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Migraine neurobiology and treatment

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Fast tracking of new drugs for migraine has faced the major challenge of poorly predictive preclinical models. Indeed, novel migraine-specific preventive drugs have not been developed in decades. Furthermore, the acute therapy armamentarium remains suboptimal, with no new chemical entities since the triptans. On the other hand, human experimental studies are surfacing as a powerful tool in targeted migraine therapy. To this end, human studies have identified three novel targets: inhibitors of cortical spreading depression, antagonists of calcitonin gene-related receptors and chemicals that prevent the production of nitric oxide. Two of these novel mechanisms are in phase 3 clinical development and one is in phase 2. These encouraging observations, which are based on 20 years of research in human models, have led us to develop a research paradigm for the identification of novel migraine drug targets, which combines human provocation studies and preclinical models.

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Chronic headaches—Goals and obstacles

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Most patients with chronic headache are severely affected and characterized as refractory to treatment. The individual and societal burden of chronic headache is very high. Pharmacological treatment may be insufficient and is often associated with side-effects so other aspects of pain management are often required. A high number of these so-called refractory patients are also suffering from medication-overuse headache, i.e. 20–25% of new patients to tertiary headache centres and a detoxification of analgesics and triptans is thus essential before they can be classified as treatment resistant. A combination of patient education, optimal pharmacological treatment, stress- and pain-management and physical therapy are often required. In recent years international guidelines for multidisciplinary treatment of headache have been introduced and many headache centres have successfully included these elements in their treatment strategies. Evidence for the effect of such integrated headache care is now accumulating and a review of the existing literature will be presented.

Recommended reading

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- [2] Steiner TJ, Antonaci F, Jensen R, Lainez MJ, Lanteri-Minet M, Valade D. Recommendations for headache service organisation and delivery in Europe. *Journal of Headache and Pain* 2011;12:419–26.

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Trigeminal neuralgia and other cranial neuralgias

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Trigeminal neuralgia is an extremely painful disease, which may be difficult to treat. There is a huge lack of high quality research in this field and essential aspects such as epidemiology, pathophysiology, diagnosis and optimal treatment are far from understood. Differential diagnosis from other types of cranial neuralgias and facial pains may be difficult. Management consists of prophylactic pharmacotherapy and surgery in selected cases. This presentation will focus on the practical management of trigeminal neuralgia. Recommendations will be given based on available scientific evidence and international guidelines. How is correct diagnosis obtained, and which clinical and paraclinical examinations should be performed? Which drugs should be used, in which combinations? How is the occasional acute severe worsening of pain handled? When should surgery be performed, and which kind of surgery is recommended? How should the patients be followed up in the out-patient clinic? It is the aim that the audience will get a better understanding of how patients with this extremely painful disorder are optimally managed.

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Temporomandibular disorders: Pathophysiology and diagnosis

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Temporomandibular disorders (TMD) are a heterogeneous group of musculoskeletal problems in the craniofacial region [1]. It is important to recognize that not all TMDs are painful, but pain in the masticatory muscles and temporomandibular joint (TMJ) are frequent complaints and can lead to impaired jaw function, for example difficulties to eat or yawn, as well as a range of emotional and psychosocial problems. Some of the TMDs may overlap with headache and other orofacial pain conditions and may share many of the clinical manifestations and perhaps underlying pathophysiology [2]. It is therefore important that there are reliable and valid diagnostic criteria available. The talk will briefly describe the current international classification system for TMDs.

Clinical experience and research over the last decades have clearly demonstrated that there are no simple or mono-causal explanation for most TMDs and a multitude of etiological factors and pathophysiological models have, indeed, been proposed [1]. The talk will critically review some of the possible risk factors and underlying mechanisms of persistent TMD pain. Implications for a best-evidence management of TMD will be mentioned [3].

Recommended reading

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- [2] Nixdorf DR, Drangsholt MT, Ettlin DA, Gaul C, De Leeuw R, Svensson P, Zakrzewska JM, DE Laat A, Ceusters W. Classifying orofacial pains: a new proposal of taxonomy based on ontology. *Journal of Oral Rehabilitation* 2012;39:161–9.

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HIV-associated painful polyneuropathy

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According to WHO/UNAIDS data, there are approximately 33 million people in the world who are currently living with HIV, with the major burden of disease affecting low/middle resource communities in sub-Saharan Africa, Asia and South America. In the Scandinavian/Nordic countries, where there are effective infection prevention programmes and essentially full antiretroviral (ARV) drug access, there are ~24,000 people living with HIV (prevalence ~0.1–0.4%). A success story has been the advent of combined ARV therapy, which is now available to essentially all patients in wealthy countries and an increasing number of people in low and middle resource regions. This advance is converting HIV infection from a largely fatal disease (via the manifestations of AIDS), into a controlled chronic illness where people live relatively normal lives, and perhaps even normal life expectancies (although it is too early to tell), as a result of undetectable viral loads and lack of suppression of CD4 cell function. Therefore, a major issue in the management of people living with HIV is now the control of quality of life-limiting symptoms resulting from the manifestations of HIV infection which are either not suppressed by ARV therapy or occur as a result of the adverse effects of ARV drugs. Thus, although new infection rates may be decreasing, the increasing number of HIV positive people surviving by accessing effective ARV therapy implies an increasing healthcare burden.

Data from both high and poor resource settings indicates that HIV-associated peripheral sensory polyneuropathy (HIV-SN), usually accompanied by neuropathic pain, afflicts ~40% HIV positive people whose infection is otherwise well suppressed by ARV drugs. This makes HIV-SN one of the most prevalent manifestations of HIV infection in the ARV era and thus it will assume increasing healthcare importance as global access to ARVs continues to improve. Although, particularly in the context of AIDS, many, often exotic, mono- and poly-peripheral neuropathies have been described as being associated with HIV infection, HIV-SN is now by far the most prevalent. The broad banner of HIV-SN covers two aetiologically distinct, but clinically indistinguishable entities, originally called AIDS-Associated Sensory Neuropathy and ARV Toxic Neuropathy. However, since there are now clear data from a number of regions demonstrating that the incidence of HIV-SN has not decreased as less neurotoxic ARV drugs have been introduced, perhaps the importance of ARV Toxic Neuropathy in contributing to the clinical picture of HIV-SN may have been overestimated. The usual clinical presentation of HIV-SN is of a painful distal symmetrical sensory polyneuropathy characterised by a “die back” pattern of axonal degeneration, mainly of small fibres.

The lecture will commence with a brief summary of what is known about the prevalence of, risk factors for and clinical presentation of HIV-SN. This will be followed by a meta-analysis of analgesic clinical trials for HIV-SN, revealing an area of therapeutic need. Drugs that are effective for other forms of peripheral neuropathic pain, such as amitriptyline, gabapentin and pregabalin are not effective for pain relief in HIV-SN, although pregabalin does have efficacy for a subset of patients characterised by a pin prick hyperalgesia sensory profile. Cannabis is efficacious, although the barriers to this approach, particularly that of long term psychosis

risk and legality preclude this as a routine therapy. Although the initial clinical trial of topical 8% capsaicin for HIV-SN indicated efficacy, this is now counterbalanced by a more recent study in which efficacy was not demonstrated. Surprisingly, despite their widespread use and guidelines promoting their use, opioids have not been adequately assessed for analgesic therapy in HIV-SN. The discussion will then move to what we have learned about the pathophysiology of HIV-SN from animal models. In particular, the role of the HIV glycoprotein GP120 will be discussed: although it was originally hypothesised that this was due to a direct interaction between GP120 and sensory neurones involving CCR5 and/or CxCR4 chemokine receptors, it is now apparent that an indirect GP120 driven processes via macrophages, Schwann cells and/or other non-neuronal intermediary cells predominates. The release of neurotoxic cytokines, such as TNF- α , appears to be a key intermediary step in GP120-induced axonal degeneration. Finally, identification of novel analgesic targets using gene microarrays of dorsal root ganglia harvested from animal models of HIV-SN will be briefly described.

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Recommended reading

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Keynote: Neuronal and glial signalling in pain neuroplasticity

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A body of evidence has emerged indicating that pain behaviours resulting from injury to peripheral nerves are critically dependent upon interactions between neurons and glia in the dorsal horn of the spinal cord. Microglia have been found to play a causal role in neuropathic pain behaviours resulting from peripheral nerve injury, and specific neuron–microglia–neuron signalling pathways have been elucidated. Within the dorsal horn, microglia suppress neuronal inhibition by a sequence of steps involving activation of microglial P2X4 receptors causing the release of BDNF. BDNF acts on trkB receptors, which leads to a rise in intracellular chloride concentration in dorsal horn nociceptive output neurons, transforming the response properties of these neurons.

In addition to suppressed inhibition, evidence indicates that following nerve injury there is activity-dependent facilitation at dorsal horn glutamatergic synapses which enhances nociceptive transmission. This enhancement is mediated by intracellular signalling networks involving serine/threonine and tyrosine kinases within nociceptive transmission neurons. Key for this enhancement is facilitation of NMDA receptor function by the non-receptor tyrosine kinase Src. Src is anchored within the NMDA receptor complex by the protein ND2. Disrupting the ND2-Src interaction in vivo