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Recent advancements in clinical oral physiology with a focus on orofacial pain - a selective review

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ABSTRACT : Clinical oral physiology is a part of dentistry dealing with orofacial pain, jaw function, occlusal problems, and saliva physiology. Essential to this field is deep-seated physiological knowledge as a prerequisite to understand, diagnose, and manage pathophysiological conditions in the orofacial region. This review describes some of the milestones within the knowledge base of orofacial pain. Today, there is significant progress in the classification and diagnostic criteria for most of the orofacial pain conditions. This is matched with an appreciation of the immense complexity of chronic pain, and the need for an interdisciplinary approach for successful management.

Key Words : orofacial pain, trigeminal physiology, pain classification, risk factors

Introduction

Clinical oral physiology has existed at Aarhus University, Denmark since 2001 when it replaced the more traditional field of stomatognathic physiology. In 2015, the name of the section was changed to "orofacial pain and jaw function" to better indicate the clinical scope for patients and colleagues. Nevertheless, all functions remain profoundly anchored in clinical oral physiology. This selective review will briefly cover the most recent achievements within the field and discuss the implications for research, teaching and clinic.

1. Research shows the way forward

One of the core topics in oral physiology research at Aarhus University has for decades been to expand the understanding of complex orofacial pain conditions. This has been attempted through series of both experimental and clinical studies on patients with different types of

orofacial pains *e.g.* painful temporomandibular disorders (TMD) involving the jaw muscles and temporomandibular joints (TMJ), persistent pains following damage to the trigeminal nerves (neuropathic pains) and idiopathic types of orofacial pain such as atypical odontalgia or atypical facial pain. Great emphasis has been devoted to the possibility to develop tools and techniques for differential diagnosis, for example, through systematic studies on somatosensory function using so-called quantitative sensory tests (QST)¹⁻⁵⁾ in addition to electrophysiological measures of trigeminal neuronal excitability (*e.g.* blink reflexes)⁶⁾. These studies have provided good evidence that QST tools and trigeminal reflex measures are sufficiently reproducible and sensitive to contribute with important information about the trigeminal nerve function^{3, 7-12)}. Unfortunately, QST and blink reflexes are technology- and device heavy tools which may not be realistic or even desirable to implement in primary dental care settings. Therefore, research activities have also been focused on the development of easier-to-use

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and more simple techniques such as “semi-quantitative sensory tests” and “qualitative sensory tests” in order to screen for changes in somatosensory function both intra- and extraorally¹³⁻¹⁶. In fact, such studies have paved the road for dentists to assist in the differential diagnosis of trigeminal neuropathic pain conditions.

Simultaneously with these original research projects there has been active Danish participation during the last 4-5 years in the establishment of international guidelines for diagnosis of TMD, trigeminal neuralgia and chronic pains¹⁷⁻¹⁹. For many dentists the diagnosis of more chronic orofacial pain may have been a rather challenging and difficult task due to uncertainty in diagnostic criteria and lack of specific techniques for assessment and examination, however, today and thanks to international consensus work on pain classifications significant improvements have been made. Better and clearer diagnostic criteria are important steps forward both in dental practice and in research settings. Now more emphasis needs to be devoted to the particular types of orofacial pain conditions which falls in-between the main categories of chronic pain such as persistent idiopathic orofacial pain which unfortunately are quite resistant to treatment. It will be one of the main targets for future research endeavors to increase our understanding about pathophysiology and underlying pain mechanisms.

Generally speaking, for all types of chronic (orofacial) pain conditions there is a complex interaction between bio-psycho-social factors, or perhaps more correctly, psycho-bio-social factors to better reflect the immense importance of psychological factors and distress in chronic pain conditions. Several recent case-control studies have identified numerous biological markers for chronic orofacial pain (for a review see : 20) and for example, very recently it has been shown that patients with myofascial TMD have increased levels of interstitial 6, 7, 9 and 13, which could indicate an inflammatory component in TMD pain pathophysiology²¹. Previously it has also been demonstrated that the excitatory neurotransmitter glutamate²² is increased in jaw muscle tissue in patients with chronic TMD pain as well as an increase in plasma levels of dopamine²³. Notwithstanding the importance of such biological markers of chronic TMD pain, many studies have clearly demonstrated the tremendous impacts of psychosocial factors (see reference 24). In order to create a better overview on the many and different types of psychological factors that may be at play in the individual orofacial

pain patient, special techniques and plots have been developed to better provide a “psychological profile”²⁴. Interestingly, it has also recently been shown that so-called perceptual distortion is a robust phenomenon both in response to acute painful stimulation of the orofacial area but also to transient deafferentation using local anesthetic blocks²⁵⁻²⁸. Perceptual distortion is the odd feeling (illusion) that a part of the face may feel “larger” or “swollen” despite the fact that there are no physical swellings or bodily enlargements. More importantly, also chronic orofacial pain patients, and in particular patients with trigeminal nerve damage, will consistently report perceptual distortion when carefully interviewed²⁵⁻²⁸. It can be proposed that there is an urgent need to better understand both neurobiological and psychological mechanisms involved in our own natural perception of the face and mouth and how such mechanisms may contribute to the chronification of orofacial pains. Fig. 1 shows schematically such an attempt to investigate the neurobiology of perceptual distortion.

Genetics and in particular epigenetics are also implicated in shaping the individual pain sensitivity and expression even though the total contribution from such variables may be relatively minor²⁹. For example, a recent study has shown that the specific genotype

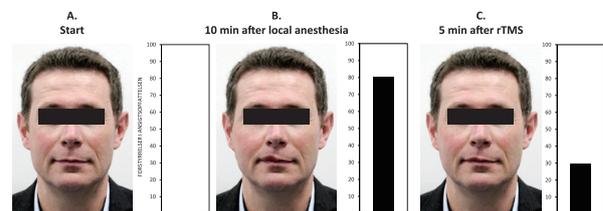


Fig. 1 Illustration of the phenomenon “perceptual distortion” evoked experimentally by injection of local anesthetics around the infraorbital nerve.

The nerve block is associated with a sensation of being “swollen” in the area and lip. This perceptual distortion can be visualized with the use of computer warping of the face using special software and displaying a movie clip with gradual increases in size of the infraorbital region and lip. In addition, the participant can rate the perceived degree of swelling on a 0-100 scale with 0 being “no swelling” (A) and 100 representing “feeling twice as big in the face”. In the present case, the perceptual distortion is rated as 80 on this 0-100 scale (B). Moreover, the somatosensory cortex has been stimulated with repetitive transcranial magnetic stimulation (rTMS) for 40 sec leading to a reversible inhibition of the cortical neurons within the stimulated area and a decrease in the magnitude of perceptual distortion (C). The current ongoing project is supported by a grant from the Danish Research Council to the author. Dr. Lilja Dagsdottir is thanked for assistance with the figure.

of the serotonin-receptor 5HT-3 has some influence on the analgesic effect of granisetron³⁰⁾. Undoubtedly new studies will in the future test the importance of specific genotypes on both pain sensitivity but also analgesic susceptibility³¹⁾.

Frequently the discussion on the importance of the dental occlusion on bruxism and orofacial pain will reappear although there so far is no solid evidence to suggest a strong and simple relationship amongst these factors²⁰⁾. However, most clinicians and researchers will be able to agree on the fact that the etiology and pathophysiology of persistent TMD pain are both complex and multifactorial. The practical problem has been to identify and rank the individual risk factors. A huge and impressive US research project (OPPERA) has during the last 10 years collected and analyzed several hundreds of potential risk-factors in several thousands of individuals. These risk-factors have recently been attempted to be ranked in a "top hundred" hit list to show their relative importance. This has beyond any doubts demonstrated the justification of a psycho-bio-social approach to chronic TMD pain²⁹⁾. We have recently tried to combine the existing knowledge about risk-factors and the pathophysiology of chronic orofacial pains into a new conceptual model termed "stochastic variation"²⁰⁾. The rationale for such an approach is similar to models for caries and gingivitis in which it is the unique and individually different interaction between multiple risk factors that may govern if an individual exposed to risk factors may or may not develop pain (or caries or periodontal diseases). Computer simulations do indicate that a random sequence may have significant impact on the likelihood (risk) to become a chronic pain patient. Obviously such models and simulation have limitations but may serve the important purpose as new concepts and to stimulate lateral thinking to better understand chronification of (orofacial) pain and inspire novel directions for their prevention and management. It seems highly prudent not to focus on mono-therapy but rather to implement poly-therapeutic approaches for the individual patient in pain composed of both psychological, physical/physiotherapeutic and pharmacological approaches. Future research should focus on better identifying and understanding the significance of individual risk factors for the individual patient and to "tailor" management in a high-precision medicine manner²⁰⁾.

In general, there is a concerted action devoted to the identification of new biomarkers - not only for pain -

but also for other oral health conditions like caries and periodontal diseases. One approach is to use genetic analyses of blood and as another obvious candidate also to use saliva as a diagnostic media. Saliva indeed has a very important role for oral function and health and deserves special attention in future research projects.

Although diagnostic gen tests must be considered to represent amazing new opportunities in an era of precision medicine, then they may not stand alone in the battle against chronic orofacial pain and functional disturbances. The complexity of orofacial pain is simply enormous and research will need to be highly coordinated within both the basic neurobiological sciences but also in the fields of psychological distress and clinical sciences. This simple fact causes an important problem not only for orofacial pain research but also for teaching and clinical management.

2. Challenges or problems?

The research-related issue can briefly be stated to be directly linked to the limited resources that for most countries in the world are allocated to oral health research. Most often oral health research will have to survive on only modest funding and is rarely supported by larger national or international grants. In view of our current knowledge about the complexity of orofacial pain and functional disturbances our research strategies need to incorporate an interdisciplinary and translational approach. Therefore oral health research must seek collaborations with the general health research and life sciences. It is also unfortunate that most countries in the world do not have formalized post-graduate clinical training programs in orofacial pain and functional disturbances. Moreover, the undergraduate programs in this field are not always optimal or adhere to the core curriculum guidelines provided by the International Association for the study of Pain. From a clinical perspective the problem with an impaired knowledge transfer and dissemination will lead to diagnostic errors and suboptimal management or even malpractice. From an educational perspective it must be considered of the utmost importance that clinical oral physiology including orofacial pain and functional disturbances are given high priority and to be included in the "core curriculum" for dentistry in order to provide a strong foundation for clinical management.

Furthermore, it seems important and appropriate

to integrate a good understanding of orofacial function together with topics such as prosthodontics and orthodontics and actively link the current knowledge related to the complexity of orofacial pain with other topics such as endodontics, oral surgery and oral medicine.

Due to the current situation for oral health research, at least in Scandinavia, we have taken the initiative to establish a collaboration between sister sections within Sweden and Denmark - SCON which stands for Scandinavian Center for Orofacial Neurosciences. At present SCON is represented by professors Malin Ernberg og Mats Trulsson at Department of Dental Medicine, Karolinska Institutet and professor Thomas List og Per Alstergren at Malmö University and Section for Orofacial Pain and Jaw Function at Institute for Odontology and Oral Health, Aarhus University. In total about 40 active researchers are members of SCON and a wide range of research techniques and competencies are available which allows bigger and more ambitious research projects to be planned and executed. Likewise the SCON collaboration offers both under- and postgraduate training and courses. SCON is one example of novel thinking to prevail in research and education when resources and funding are limited. Networking and international collaboration seems to be even more important for oral health research in the future, if not only there is a need for more research, but also for better research.

Summary

The field of clinical oral physiology has developed rapidly during the last two decades and is emerging to be a significant and strong part of classical dentistry. This achievement is based on solid research activity projecting directly into the clinic with better techniques and guidelines for diagnostics as well as management. The challenge - or problem - will be to secure a continued growth and development within the field, for example, by strategic interdisciplinary collaborations with medicine and life sciences in addition to more formalized postgraduate programs specifically related to orofacial pain and functional disturbances.

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