses, deafferentation, or lesion of the peripheral afferent fibers may each have a long-lasting effect on the central neurons.[85,86] Such phenomena also occur after minor trauma, even if it is limited to a section of the apical nerve. Indeed, pulpectomy or pulpotomy causes degeneration-like alterations at the central endings of primary trigeminal afferents[87] and at the level of the second-order neurons.[88,89] Similarly, lasting impairment of the properties of the sensory trigeminal complex neurons has been noted after pulpotomy.[90–92] The clinical counterparts of these phenomena would be hyperesthesia and allodynia (for review, see Urban et al[93]). The mechanism depends at least partly on the involvement of a certain class of receptors for excitatory amino acids, the N-methyl-D-aspartate (NMDA) receptors. Activation of these receptors triggers a chain of events that produces long-lasting modification of neuronal activity (for review, see Dray et al[94]).

These phenomena may explain some of the features of chronic pain. It is noteworthy, however, that the changes observed following pulpectomy, pulpotomy, or nerve lesions in animals regressed rapidly, over a period of days or weeks, as they usually do in clinical practice. This makes the work of Gracely et al[95] particularly interesting. They showed in humans that small but steady afferent input from the periphery can prolong a central sensitization, which by itself would be transitory. They described several cases in humans in which a small, well-healed, non-painful scar at the extremity of a limb contributed to the prolongation of chronic pain referred to a region remote from the site of the scar. The relationship of the scar to the referred pain was documented by the analgesic action of a local anesthetic administered at the scar site. The afferent nerve activity from this scar was probably minimal, given the fact that the scar itself was asymptomatic. However, it was tonic, as the referred pain was found to return after the anesthesia had worn off. Thus, even very slight peripheral activity caused by an old traumatic injury may be sufficient to maintain central hyperexcitability initially induced at the time of that trauma. This peripheral activity may also be initiated by subtle trauma and maintained by the consequent mechanisms noted above. The richness of trigeminal innervation, both tactile and nociceptive, and the many potential causes of inflammation of the teeth and oral cavity could help maintain a low degree of ongoing input from the periphery.[96,97] Sympathetic activity could also help to maintain central sensitization.

Role of the Sympathetic System

Involvement of the sympathetic nervous system in the pathophysiology of atypical facial pain[53] and atypical odontalgia[47] has often been suggested.[4] Reorganization and/or abnormal activity of the sympathetic system may follow trauma and may maintain the painful state. Many different theories have been proposed for these types of pain.[98,99] The most widely accepted of these assumes the formation of a functional relationship between the sympathetic efferent and the primary afferent fibers after trauma involving a peripheral tissue.[100] This may occur by the expression of α receptors on the peripheral endings of injured C-fibers. This results in C-fiber activation by systemic norepinephrine or norepinephrine released from efferent sympathetic fibers.[98] By allowing for sensitization of the primary afferent fibers, this reorganization might in turn favor the maintenance of central sensitization, together with a tonic reflex increase in sympathetic activity.

Relationship with Complex Regional Pain Syndrome

Atypical Facial Pain and Complex Regional Pain Syndrome of the Face

The terms *neuroalgodystrophy* and *causalgia*[101] were recently defined at a consensus conference[101] to describe 2 separate entities, now classified as type I and type II CRPS. For type I CRPS (neuralgodystrophy), the illness follows a triggering event that is usually minor compared with the degree of pain experienced. For type II CRPS (causalgia), the signs follow a lesion of the nerve trunk. Both are characterized by spontaneous pain and/or hyperesthesia/allodynia and are accompanied to varying degrees by muscular dysfunction, edema, vasomotor or sudomotor problems, and other forms of dystrophy.[75,101–103] A link with the sympathetic system has long been supposed, so treatment has been based on synaptic or conduction blockade of sympathetic nerves.

The condition of CRPS was initially described for limbs, but it seems the syndrome is also found nearer the trunk and in the head and neck.[53,104,105] The symptoms described for CRPS of the head and neck (continuous burning pain with hyperesthesia and allodynia and various sympathetic signs such as edema), along with the fact that it can be triggered by tooth extraction, surgical intervention, or trauma, may cause it to be confused with atypical facial pain (Table 1). It is stressed that the term *atypical facial pain* is used to describe a relatively homogeneous subgroup of facial pain.[3] It is not used as a wastebasket term for gathering all the intermediate clinical situations that do not fit well-defined categories of facial pain. It is noteworthy that, in the past, these terms were used to qualify such pain entities as myofascial pain, cluster headache, or facial migraine,[106] which had not been defined at the time. The similarity between facial CRPS and atypical facial pain is accentuated by the fact that these 2 illnesses differ in the same way from CRPS of the extremities. Sudomotor phenomena are usually absent,[53,107] and edema and vascular signs are less visible and/or less frequent than in the limbs.[107] These differences may be due to the relatively low proportion of sympathetic nerve fibers in the trigeminal nerve compared with the dorsal roots of the spinal cord.[108] Another reason for an apparent lack of intraoral sympathetic activity in the trigeminal system may be due to difficulties of visualization of change against the oral mucosa.

In addition, the diagnosis of facial CRPS has been based in some studies on the remission of pain following blockade of the sympathetic efferents by local anesthetic at the stellate ganglion[53,104,107] or by other means[109] aimed at assessing possible ongoing sympathetic activity.[4] Similarly, in a study of "neuropathic orofacial pain" by Lynch and Elgeneidy,[53] 10 of the 14 patients who received anesthesia of the stellate ganglion experienced pain relief. Interestingly, the criteria used to enter these 14 patients into the study emphasized the presence of autonomic dysfunction, but the clinical picture was clearly reminiscent of atypical facial pain.

Are There Criteria Indicating Sympathetic Activity?

Until recently, relief of symptoms following sympathetic nerve blockade was considered an essential diagnostic criterion of CRPS.[110] This is now contested, because the results of these blockades have not been controlled and because the reliability of these types of tests is low.[111] Hence many authors are now seeking quantifiable elements that may be used as reliable and valid diagnostic criteria. Criteria based on measurements such as cutaneous temperature, cutaneous blood flow, and sudomotor reflex have been used to define CRPS[111] by comparing the affected with the contralateral side. Some of these signs may also be present in atypical facial pain or atypical odontalgia,[112,113] and they may, in the future, help to diagnose a sympathetic component in the pathophysiology of individual patients.

Psychologic Factors

Is Idiopathic Orofacial Pain Psychologic?

The different types of idiopathic orofacial pain, particularly stomatodynia and atypical facial pain, are often classified as psychogenic pain, implying that their main etiology is psychologically based. However, many of the earlier reports suggesting that different forms of idiopathic orofacial pain are psychiatric disorders were anecdotal or based on poorly designed studies of clinical cases, eg, the findings were not compared with those of other chronic pain patients, or even with healthy controls.[106,114–117] A positive response to treatment with psychotropic drugs such as the tricyclic antidepressants was sometimes taken as an argument in favor of a psychogenic etiology.[116,118] It

Table 1 Comparison of Principal Characteristics of Atypical Facial Pain and Type I Complex Regional Pain Syndrome

Characteristic	Atypical facial pain	Complex regional pain syndrome
Epidemiology		
Prevalence	Unknown	Unknown
Sex	1 male for 2 to 10 females	More women than men[103]
Age	Average 52 years (from 24 to 82)	All ages, maximum at 50 years[103]
Pain characteristics	Deep, diffuse, variable localization	Deep, diffuse, variable localization[103,171]
	Localized in the face but no correspondence with nerve pathways	Localized in the limbs but no correspondence with nerve pathways[103,171]
	Spontaneous, continuous, and daily	Spontaneous and continuous in 75% of cases[171]
	Intensity moderate to high	Fluctuating intensity, from mild to high[76]
	Descriptors: Emotional, mechanical, or burning	Descriptors: Burning or deep aching[171]
	Sometimes allodynia, hyperalgesia, or dysesthesia; no hypoesthesia	Allodynia, hyperalgesia, dysesthesia, and hypoesthesia in over 70% of cases[171]
Associated signs		
Sympathetic manifestations	Edema often described by the patient; sometimes visible	Edema often described by the patient; visible in 50% of cases
	Impression of heat	Impression of thermal modification associated with a change in skin color and confirmed by thermography[171]
	Poor health of the buccal mucosa (erythema)	
		Modification of sweating[103,171]
Motor modifications	Reduced masticatory force	Reduced strength, trembling, and limited movements[103,171]
	Difficult or impossible to wear dentures	
	Motor function often intact	
Trophic modifications	Discrete osteoporosis	Osteoporosis, often marked[103]
		Poor condition due to painful hygiene[103]
	Symptoms vary both in expression and combination	Symptoms vary both in expression and combination[103]
Progression		
Initial circumstances	Usually after trauma (tooth extraction, antral surgery, accident, etc)	Nearly always follows a nociceptive incident (trauma, surgery, etc)[103]
	Onset often brutal	Onset often brutal[103]
Influence on sleep	Does not disturb sleep	Not described
Long term	Fluctuation of localization of pain: initially in one quadrant, may extend to the opposite or opposing arches	Fluctuation of localization of pain[76]
	Progression over many years with possibility of remission or spontaneous aggravation	Progression over many years with possibility of remission or spontaneous aggravation for certain patients[103]
Treatment	Considered to be the most difficult of the chronic pain entities to control	Very difficult
	A multidisciplinary approach is recommended	
	Even minor surgery is contraindicated due to risk of aggravation	Sympathetic lesion by surgery or pharmacology (guanethidine)
	Repeated anesthesia of the sympathetic ganglia (including the sphenopalatine)	Repeated anesthesia of the sympathetic ganglia
	Locoregional somatic anesthesia	Locoregional somatic anesthesia
	Pharmacotherapy	Pharmacotherapy
	Psychotherapy	Psychotherapy
	Physical therapy, physiotherapy, transcutaneous electrical stimulation	Physical therapy, physiotherapy, transcutaneous electrical stimulation

The description of atypical facial pain is from a preceding review[3] and that of type I CRPS is from 3 references.[76,103,171]

is, however, well known that the analgesic activity of antidepressants is largely independent of their antidepressant activity,[119–121] and these drugs have been shown to be active in non-depressed patients.[2,117] Other studies suggested that a psychogenic pain mechanism might be triggered by a preceding adverse life event,[1,14,122–124] but when a control group was included in the study design there was no difference in the correlation with time of pain onset.[125,126] Another frequent suggestion was that there was a specific personality profile at risk for these pain entities, and that such subjects were more inclined to develop orofacial pain than others. There is now a consensus against such a pain-prone personality profile.[1,54,127–130]

Whatever the truth of the personality issue, there are now many indications that high scores in psychometric scales are found in groups of patients with idiopathic orofacial pain.[131] For example, it is established that there is a comorbidity linking stomatodynia with depression and anxiety.[125,132–134] Some correlation probably also occurs between these psychologic disorders and atypical facial pain or masticatory muscle and TMJ disorders.[9,122,128,130,135] This is more contentious in the case of atypical odontalgia.[127,136] An important point is that this correlation is no more pronounced than with any other chronic pain entity,[137–141] and in many cases, the presence of a psychologic disorder could be the consequence and not the cause of pain.[129] Several psychometric studies indicate that persistent pain sufferers, unlike dysfunctional but pain-free patients,[142] exhibit negative mood changes.[143] The observation of an onset of psychologic disorders preceding the onset of idiopathic orofacial pain symptoms might, however, be a good indication of a causal relationship. Data weakly indicative of such a sequence exist for stomatodynia[125] and for atypical facial pain,[122,124] and a prospective longitudinal study of a large sample of masticatory muscle and TMJ disorder subjects has shown that depression score was a marginally significant predictor of pain onset.[144]

It must also be emphasized that the correlation between psychologic factors and idiopathic orofacial pain noted above does not seem to hold in every case. Several studies have shown that in a given sample of chronic orofacial pain patients, some have high psychologic scores and others do not.[122,131,132,134,145] This observation should make us wary of diagnosis by elimination, since there is a risk of the clinician emphasizing the psychologic factors when clinical examination has revealed only non-specific symptoms with no detectable organic pathology and/or when the response to treatment has been disappointing.

It is thus currently impossible to assert that psychologic or emotional factors, personality characteristics, or life events are strong etiologic factors for all cases of idiopathic orofacial pain. However, as stressed by Okeson[5] for temporomandibular disorders, psychosocial factors may predispose certain individuals to such pain and may also perpetuate the condition once symptoms have become established. It is clear that pure psychogenic pain does exist in a few clinical cases,[146] but more generally and as stated by Gamsa,[147] ". . . psyche and soma do not function as isolated entities, i.e., . . . neither (one) plays an unimpeded role in the aetiology of pain."

Possible Mechanisms of Action of Psychologic Factors

To generate or alter a sensation felt in peripheral orofacial tissues, psychologic factors may cause modulation of the excitatory or inhibitory descending controls, which may be the link between the brain and the segmental level.[148] Central sensitization may follow and induce, for example, orofacial muscle dysfunction, involvement of the sympathetic nervous system, or a centrally triggered algesic substance release in the peripheral tissues.[2,149] Psychologic disorders and other processes—behavioral or cognitive, for example—may initiate, favor, and/or maintain the changes in the activity of the descending pathways. Cultural background and the patient's explanatory models of pain, together with the interpersonal relationship between patient and practitioner, are examples of psychosocial factors that can modify the idiopathic orofacial pain experience.[123,133,150,151] The practitioner's own beliefs and knowledge also influence the observed clinical features as well as the evolution and the treatment outcomes of orofacial pain illnesses.[152–157] This emphasizes the possibility of differences among individuals in how they adapt to the pain.[126,158,159] The different coping strategies adopted by different individuals could help explain the observed correlation between psychologic or emotional factors and pain.

Implications for the Clinical Evaluation of Pain

More recent literature emphasizes a multidimensional concept of pain in which several axes need to be explored.[160] Dworkin and LeResche[160] have

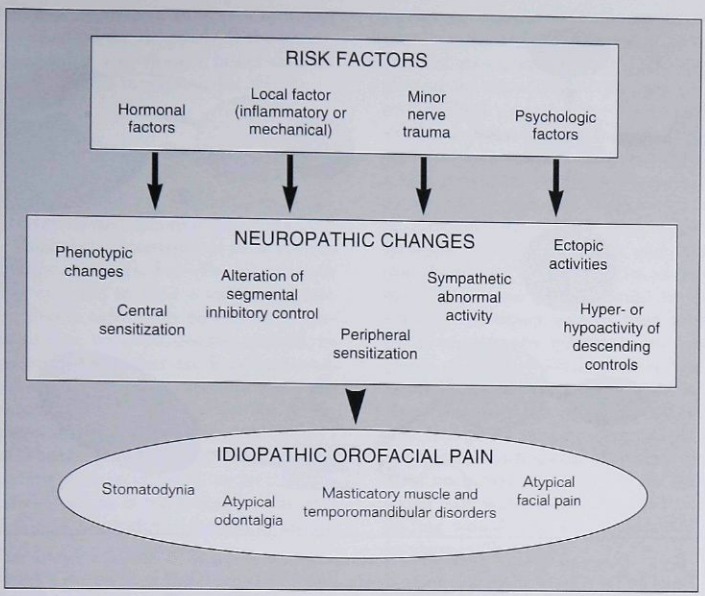

Fig 1 Diagram of a neuropathic hypothesis for the pathophysiology of idiopathic orofacial pain. For each individual, the final symptomatology of the idiopathic orofacial pain depends on the involved tissue but also on the level of activity of the different risk factors for an individual. This, in turn, triggers a particular set of neuropathic mechanisms, the identification of which would be of major importance for the choice of treatment strategy.

proposed axis I as corresponding to the organic correlates of pain (ie, the physical signs) and axis II as corresponding to the psychologic correlates. This double-axis concept is strongly supported by the fact that in the same sample the 2 factors may overlap only marginally.[161] This further stresses the need for 2 therapeutic approaches, according to the evaluation of the 2 axes in any individual patient.

Unifying Hypothesis Based on Neuropathic Mechanisms and Clinical Implications of Variability of Pathophysiologic Mechanisms

At the moment, there is not enough evidence to be conclusive about the pathophysiology of idiopathic orofacial pain, and the possibility of an undiscovered single cause, related in an unknown way to the various mechanisms described here, cannot be definitively dismissed. The following hypothesis can, however, be proposed: all these idiopathic orofacial pain conditions can be explained only by the presence of 1 or more neuropathic mechanisms whose occurrence is facilitated by the presence of 1—or more often several—risk factors (Fig 1).

Changes and/or abnormalities in hormonal status, local irritation, trauma of minor nerves, and psychologic disturbances are commonly observed and can be considered as risk factors. The role of a decrease or an increase in female hormone levels is suggested by a strong female prevalence of these orofacial pain conditions and by the effects of physiologic and therapeutic modification of estrogen levels in pain sufferers. Each of these risk factors may initiate neuropathic changes in the peripheral and/or central nervous system. Several kinds of neuropathic mechanisms may be

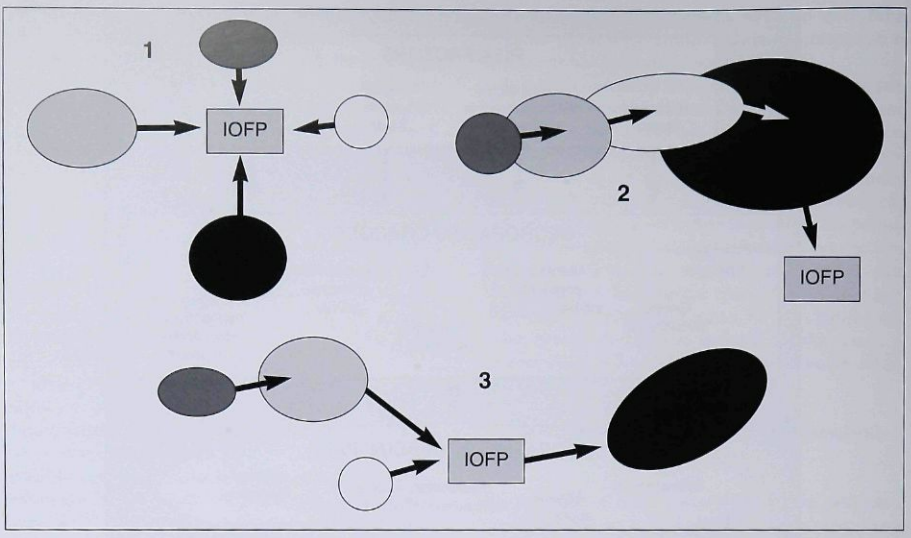

Fig 2 Diagrams showing potential interactions between proposed mechanisms (or risk factors) for the types of idiopathic orofacial pain. Each background shading represents a different mechanism. Diagram 1: The 4 mechanisms summate to cause idiopathic orofacial pain (IOFP). Diagram 2: Sequential appearance of the mechanisms is required to initiate idiopathic orofacial pain. Diagram 3: A single or several mechanisms trigger the idiopathic orofacial pain, and this induces other mechanisms responsible for additional signs.

considered. Peripheral sensitization may occur following the presence of chronic mechanical irritation, infection, or inflammation of facial, dental, or other orofacial tissues. Sectioning of the apical nerve during pulpectomy or tooth avulsion, as well as many other surgical or traumatic events, may be the cause of phenotypic changes and ectopic activities that may induce chronic pain. These peripheral changes may also induce, in central trigeminal nociceptive neurons, central sensitization, which appears to be a key mechanism in many of these idiopathic orofacial pain conditions. Central sensitization can be maintained by ectopic impulses coming from the periphery. Ongoing peripheral afferent activity could also be due to phenotypic changes following hormonal, metabolic, or degenerative variations involving the C-fibers. As inferred from certain clinical features and therapeutic responses common to atypical facial pain and atypical odontalgia, the sympathetic nervous system might also participate in the maintenance of central sensitization. The loss of segmental inhibitory control is also a possible mechanism, which would result from deafferentation following nerve injury and impairment or loss of inhibitory interneurons. In the cases in which psychosocial factors do exist, they could be based, at least in part, on central sensitization maintained by net descending excitatory controls from the brain on trigeminal nociceptive neurons. Any one of these various neuropathic mechanisms may be present in a particular case of the different types of idiopathic pain, suggesting that a different set of mechanisms acts on the different target tissues (Fig 1). In addition, these mechanisms may interact in as-yet unknown ways (Fig 2).

It can be deduced from this discussion that, in each individual, the final symptomatology of the idiopathic orofacial pain depends upon the tissue involved and on the types of risk factors and neuropathic mechanisms that are implicated in that particular patient. The identification of the neuropathic mechanisms acting in any one patient would be of major importance for the choice of a treatment strategy. This identification could be based on the use of clinical tests and symptomatic

investigation[61] and could lead to a new rationale for treatment based on the diagnosis of the pathophysiology involved in a given case, rather than on the choice of an item in a taxonomic list.[162]

Perspectives for Further Research

Three research directions are suggested from the foregoing. The first would aim to improve the definition of the clinical characteristics of these entities by epidemiologic methods. For clinical research purposes, it is essential to have a validated taxonomic system that is sufficiently sensitive and specific to differentiate between disease entities, to form groups of patients that are homogeneous, and to avoid the creation of specious compartments. The second would be to test for the different pathophysiologic mechanisms and factors hypothesized, because knowledge of the pathophysiology of atypical facial pain, atypical odontalgia, and stomatodynia is still tentative. The goal of the third would be to define mechanism-based diagnostic and treatment strategies.

Concerning the first aim, a precise classification using validated diagnostic criteria needs to be established as a priority. It may still be premature to define a precise system of classification, and either the individualization into 4 or more entities or the grouping of all these entities under the single term *idiopathic orofacial pain* may yet prove misleading. The precision of this classification could be improved by studying a large number of patients for whom all the possible symptomatic characteristics are recorded. The analysis of the distribution of the various signs and symptoms would demonstrate the existence or absence of distinct nosologic entities and allow the definition of diagnostic criteria for each entity. Along the same lines, precise diagnostic criteria would be useful to clinically differentiate atypical facial pain and atypical odontalgia from the recently described types of facial or oral migraine.[163,164] A vascular mechanism acting in these types of idiopathic pain has often been cited in the initial description because of the pulsatile nature of the pain, the sympathetic signs, and the presence of a preceding or coincident migraine.[106,115,165] The link with migraine may now be reconsidered because of the action of sumatriptan in the relief of certain cases of idiopathic orofacial pain.[166,167]

The second aim is to encourage research projects that test for the proposed pathophysiologic mechanisms. The potential role of the endocrine system has already been discussed. Again, epidemiologic studies are required to further support the relationship between atypical facial pain or stomatodynia and decreased serum levels of female sex hormones, as observed in the case of young premenopausal women after ovariectomy. Animal studies could help test for suprasensitivity of the orofacial sphere to the female sex hormones that might induce or maintain the pain phenomena, particularly in this part of the body. It would also be interesting to examine the possible correlation between atypical facial pain and osteoporosis of the skull and jaws. The incidence of intramedullary bone defects could be evaluated by imaging techniques such as bone tomodensitometry or scintigraphy performed on a homogeneous group of atypical facial pain sufferers. Another factor that deserves further study is the possible absence of pain during sleep for all these pain entities. This point has often been alluded to in questionnaires, which should dissociate disturbed sleep from nocturnal pain.[168,169] If the absence of nocturnal pain was conclusively determined, then this finding would need to be explained, perhaps by focusing on the circadian cycle of the expression of certain substances, such as serotonin, that are involved in the mechanisms of pain and psychological disorders, but also of sleep control. A neuropathic mechanism triggered by estrogen variations, slight trauma (for example, in atypical facial pain), or by a psychologic shock (as in stomatodynia), has often been suggested. In most instances, this certainly implies phenotypic modifications that may be the common basis of consequent neuropathic changes.[170] It is of the greatest importance to search at the cellular level for modifications in peripheral innervation in subjects suffering from idiopathic orofacial pain. Many phenotypic modifications can be expected, such as density and/or affinity of the different ionic or non-ionic membrane receptors, the increased or decreased presence of which in the peripheral innervation could alter peripheral perception. Other possible pathophysiologic etiologies that have not been discussed in this review include all the peripheral mechanisms related to neurogenic inflammation, which are common to pain, inflammation, and immune mechanisms. Alteration of the complex interactions between these elements by the risk factors discussed above could form the link between the different types of idiopathic orofacial pain. A similar hypothesis has already been proposed for masticatory muscle and TMJ disorders[149] and is currently being studied.

The third research direction is toward defining mechanism-based diagnostic and treatment

strategies.[162] Until now, investigation of the mechanisms underlying each particular clinical case has mostly been empirical. As a priority, such an approach requires the most frequent combinations of types of pathophysiology to be formulated, taking into account the presence of available corresponding therapies. Possible pertinent mechanisms that should be diagnosed include pathologic modification of either C- or A-fiber afferents, leading to tonic or paroxysmal activity in the afferent fibers. Others include lack of segmental or suprasegmental inhibition, implication of sympathetic system activity, and maintenance of central sensitization by peripheral or central inputs. The second step would be to establish diagnostic tests based on objective measurements to characterize the different possible mechanisms. Examples would be response to local anesthetics, topical application of anesthetic cream or capsaicin, and application of mechanical vibration. Also, blood flow measurement by plethismography or thermography might give an indication of sympathetic dysfunction. Diagnosis of the mechanisms by these and other tests would allow appropriate treatment to be chosen and could help in developing new treatments.

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