Neuroscience Meets Clinics

Annual Scientific Meeting of the European Academy of Craniomandibular Disorders September 18–21, 2008 Zurich, Switzerland

The title of the open scientific meeting of the European Academy of Craniomandibular Disorders (EACD) underscores the scientific evolution that the field has made in the past 30 to 40 years, and the fact that it is today impossible to deal with patients with craniomandibular disorders (CMD) and orofacial pain without a sound knowledge of neurophysiology, pain mechanisms, joint-muscle physiology, and basic treatment principles. To treat orofacial pain one must know "what is going on in the patient's mind."

The meeting provided a mix of basic and clinical science, starting on Thursday morning with a symposium entitled "An update on head and neck pain" that gave insight into the latest information on the pathophysiology and therapy of primary headaches and cervicogenic pain. The second and third day were dedicated to topics more closely related to CMD and orofacial pain. The Sunday morning was devoted to presentations by Academy candidate members. It is the Academy policy that a candidate must give two presentations, evaluated by a scientific panel, in order to become a full member. A number of posters rounded out the program. The following is a summary of the 3-day meeting.

An Update on Head and Neck Pain

Migraine, which is often co-morbid with CMD, is considered a disorder of neurovascular transmission without structural lesions. It has been suggested that the problem is primarily a central nervous system disorder without abnormal peripheral input. There is, however, abundant evidence to refute this hypothesis. As Messoud Ashina (Glastrup, Denmark) pointed out, a solid body of evidence shows that the input arises from perivascular sensory nerve terminals of the trigeminal nerve.

Central factors play a crucial role in the etiology of tension-type headache, particularly in the more severe forms of the disorder. According to Lars Bendtsen (Glostrup, Denmark), it is likely that frequent nociceptive input from muscles in the cephalic region induces central sensitization of the upper cervical spinal dorsal horn/trigeminal brainstem neurons, with secondary sensitization of supraspinal neurons and impaired descending inhibition.

Primary headache syndromes such as migraine and cluster headache manifest normally with pain in the frontotemporal, orbital, or supraorbital regions. However, clinical experience shows that otherwise typical primary headache syndromes can present with pain localized in the 2nd and 3rd rather than the 1st division of the trigeminal nerve. Peter Sandor (Zurich, Switzerland) noted that these orofacial pains need to be recognized as ectopic manifestations of primary headaches as they respond to pharmacotherapy targeted at the suspected underlying primary headache syndrome.

Possible links between masticatory as well as neck muscle disorders and vertigo were discussed by Dominik Straumann (Zurich, Switzerland). In these patients neck muscles become stiffer leading to slower head movements and less vertigo. Similarly, muscle spindle input on the side of a vestibular deficit increases, which leads to a greater effectiveness of cervico-postural and cervico-ocular reflexes. A hypothetical mechanism of disrupted reflex pathways from the vestibular labyrinths to head and neck muscles implies that the vestibular deficit is primary and the cervical and masticatory dysfunctions are secondary (Dominik Straumann, Zurich, Switzerland).

From the Image of Pain to Pain Imaging

Neuroimaging has greatly improved our understanding on pain processing and modulation by depicting those brain areas that are activated

during painful stimuli. This has led to the concept of the "pain matrix," eg, of all the brain areas that are involved during a painful experience and also during painful tooth stimuli as described by Dominik Ettlin (Zurich, Switzerland). With regard to emotional processing of dental pain, it is remarkable that the amygdala responds more strongly to contralateral stimuli, which may reflect a peculiarity of dental pain processing. Carlo Porro (Modena, Italy) reported that the brain is activated not only during but also before a painful stimulus, eg, when a painful condition is anticipated. Anticipation is a complex condition where different factors such as attention, motivation, fear, and anxiety can come into play, allowing anticipatory adaptation and coping with emotional stimuli, influencing behavior as well as pain perception.

Commonalities of Psycho- and Pharmacotherapy

David Linden (Bangor University, Wales) made clear that cognitive-behavioral therapy and other psychological interventions are more than just mere words as they effectively modulate the activity of specific brain areas. For instance, during hypnosis, nociceptive stimuli produce less activation of brain areas that process the sensory and affective components of pain, in parallel with a decrease in pain intensity. In phobic patients, cognitive behavioral therapy results in decreased activity in limbic and paralimbic areas. Interestingly, similar effects have been observed after successful intervention with selective serotonin reuptake inhibitors, indicating commonalities in the biological mechanisms of psycho- and pharmacotherapy.

This commonality is present also in placebo research, as Fabio Benedetti (Turin, Italy) demonstrated. Indeed, placebo interventions lead to the release of dopamine and opioids in the brain, as the placebo effect is eliminated by naloxone. Conversely, nocebos may activate cholecystokinin through the induction of anticipatory anxiety. Patients with Parkinson's disease activate endogenous dopamine following placebo administration and changes in neuronal activity have been registered by means of single-neuron recording during the placebo response from awake Parkinson patients. Placebo interventions are therefore able not only to decrease pain but also parkinsonian tremor.

The Plastic Brain

Recent neuroscientific evidence has revealed that the adult brain is capable of substantial plastic change in areas such as the primary somatosensory cortex that were formerly thought to be modifiable only during early experience. Lutz Jänke (Zurich, Switzerland) showed that the musician's brain is shaped by exercise, that there are strong differences in the neuroanatomical architecture and neurophysiological functioning between professional musicians and non-musicians, and that there are rather subtle and strong differences between the musicians themselves, depending on the amount of practice. While a continuous incoming stimulus barrage leads to an expansion of the cortical representation area as shown by the reorganization of musician brains, sensory deafferentation also leads to somatosensory cortical map reorganization. This occurs also after the extraction of the central incisor in naked mole-rats, as explained by Erin Henry (Saint Louis, Missouri). After extraction the deactivated tooth zone becomes activated by stimulation of surrounding orofacial structures.

CMD Pain: Not an Occlusion-Related Issue!

If the participants had not realized how far the field of orofacial pain has moved in the past decades, this became evident during the lecture by Christian Stohler (Baltimore, Maryland). He started by saying that today's knowledge of orofacial pain states presents a compelling case for studies aimed at identifying disease genes that confer liability. To illustrate the new thinking of the causation of clinically relevant orofacial pain, he discussed the role of gene variants affecting the function of catechol-O-methyltransferase (COMT) and the vulnerability mediated by gene variants influencing the function of neuropeptide Y (NPY). The vulnerability of an individual to pain sensitivity is genetically determined, and one of the genes involved in pain processing is COMT that is involved in the inactivation of catecholamine neurotransmitters. This gene modulates for instance the intensity of the pain elicited by the injection of a hypertonic saline solution in the masseter muscle. Highly expressed NPY diplotypes predicted significantly higher levels of stress-induced μ-opioid activation in several brain regions after pain generation in the masseter muscle through an injection of hypertonic saline. Thus, clinicians need to consider persistent orofacial pain states as

conditions with a genetic underpinning that mediate either resiliency or, alternatively, susceptibility to disease through a host of genes.

Neuropathic Pain: A Diagnostic Challenge

After pointing to the interrelationship between herpes virus and neuropathic pain, Craig Miller (Lexington, Kentucky) discussed the possibilities of using recombinant alpha herpes virus for the delivery of transgenic products with analgesic potential to neurons of the dorsal root/trigeminal ganglia. This therapy raises new hopes for patients suffering from chronic pain because it bypasses many of the debilitating side-effects associated with traditional painkillers.

At present there are no specific diagnostic tools that permit an unequivocal diagnosis of orofacial neuropathic pain, said Peter Svensson (Arhus, Denmark). Accordingly, he discussed a recently proposed grading system that should allow diagnosing the presence of neuropathic pain with different levels of certainty. This classification system relies on four criteria. The first criterion relates to pain distribution, the second to establishing a link between history and the pain distribution, the third to a clinical examination with demonstration of neurologic signs (negative or positive sensory signs) that support the presence of a lesion or disease consistent with the distribution of pain, and the fourth to diagnostic tests for the presence of a relevant disease or lesion affecting the somatosensory system.

One form of neuropathic oral pain is postimplant pain. This topic was discussed by Gary Heir (Bayonne, New Jersey), who reported unpublished data indicating that the activity of Aδ and Aβ, fibers can be enhanced up to 3 months after implantation.

Cartilage Mechanobiology

Luigi Gallo (Zurich, Switzerland) demonstrated, contrary to the firm belief of many practitioners, that the temporomandibular joint (TMJ) is loaded under function. Prolonged static loading of disc cartilage seems to modify its mechanical response, increasing not only compressive stresses but also tractional forces. Studies on the dynamics of compression areas in the TMJ show that plowing forces can occur through the disc during functional movements, due to stress-field translation. Disc loading patterns appear to be related to condyle and fossa anatomy. Thus, the loading patterns might contribute to cartilage wear and fatigue because of the anisotropic material properties of the disc, which is weaker mediolaterally. Furthermore, excessive loading patterns can initiate a catabolic reaction of the chondrocytes due to mechanotransduction. Peter Torzilli (New York, New York) insisted that dynamic loading is a precondition for a normal cartilage function since the chondrocytes are nourished through the liquid phase diffused in the pores of this avascular tissue. In normal healthy tissue, the cellular metabolic rate is fairly low but the synthesis and degradation of proteoglycan is stable, maintaining mechanical function. Clinical evidence indicates that the initial damage to the articular cartilage occurs at or just below the articular surface.

Are Myogeneous Masticatory Pain and Work-related Pain Linked?

There is good evidence that prolonged low-level muscle contractions or repetitive muscle work are risk factors for myogeneous pain. Mauro Farella (Zurich, Switzerland) noted that wake time parafunction is more similar to prolonged/monotonous muscle work and therefore a larger risk factor for myalgia than sleep bruxism, because the former accompanies prolonged, low-level clenching. Indeed, patients affected by masticatory muscle pain report wake time tooth clenching habits more frequently than normal subjects. Local tissue damage has been documented in muscles of patients with work-related myalgia. One of the hypotheses is that some motor units containing type I fibers ("Cinderella motor units") are contracting throughout the entire motor task, and may therefore become overloaded and damaged leading to focal inflammation and, eventually, to nociceptor sensitization and muscle pain. Motor unit territories in the human jaw muscles are focally distributed, and are related to anatomical compartments, providing an anatomical substrate for selective regional motor control. Consequently, it is possible that during specific tasks, eg, parafunctional habits, selected muscle fibers contract for longer periods; indeed, motor units that are continuously active during prolonged low-level clenching tasks (up to 30 min) have been recorded in the masseter muscle. Farella's point of view was substantiated by Andreas Klipstein (Zurich, Switzerland) who reported that the pathomechanism of musculoskeletal disorders depends on the localization, the type of tissue involved, the force levels, and the possibility of recovery. Interestingly,

work-related muscular neck pain is often triggered by computer work that is also characterized by low force demands, exactly as low-level clenching during wake time parafunction. He added that psychosocial stress is also a risk factor for musculoskeletal disorders, underlining the multifactorial etiology of muscle pain.

A Specific Therapy for Myogeneous and Arthrogeneous Pain?

The introduction of the Research Diagnostic Criteria for Temporomandibular Disorders aimed to provide a better definition of subgroups of patients by the use of clear inclusion and exclusion criteria. Antoon De Laat (Leuven, Belgium) noted that the distinction between myofascial pain and arthralgia is mainly made on the basis of positive signs upon palpation of the tissues involved, inspired by the presumed etiological factors, eg, overloading muscles by parafunctions, or disc displacements causing inflammation/irritation of joint tissues. The underlying pathophysiological mechanism for these pains appears similar, raising the question of whether myogeneous and arthrogeneous pain must be approached in different ways. He concluded that in clinical reality, the management approach appears very comparable. He added that it is important to develop instruments able to depict those cases at risk for developing chronic pain in order to address from the beginning the emotional, affective, and cognitive pain dimension by means of a multimodal approach.

Patient-Doctor Relationship: The Key to Treatment Success

Empathy, the ability to share and understand other's emotions, is essential for positive interactions with the patient and therefore for a successful therapy. Overlapping brain regions are activated when we experience emotions and when we observe someone else in an emotional state. Susanne Leiberg (Zurich, Switzerland) reported a large-scale network for empathy is composed of the mirror neuron system, the insula, and the limbic system, where a crucial role in understanding our own and others' emotions falls to the insula. Empathic responses are not automatic but can be modulated by contextual factors. It is suggested that impaired empathic abilities, as found in alexithymia or Asperger syndrome patients, are associated with insula hypofunction.

New Drugs for Persistent Pain?

The loss of inhibitory control by GABAergic and glycinergic dorsal horn neurons plays a major role in central sensitization in particular in the generation of allodynia and spontaneous pain. Spinally produced prostaglandin E2 inhibits strychnine-sensitive glycine receptors, and factors released from activated microglia impair the chloride homeostasis in dorsal horn neurons and render GABAergic and glycinergic inputs less inhibitory or even excitatory. These observations led Ulrich Zeilhofer (Zurich, Switzerland) and his group to investigate whether and which kind of benzodiazepines could be used to manage hyperalgesia. He reported that application of the compound L-838,417, a benzodiazepine acting upon spinal GABAA receptors containing the $\alpha 2$ and/or $\alpha 3$ subunits and sparing activation of the $\alpha 1$ subunit, exerted a pronounced anti-hyperalgesic action in animals without producing sedation, motor impairment, or tolerance development as these side effects are mediated by the $\alpha 1$ subunit. These experiments may open the door to the development of a new class of drugs for the treatment of chronic pain syndromes, which have become unresponsive to classical analgesics.

For many years capsaicin has not only been used to study the function of sensory neurons, but also to treat peripheral neuropathic pain. For topically applied capsaicin, there is evidence of effectiveness beyond placebo. However, as Marlen Petersen (Mannheim, Germany) pointed out, capsaicin is effective only when spontaneous activity originates in the primary nociceptive neuron. The action of capsaicin is mediated by the TRPV1 receptor, leading to membrane depolarization. Initially, the topically applied capsaicin evokes a burning sensation or pain and neurogenic inflammation. For intraoral use, a concentration of 0.025% is recommended. To decrease the burning sensation lidocaine can be added.

Possibilities and Limits of Pharmacotherapy in the Treatment of Chronic Pain

It is well known that the efficacy of currently available drugs for the treatment of chronic pain is limited. More than ever is interdisciplinary therapy indicated, as became apparent during the lecture by Herta Flor (Mannheim, Germany). She reported that chronic pain must be viewed as the result of a learning process with resulting central

neuroplastic changes that are difficult to manage with pharmacotherapy. In chronic pain states the initial cause of the pain is often no longer relevant and central factors play a major role. As a consequence, pharmacotherapy is most appropriate in acute pain whereas in chronic pain states behavioral approaches such as operant behavioral and cognitive-behavioral treatments, biofeedback, and relaxation techniques are more suitable. Moreover, new treatment modalities aimed at modifying the input into the affected brain region seem promising for the treatment of chronic pain states. Indeed, patients who systematically used a myoelectric prosthesis providing sensory and visual as well as motor feedback to the brain showed much less phantom limb pain and cortical reorganization than patients who used either a cosmetic or no prosthesis. Other new therapeutic modalities are focussing on the combination of behavioral and pharmacological interventions in the hope that this approach is more effective than behavioral treatment alone in the extinction of pain memories.

Paul Nilges (Mainz, Germany) addressed the issue of pain acceptance. He distinguished between assimilative and accommodative (flexibility) coping. The first involves active attempts to alter unsatisfactory life circumstances and situational constraints in accordance with personal preferences. The second is directed towards a revision of self-evaluative and personal goal standards in accordance with perceived deficits and losses. Assimilative coping might inhibit any further effort to fight pain and, thus, reduce negative affect due to recurring treatment failure. Conversely, accommodative coping, eg, flexibility, operates as a protective resource and helps to maintain a positive life perspective. Most important, the ability to adjust personal goals attenuates the negative impact of the pain experience on psychological well-being. Indeed, the higher the acceptance the lower the pain intensity, the number of physician visits, the drug intake, the disability, the inactivity, the depression, and pain-related anxiety.

"Make People Feel Better While They Get Better"

To crown the 2-day event, Guido Macaluso and Giovanni Mauro (Parma, Italy) discussed whether TMD therapies are effective or efficacious. The first term describes the real therapeutic impact, while the second explains the subjective, perceived impact of a given successful treatment experience. In this sense a placebo should be by definition a treatment without efficacy, ie, which produces no specific biologic effects on the medical condition or symptoms that a patient is experiencing. Nevertheless, as already pointed out previously, increasing evidence suggest that placebos have a great effectiveness. A thorough evaluation of the literature on CMD management suggests that every treatment for pain contains a placebo component, which sometimes is as powerful as the so-called "active" counterpart. While the deceptive use of placebos must be considered unethical, every health provider who is treating pain patients must be aware of this important phenomenon in order to harness its huge potential. Thus, the take home message was "make people feel better while they get better."

Concluding Comments

All in all it was a very stimulating scientific meeting, in which the topic of CMD and orofacial pain was discussed from different perspectives, each speaker relying on sound, up-to-date, and scientifically based evidence. No room was left for speculations and expert opinions. Research on these topics is very active and, unfortunately, the gap between basic research findings and clinical application is still wide, especially as far as the development of new drugs for the treatment of chronic pain. The presentations made it clear that today it is impossible to practice in the field of orofacial pain without a deep knowledge of orofacial pain. The time in which TMD was seen as a consequence of peripheral myoarthropathic changes, not to say of condylar position changes or of a malocclusion is over forever. Lastly, the organizing committee has to be congratulated for an excellent social program that provided enough time for stimulating scientific and non-scientific discussions among the participants.

Sandro Palla
Associate Editor