



Award winners from the EuroHead Team at the International Headache Congress in Kyoto

At the 12th International Headache Congress, held in Kyoto, Japan, in October 2005, 5 of the 7 awards for the data being presented went to members of the EuroHead Project: **Arn van den Maagdenberg (Leiden, The Netherlands) was awarded for his oral presentation on “Transgenic knock-in mouse model expressing the CACNA1A mutation S218L causing familial hemiplegic migraine and fatal excessive cerebral oedema after minor head trauma”**; **Manjit Matharu (London, United Kingdom)** for his oral presentation on “**Posterior hypothalamic activation in paroxysmal hemicrania**”; **Line Buchgreitz (Copenhagen, Denmark)** for her oral presentation on “**Altered Pain perception is re**

lated to headache frequency”; **Cristina Tassorelli (Pavia, Italy)** was awarded for her poster on “**Activation of the transcription factor NF-kappa B in the nucleus trigeminalis caudalis in an animal model of migraine**”, while Robin J Stores (London, United Kingdom), was awarded for his poster titled “**Topiramate has a locus of action outside of the trigeminocervical complex**”

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Toward a diagnostic basic headache diary

The Eurohead team held a consensus



EUROPEAN HEADACHE FEDERATION (EHF)
8th HEADACHE CONGRESS
Valencia, Spain, April 26-29, 2006

meeting on diagnostic basic headache diary during the 8th Congress of the European Headache Federation.

The diary was devised by the experts working at the Danish Headache Centre in Copenhagen (J. Olesen and R. Jensen) and at the Headache Center of Pavia (G. Nappi, G. Sances, G. Sandrini, C. Tassorelli and P. Torelli), with the aim to provide a simple and useful tool to aid the diagnosis of migraine and tension-type headache. The basic headache diary will be helpful for general practitioners who want to become familiar with the second edition of the Classification of Headache Disorders of the

International Headache Society (ICHD-II). The diary is based on the specific diagnostic criteria for these two types of primary headaches given in ICHD-II.

The preliminary results obtained in a pilot study performed in Copenhagen and Pavia are encouraging, as they demonstrate that the diary is correctly filled-in even by untrained patients and leads to the correct diagnoses with a satisfactory specificity and sensitivity.

Representatives of Italy, Denmark, United Kingdom, Switzerland and Russia, as well as the Presidents of the European Headache Alliance and World Headache Alliance - umbrella organizations that collect European and world national advocacy groups - attended the Consensus meeting and gave rise to an animated and stimulating discussion aimed at a further refinement of the diary.

Two issues, in particular, were raised and addressed: simplification of the item regarding the aura phase and a

modality for extrapolating definite diagnoses that need an observation period of 2-3 months from a 4-week period of compilation.

The meeting was closed with the agreement to test the revised version of the diary, which will be prepared in the following weeks, in several European Countries. Some of representatives who were unable to attend the

meeting (Belgium, Bulgaria, Germany, Norway, Portugal and Spain) notified, however, their willingness to participate in the experimental phase.

Those who might be interested in testing the revised version of the diary may contact Dr. Cristina Tassorelli (cristina.tassorelli@mondino.it).

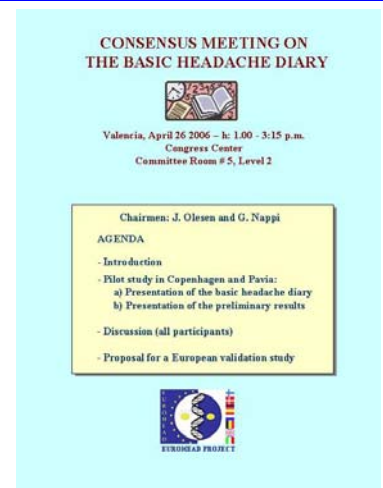
Events

Consensus meeting on the basic headache diary Valencia, April 26 2006

Chairmen: J. Olesen and G. Nappi

AGENDA

- Introduction
- Pilot Study in Copenhagen and Pavia
 1. Presentation of the basic headache diary
 2. Presentation of the preliminary results
- Discussion (all Participants)
- Proposal for European validation study



Consensus Meeting

Litterature Highlights

Transgenic knock-in mouse model expressing the CACNA1A mutation S218L causing familial hemiplegic migraine and fatal excessive cerebral oedema after minor head trauma

by A.M. van den Maagdenberg et al.

Departments of Human Genetics and Neurology, Leiden University Medical Centre, Leiden, the Netherlands

The gene *CACNA1A* encodes the Cav2.1 subunit of P/Q-type calcium channels. These channels are widely expressed in the brain and the neuromuscular junction, and mediate neurotransmitter release. Mutations of this gene cause a spectrum of diseases, which include familial hemiplegic migraine type-1 (FHM1). In particular, mutation S218L mutation has been associated to FHM and fatal cerebral oedema after minor head trauma.

The authors generated a knock-in (KI) mouse model by introducing the S218L mutation in the endogenous *Cacnala* gene by gene targeting and studied its *in vivo* consequences. Homozygous S218L KI mice showed mild ataxia and increased lethality. Neuromuscular junctions in S218L KI mice showed a ~12-fold increase in spontaneous acetylcholine release, while the low-rate evoked release in low extracellular Ca²⁺ concentration was ~150% higher.

The data presented support the hypothesis that *CACNA1A* mutations lead to synaptic function defects, possibly con-

tributing to symptoms of FHM1. The consequences of S218L mutation seem more dramatic than those associated to the R192Q mutation, previously described. S218L knock-in mice will be valuable tools to study migraine and trauma-related events.

Posterior hypothalamic activation in paroxysmal hemicrania using PET

by M.S. Matharu et al.

Headache Group and Wellcome Department of Imaging Neuroscience, Institute of Neurology Queen Square, London, UK

Paroxysmal hemicrania (PH) is a severe unilateral headache lasting 2-30 min, which occurs more than five times per day, is associated with trigeminal autonomic symptoms, and specifically responds to indomethacin. Positron emission tomography (PET) was performed in 7 patients in different states: a) acute PH attack without treatment; b) painfree phase; and c) pain-free phase induced by intramuscular indomethacin (100 mg). No significant activation was observed when comparing state *a* with *b*. However, pain neuromatrix activation was detected when comparing states *a* and *b* with state *c*. This finding points to a persistent activation of the pain neuromatrix during the acute PH attacks and

the interictal pain-free state when off indomethacin. The activation is turned off by the administration of indomethacin. The authors also report a significant activation of the contralateral posterior hypothalamus during headache and a significant activation of the contralateral ventral midbrain, which extended over the red nucleus and the substantia nigra.

Altered pain perception is related to headache frequency. A population study

by Line Buchgreitz et al.

Danish Headache Centre, Department of Neurology, Copenhagen University Hospital, Glostrup, Denmark, and Research Centre for Prevention and Health (RCPHJ), Copenhagen University Hospital, Glostrup, Denmark

The authors evaluated pain sensitivity in primary headaches in the general population.

A total of 523 subjects participated in a cross-sectional study started in 2001 in Denmark. The study consisted in the investigation of the stimulus-response function for pressure vs. pain. Information about headache was obtained by interview and classified according to ICHD.

A clear relation between steeper and more leftward-shifted stimulus-response functions with increasing headache frequency was seen.

In addition, 388 subjects participated in a 12-year follow-up study with measurement of pressure pain threshold and tenderness. Pressure pain threshold decreased significantly only in those patients who developed chronic tension-type headache in the follow-up period ($P = 0.04$).

This study demonstrates, for the first time in a population-based study, that increased pain sensitivity is closely related to headache frequency and may be a consequence of chronicification.

Activation of the transcription factor NF-kappaB in the nucleus trigeminalis caudalis in an animal model of migraine

by Cristina Tassorelli et al.

Laboratory of Pathophysiology of Integrative Autonomic Systems, IRCCS Neurological Institute 'C Mondino' Foundation and University Centre for the Study of Adaptive Disorder and Headache (UCADH), Pavia, Italy, and 'Chair of Neurology, University 'La Sapienza', Rome, Italy

Nitroglycerin (NTG) induces an inflammatory state in perivascular meningeal tissues of rat via the activation, *inter alia*, of nuclear factor kappa B (NFkappaB). The authors sought to elucidate whether NF-kappaB activation might have a role in the determinism of migraine attacks also at the neuronal level. The transcriptional activity of NFkappaB was therefore evaluated in the brainstem of rats systemically injected with NTG and in control animals.

A significant increase of nuclear immunostaining of p65, an

indicator of NF-kappaB activation, was detected in lamina I and II of nucleus trigeminalis caudalis in rats injected with NTG. Western blot analysis confirmed the activation of the NF-kappaB pathway in the lower brainstem.

The study confirmed the involvement of NFkappaB in the determinism of NTG-triggered migraine-like attacks and paved the way to new biomolecular and pharmacological avenues for the development of innovative migraine therapies.

Topiramate has a locus of action outside of the trigeminocervical complex

by Robin James Storer and Peter J. Goadsby

Headache Group, Institute of Neurology & The National Hospital [or Neurology and Neurosurgery, London, UK

Drugs for migraine prophylaxis are likely to inhibit the trigeminocervical complex, or neurons that modulate sensory input. The authors examined the effect of topiramate (TPM) on trigeminocervical activation in order to improve our understanding of its preventative action.

A group of cats were anaesthetized and physiologically monitored, while their superior sagittal sinus (SSS) was stimulated to activate trigeminovascular nociceptive neurons. Extracellular recordings were made from these neurons in the trigeminal nucleus caudalis. Topiramate was delivered microiontophoretically but produced no significant inhibition of SSS linked trigeminocervical cells, however cell firing induced by electrical stimulation of the SSS was partly inhibited by the drug. The intraventricular administration of topiramate markedly inhibited l-glutamate-evoked firing of SSS linked cells. These data suggest that the mechanism mediating the prophylactic effect of topiramate in migraine is located outside the trigeminocervical complex.

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