FW 1-1

Assessment of neuropathic pain: peripheral neurophysiology and reflex responses

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The standard nerve conduction study, although it does not provide information on small-fibre function, is a most useful tool for documenting and assessing peripheral neuropathies. So far, microneurography cannot be suggested as a routine procedure for the assessment of patients with peripheral neuropathic pain (Good Practice Point). However, we encourage new studies in selected groups of patients with neuropathic pain, to understand the frequency and pathophysiological role of spontaneous ectopic activity, and the potential efficacy of drugs in reducing ectopic impulse generation in peripheral nociceptors. Pain-related reflexes appear to be diagnostically useful only for facial pains. For the upper limb, the cutaneous silent period (CSP) is probably inadequate in neuropathic pain. Regarding the lower limb, the nociceptive flexion reflex (RIII) is still being used in physiological and pharmacological studies of modulation of nociception, but not in patients with neuropathic pain. The trigeminal reflexes mediated by A-beta fibres are useful in the diagnosis of trigeminal pain disorders, as they are abnormal in patients with structural damage, in conditions such as trigeminal neuropathy and PHN, and normal in patients with classic trigeminal neuralgia (grade A).

FW 1-2

Pain-related evoked potentials for the assessment of the nociceptive system

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Since standard electrical nerve stimulation with recording of somatosensory evoked potentials (SEP) only is a test for thickly myelinated Aβ-fibres and the dorsal column pathway, they are not suitable to examine the nociceptive system. As functional test for the nociceptive system recording of laser-evoked potentials (LEP) has been established and is recommended as diagnostic test in the EFNS guidelines for the assessment of neuropathic pain (Cruccu et al. 2004). Induced by brief contact-free infrared noxious heat stimuli, LEP reliably indicate lesions – by means of amplitude reduction and/or latency prolongation – of peripheral thinly myelinated fibres like in small fibre neuropathies, spinothalamic tract lesions like in MS, syrinx or trauma, and brain stem lesions like in Wallenberg’s syndrome. This will be demonstrated in clinical case examples. An important aspect will be the relationship of ongoing neuropathic pain and LEP amplitudes, and LEP as a potential predictor for surgery outcome after spinal root decompression. Finally, a brief look at alternative methods to record evoked potentials following stimulation of electrical, mechanical, heat, and cold stimuli will round up this overview on pain-related brain potentials.
FW 1-3

Functional brain imaging to study pain patients

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Although there is fascination for images in medicine, anatomical lesions cannot account for the mechanisms leading to chronic pain. Neurophysiology and functional imaging techniques can, on the contrary, contribute relevant elements for this. Acute pain gives rise to a coordinated activation of a complex network of cortical and subcortical structures. This network has variable boundaries, but it includes a relatively stable core commonly termed « Pain Matix » (PM) comprising the thalamus, the primary and second somatic areas, the insular cortex, the mid- and anterior cingulate areas, and less consistently the cerebellum, the dorsolateral frontal and orbitofrontal cortices. Combination of activity in these different regions underlies different aspects of the pain experience. While the PM level of activity tends to increase with the intensity of experimental pain, in chronic neuropathic pain there is a decrease of metabolic activity in some of these regions, in particular in the thalamus. This paradoxical result is probably explained by changes in electrophysiological activity documented with intracerebral and intrathalamic recordings. This reminds of focal hypometabolism observed in epilepsies. Hyperalgesia and allodynia do not appear as a mere exaggeration of normal pain responses, but rather as the result of a complex interaction between hypo- and hyper-activities within the PM network. Particularly important appears the ratio of activity between insular regions in both hemispheres, and between the mid- and perigenual regions in the cingulate gyrus. Functional imaging during neurostimulation for pain relief contributes to the understanding of some of the mechanisms involved in the genesis and maintenance of chronic pain. Motor cortex stimulation enhances the activity of ipsilateral thalamus (which tends to be hypoactive in chronic pain) and in other structures involved in the processing and control of pain (perigenual cingulate, orbitofrontal cortex, brainstem). The time constant of these changes may outlast by hours the neurostimulation itself, suggesting slow neurotransmitter activity. PET-scan has recently suggested that enhanced endorphine secretion may contribute to the analgesic action of motor cortex stimulation.

Clinical phenotypes of myasthenic syndromes

FW 2-1

Signs and symptoms of autoimmune myasthenia gravis and the Lambert-Eaton myasthenic syndrome

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Three well defined autoimmune diseases of the neuromuscular synapse are known. The most frequent form is myasthenia gravis with acetylcholine receptor antibodies (AChR-MG). MG with antibodies to Muscle-Specific Kinase (MuSK) or the Lambert-Eaton myasthenic syndrome (LEMS) are about 20 times rarer. The reported incidence of AChR-MG varies between 2 and 20 per million inhabitants per year, while the prevalence is 1-2 per 10,000 persons with slight variation between populations. In both AChR-MG and LEMS a tumour and a non-tumour related form exists. The non-tumour related form of both diseases shows a bimodal distribution in their relation to sex and age, while the incidence in females is increased compared to men under the age of 40. Above the age of 60 the incidence in males outnumbers that in women. These two diseases are associated with the same HLA DR3-B8 haplotype, which is mainly found in the younger age group. In contrast, MuSK MG is associated with HLA-DR14-DQ5. For MuSK-MG only a non-tumour form has been described, and the disease has so far been described mainly in female patients. A relatively large proportion of patients have a young onset, while the incidence at older age is very low. Maybe at this age older persons with bulbar weakness are not yet recognized as myasthenic patients. The distribution in age, geographical distribution, genetic background and IgG subtypes of the antibodies in MuSK MG are all different from AChR MG despite sharing similar clinical features. In contrast, the pattern of weakness in AChR MG is different from that in LEMS, but these diseases share a similar age distribution, genetic background and IgG subtypes of their antibodies. AChR-MG makes up 80% of all generalised MG patients. In about 15% of the patients the disease can be classified as paraneoplastic, usually associated with a thymoma. The non-thymoma group can be sub-divided into pure ocular MG, those with disease onset before the age of 40-50 years, and an increasing group with late-onset generalized MG patients. In about 15% of the patients the disease can be classified as paraneoplastic, usually associated with a thymoma. The non-thymoma group can be sub-divided into pure ocular MG, those with disease onset before the age of 40-50 years, and an increasing group with late-onset generalized MG patients. MuSK MG can be considered a separate disease entity given the characteristic pattern of weakness and course of disease and the pathophysiology. These patients show predominant involvement of the cranial and bulbar muscles and seem to be at higher risk of respiratory crisis, while limb muscle weakness tends to be less severe. The thymus is usually normal. Serum antibodies against MuSK are predominantly of the IgG4 isotype. LEMS is associated with Voltage-Gated Calcium Channel (VGCC) antibodies in about 90% of the cases. In half of the cases an associated small cell lung cancer is detected. LEMS starts almost exclusively with proximal weakness of the legs. In a few percent of the patients the disease remains relatively mild and restricted to proximal lower limb weakness. In most LEMS patients the weakness eventually extends to other muscles. In almost all patients with LEMS, proximal limb weakness was the first symptom and oculobulbar weakness developed later on in the course of the disease. These myasthenic disorders show remarkable characteristic differences in their clinical presentations, given the fact that all three have in common the antibody-mediated attack on neuromuscular synapses. The clinical information can help to diagnose these diseases more easily and to understand the pathophysiology of these disorders in greater detail.
**FW 2-2**

**Myasthenia gravis (MG) in the elderly and MG with anti-ryanodine receptor (RyR) antibodies**

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**Objectives:** MG is a disorder with well-defined pathogenetic autoantibodies. MG-subclassification is based on muscle weakness localisation, autoantibodies, thymus pathology and age. This subgrouping reflects disease pathogenesis and response to therapy. Main subgroups are Late onset (>50 years), Early onset (<50 years) with thymic hyperplasia, Thymoma, Ocular, and Undetectable neuromuscular antibodies.

**Results:** Prevalence is 100-175 per 106, yearly incidence 10-20 per 106. Incidence is increasing by age for both sexes, and highest at 70-85 years. Clinical manifestations are similar in elderly and young patients. Ptosis, facial weakness and articulation problems are easier to detect in the young. MG-symptoms in the elderly are often mistaken as cerebrovascular, or normal ageing. Thymoma occur with the same frequency above and below 50 years. Concomitant autoimmunity is more common among early onset. MG with RyR-antibodies have either a thymoma or debut >50 years. RyR-antibodies increase the risk of severe MG. MG with debut >50 years are usually not recommended for thymectomy, unless thymoma. With thymic hyperplasia on CT/MR, thymectomy can be recommended up to 65 years. RyR- and titin-antibodies without thymoma counts against thymectomy.

**Conclusions:** All MG-patients should be diagnosed regarding a subgroup. Debut >50 years represent the most common group. Such patients can have a thymoma, be MuSK-associated, and have ocular MG. Therapeutic response differs according to subgroup. RyR/titin antibodies can direct therapy. MG in the elderly can be overlooked or mistaken for cerebrovascular disease. The threshold for AChR antibody examination should be low.

**FW 2-3**

**Congenital myasthenia: contrasting rapsyn and Dok-7 phenotypes**

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The congenital myasthenic syndromes (CMS) comprise a heterogeneous group of genetic disorders affecting the neuromuscular junction (NMJ). There are to date twelve genes implicated and these span the NMJ involving presynaptic, synaptic and post-synaptic proteins. Post-synaptic syndromes comprise the largest group with the three most common due to mutations in components of the AChR clustering pathway (CHRNE, RAPSN and DOK7). Although these might be expected to have similar phenotypes, other than fatiguable muscle weakness and autosomal recessive inheritance, there are remarkable differences. Rapsyn CMS is often associated with mild arthrogryposis, and strabismus without ophthalmoplegia. It usually presents at birth with respiratory and bulbar difficulties, episodic crises and apnoea are common during early life and the symptoms characteristically improve during childhood. Patients frequently respond dramatically to anticholinesterases. Dok-7 CMS patients usually have normal early motor milestones and present in early childhood with walking difficulties. It is not uncommon for bulbar and respiratory problems to develop later. Ophthalmoplegia is usually absent, and a limb-girdle phenotype is typical. The majority gets worse or gains no benefit from anticholinesterases and about half note the same with 3,4-DAP treatment. However ephedrine can produce a dramatic improvement over months. Both these syndromes have a common mutation facilitating screening. The phenotypic differences are not completely understood but in addition to the different protein functions, protein expression differences in specific muscle groups and at different stages of development, and variations in neuromuscular innervation e.g. in ocular muscles, may be contributory.
Nutrition and stroke

FW 3-1
Pathophysiology of stroke-Role of Nutrition
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Stroke is a common and devastating event, which often results in death or major loss of independence with immense human and financial costs. Nutritional factors may have an important role to play in incidence and treatment of stroke. Many epidemiological studies report that people who eat a relatively large quantity of fruits, vegetables and grains have a lower risk of death, particularly from cardiovascular disease. Some of these studies consistently revealed an association between increased risk of stroke and low plasma concentrations of antioxidants. There is also strong indirect evidence that free radical production appears to be an important mechanism of brain injury after exposure to ischaemia and reperfusion. Furthermore moderately raised concentrations of total homocysteine have been associated with an increased risk of stroke. The mechanism of stroke may also involve endothelial dysfunction which may be partly caused by oxidation related to the effects of raised total plasma homocysteine. Although a number of recently completed randomised trials on specific dietary supplements and risk of stroke do not provide clear evidence of benefit, more experimental and clinical studies are needed to elucidate the role of diet in the incidence and outcome of stroke.

FW 3-2
Nutrition and prevention of stroke: present knowledge, limitations and future perspectives
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Dietary modifications could play an important role in ischemic stroke prevention. A dietary pattern typified by higher intakes of red and processed meats, refined grains, sweets and desserts, energy-dense drinks and white bread may increase stroke risk, whereas consumption of a diet rich in fresh fruits and vegetables of all colours, whole grain, legumes, olive oil, dietary fibre, fish, omega-3 polyunsaturated fatty acids, soybean products, Ca, Mg and tea consumption may protect against stroke. Diets low in saturated fat and cholesterol, low in sodium and high in potassium lower blood pressure which will likely reduce stroke risk. Some studies suggest that vitamins C, E and beta carotene may be protective and that folate, B6, and B12, by lowering homocysteine levels, may reduce stroke. Determination of homocysteine plasma concentration, vitamin B12, vitamin E, C and folic acid plasma levels can be part of the individual risk profile, especially for elderly subjects and patients with hypertension, diabetes who are at risk for stroke. However, unequivocal demonstration of a protective or adverse role of single foods and nutrients against risk of stroke has been difficult to achieve due to confounding by biological variability, methodological inadequacies in the assessment of individual nutritional habits and difficulty to carry out long-term randomised controlled trials in the nutritional area. Both public and professional education should promote the awareness that nutrition has the potential to reduce the burden of stroke. A better understanding of mechanisms, along with well-designed controlled clinical trials will allow further progress in this area.
**FW 3-2**

**Nutrition after stroke: individual methods of approach and common recommendations**

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Patients with acute stroke may be malnourished and often having feeding difficulties in the first few weeks and months. Dysphagia affects up to 50%, but patients also may have feeding difficulties because of facial weakness, poor truncal control, neglect, impaired communication, poor hand and arm function and ill fitting dentures. Intercurrent illness and medications may affect appetite. All of these factors may lead to worsening nutritional status. Poor nutritional status has been associated with high case fatality and worse functional outcomes. We therefore need to consider what interventions may reduce the impact of these difficulties on nutritional status and improve outcome. Interventions may include: dysphagia therapy, compensatory techniques, diet supplementation and modification and enteral tube feeding via nasogastric or percutaneous endoscopic gastrostomy. In addition we need to consider strategies to improve delivery such as physical restraints and nasal loops. Some of these have been evaluated in large randomised trials, whilst the use of others is based on theory, personal experience and historical practice. This session will focus on these interventions.

**Gender issues in epilepsy**

**FW 4-1**

**Influence of sex hormones on brain excitability and epilepsy**

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**Background:** In the last years, a growing body of literature indicates that seizures of women with epilepsy are influenced by reproductive state. It appears that steroid hormones, in particular oestrogen and progesterone, may have an effect on brain excitability, and, consequently, on frequency of epilepsy.

**Objective:** We have reviewed and analyzed data from literature, including both animal and clinical studies, to clarify the relationship between hormones and epilepsy. This article analyses the mechanism by which steroid hormones act on the brain and describes the known effects of sexual hormones on epilepsy.

**Results:** Gonadal hormones exert a profound influence on neuronal excitability, seizures, and epilepsy: oestrogen is “proconvulsant”, having a seizure-activating effect in experimental models of epilepsy and in human cerebral cortex; on the contrary, progesterone is “anticonvulsant”, exerting a seizure-protective effect in experimental models and in human studies; on the other hand, androgens can decrease ictal activity in the human brain. Furthermore, levels of oestrogen and progesterone fluctuate throughout the menstrual cycle, and, in some women with epilepsy, these fluctuations may be related to the occurrence of seizures around the time of menses or an increase in seizures in relation to the menstrual cycle, also known as catamenial epilepsy.

**Conclusions:** Changes in neuronal activity induced by sexual hormones seem to have an important role in the onset and evolution of different types of epilepsy. This knowledge is important as it will open new possible perspectives for the pharmacological treatment of epilepsy.

**FW 4-2**

**Disorders of reproduction in epilepsy**

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Reproductive endocrine disorders are common among people with epilepsy. In women, menstrual disorders, polycystic ovaries, and infertility have been described, and in men, reduced potency and sperm abnormalities have been found. The reasons for this are multifactorial, including both the epilepsy itself and the antiepileptic medication. Epileptic activity can directly affect hypothalamic function. In female rats, amygdala-kindled seizures arrest ovarian cyclicity and alter endocrine function. The effects are highly lateralized. In women, patients with left temporal lobe epilepsy (TLE) have a higher GnRH pulse frequency associated with a higher frequency of polycystic ovaries. Right unilateral TLE is associated with lower GnRH pulse frequency and hypothalamic amenorrhea. Abnormal prolactin pulses after epileptic discharges will also affect reproductive function. In men, temporal limbic epilepsy may be associated with altered gonadotropin response to GnRH, more variable LH pulse frequency, and acute elevation in prolactin. In male rats, both amygdaloid and generalized seizures markedly disturb normal reproductive physiology. Antiepileptic drugs (AEDs) may also influence reproductive function. Enzyme inducing AEDs increase SHBG concentrations leading to lower bioactive testosterone and estradiol levels in both men and women. This may lead to menstrual disorders in women and reduced potency in men. In women, valproate is associated with menstrual disorders, polycystic ovaries, and hyperandrogenism. The effect seems to be age-dependent as young females are more vulnerable. In men, the clinical significance of valproate related endocrine changes is minor. Lamotrigine has so far not been shown to have any clinically important reproductive effects while information on newer AEDs is lacking.
Epilepsy and Sexuality
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Sexuality is an important and private aspect of life and sexuality and epilepsy have been intimately linked since ancient time. In the modern medical era of epilepsy, Gastaut and Collomb published that many patients with complex partial seizures have an apparent lack of interest in sexual activity. Sexual dysfunction is frequently reported by patients with epilepsy. Despite its fundamental role in human life, there has been surprisingly little research into the neurological control of human sexual behaviour. Multiple causes may lead to sexual dysfunction. The basis for hyposexuality has been attributed to both epilepsy and antiepileptic drug (AED) use, making it difficult to distinguish between the illness-specific and pharmacological impacts on sexual functioning. Low levels of androgens are associated with sexual arousal insufficiency and sexual dysfunction. When examining sexual dysfunction in men and women with epilepsy, the Arizona Sexual Experience Scale (ASEX) may be helpful in evaluating sexual function. Laboratory tests for oestrogen, free and total testosterone, and serum SHBG may also be useful in evaluating sexual health. Sporadic case studies suggest that hypersexuality is a rare but dramatic outcome of unilateral temporal lobectomy. Sexual seizure manifestations are also rare clinical phenomena during or after complex partial seizures that have received attention in the recent literature. Both, men and women with epilepsy appear to have altered gonadal function. It is still unclear whether AEDs or epilepsy cause the abnormality involving prolactin, luteinizing hormone (LH), estradiol, SHBG, and dehydroepiandrosterone (DHEA) in women and also follicle stimulating hormone (FSH), free testosterone (FT), inhibin, DHEA, and 17α-OH progesterone in men with epilepsy.

Vestibular-evoked potentials and reflexes

FW 5-1
Cervical vestibular evoked myogenic potentials (cVEMPs): usefulness in clinical neuro-otology
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Testing vestibular evoked myogenic potentials (VEMPs) may be the most important new clinical test for evaluation of vestibular function developed during the past 100 years since the introduction of the caloric test. VEMPs are easily recordable and therefore suitable for everyday testing in clinical neuro-otology. VEMPs in response to air-conducted sound stimulation using surface electrodes over the sternocleidomastoid muscles (cervical VEMPs=cVEMPs) reveal saccular function, inferior vestibular nerve function, and vestibulocollic connections. At present, VEMPs are of clinical importance for estimating the severity of peripheral vestibular damage due to different pathophysiologic processes such as Menière’s disease, vestibular neuritis, and vestibular Schwannoma. VEMPs can also be used to document vestibular hypersensitivity to sounds (Tullio phenomenon). In addition, VEMP testing constitutes an electrophysiological method that is able to detect subclinical lesions in central vestibular pathways.
FW 5-2

Ocular vestibular evoked myogenic potentials
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Since the first description of sound-evoked short-latency myogenic reflexes recorded from neck muscles, vestibular evoked myogenic potentials (VEMPs) have become an important part of the neuro-otological test battery. Recent research has shown that VEMPs can also be recorded from the extraocular muscles using surface electrodes placed near the eyes. These “ocular VEMPs” (oVEMPs) are a manifestation of the vestibulo-ocular reflex. Both cervical and ocular VEMPs provide a means of assessing otolith function. In this workshop the historical development of the oVEMP, its neurophysiological properties and characteristics in central and peripheral disorders of vestibular function will be described.

FW 5-3

vHIT (video head-impulse test)
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Clinical assessment of semicircular canal function with the head impulse test in vestibular patients relies on visual detection of the catch-up saccades that the patient generates in order to compensate for the deficient vestibulo-ocular reflex. Until recently quantitative measurement of the head impulse test had to be done with the scleral search coil technique that was not practical in a clinical setting. This workshop will introduce a novel video head impulse system that is easy to use in clinics. The light-weight video goggles are equipped with a high-speed video camera (250 Hz) and a miniature inertial measurement unit. The diagnostic accuracy of the system has been validated by simultaneous measures with video and search coil recordings across healthy subjects and patients with peripheral vestibular deficits. The test promises to be a safe, accurate and practical means of measuring the vestibulo-ocular reflex and detecting the corresponding catch-up saccades.

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