





Preface

2006 was a year of reorganization and consolidation in The Danish Headache Center. The major new undertaking was the establishment of The Danish Headache Center for Children and Adolescents within the Department of Pediatrics in close collaboration with the Danish Headache Center, Glostrup hospital. Establishing a specific headache center for children and adolescents is a major achievement and open a new, exiting avenue for prevention, treatment and research.

After 5 years of continuous expansion and very high patient flow, there has been a major replacement of the multidisciplinary team in the Danish Headache Center in 2006 and many new staff members have been introduced and trained. Simultaneously, it has proven that these highly specialized tasks attract good staff and the interest has been impressive.

At the end of 2006 the situation has stabilized again. Consequently, there was no way of meeting the continuously increasing number of referrals and the waiting list grew and towards the end of the year, the waiting time for chronic cases approached 9-10 months. This is unacceptable, and negotiations will be resumed to avoid a similar situation in the future.

The research at The Danish Headache Center continues to be very active with a very high frequency of publications and a large impact factor. At the end of 2006 a part of the research group moved into the newly opened Glostrup Research Park located at the former psychiatric area. The Research Park has 1000 m² top modern facilities with laboratories, animal facilities and an office building. 6 researchers (4 Ph.D. students and 2 senior researchers) are located here working with experimental animal trials to enlighten the mechanisms of migraine and other aspects of neurovascular signalling.

Of greater importance, The Danish Headache Center runs a Research Center called: Lundbeck Foundations Center for Neurovascular Signaling (LUCENS). The founder of The Danish Headache Center, Jes Olesen, heads 6 research groups at the Glostrup Hospital who together received a substantial grant from the Lundbeck Foundation. Nationally 26 research groups applied for this grant; however, only 3 received the grant. Researchers at the Glostrup Research Park is partly funded by the LUCENS grant, however this grant also covers exploration of the mechanisms of migraine in patients and volunteers.

During the year The Velux Foundation supported also a large grant for new equipment to measure the brain blood flow and oxygen content by means of laser. However, the equipment cannot be delivered before the beginning of 2007. It is our hope that this particular equipment can replace the present measurements of the brain blood flow, which involves microscopic amounts of radioactive substances.

During 2006 funds for a professorship in Headache and Neurological Pain was also obtained and the occupation of this chair is procrastinating through the academic appointing authorities. However, it is expected that a professor is appointed during 2007. This will prove to be a huge enforcement of the research at The Danish Headache Center.

The follow-up trial of a former population based trial in Glostrup has resulted in several important publications. Amongst the most important results are that headache seems to be a rising problem in Denmark. Migraine as well as chronic headache of tension-type becomes more and more frequent in the Danish population without any definite explanation at present.

In order to make the necessary precautions to control the increase in headache frequency it ought to be one of the main tasks of the future to analyze, why headache diseases have an increasing frequency. Is it the ever rising pace at the work stations? Is it the steadily increasing amount of chemicals and other environmental factors? Or is it that we psychologically have more discomfort amongst each other when people are occupied over the computer or TV a large amount of the time? Especially in children and adolescents is it important to elucidate the relationship between sedentary lifestyle and





increasing headache prevalence. Can an early intervention in the first or second decade prevent lifelong disabling headaches?

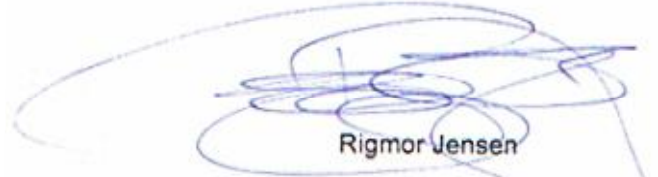
The sedentary lifestyle in modern society can also lead to overweight but can overweight lead to headache? In 2006 the Danish Headache Center has started a unique research programme on the epidemic of Idiopathic Intracranial Hypertension, a fairly rare condition with severe headaches and visual disturbances which increase 20-fold in obese individuals and may lead to permanent visual impairment or blindness. Here we talk about quite fundamental issues in the Danish society, which should demand the attention of the politicians. The Danish Headache Center has by its continuous research and establishment of clinical facilities for children as well for adults enlightened major problems, however, we cannot manage it without an active support from the authorities empowered to make grants and continuous support for research.

Throughout the year the entire staff at the Danish Headache Center worked dedicatedly to fulfil its mission. We are incredibly grateful to all the employees for their enthusiastic involvement and for always being willing to accommodate to an ever changing and expanding environment.

Glostrup, May 2007



Jes Olesen



Rigmor Jensen





2006

Organization and Staff

December 2006



Jes Olesen – MD, DrMedSci, Dr hon C/Rome University, FRCP

The center's founder and co-director Jes Olesen is Professor of Neurology at the University of Copenhagen. Professor Olesen has published over 500 scientific papers and more than 20 books on headache. His main research interests include pathophysiological mechanisms underlying migraine, headache epidemiology, classification and genetics.

Professor Olesen has held a numerous honorary positions and is the former president of the International Headache Society (HIS) and the European Federation of Neurological Societies (EFNS) as well as current president of the European Brain Council (EBC). He has received numerous national and international prizes. He is an honorary member of the Austrian, British, and French neurological societies.



Rigmor Jensen – MD, DrMedSci

The center's co-director Dr. Rigmor Jensen is a research professor at the University of Copenhagen. Dr. Jensen has published more than 170 scientific papers and book chapters. Her main research interests include headache epidemiology and the pathophysiological mechanisms underlying tension-type headache and medication-overuse headache. Dr. Jensen is the president of the Danish Headache Society, and member of the Executive Board (treasurer) of The European Headache Federation.

Staff Neurologists:



Peer Tfelt-Hansen
MD, DrMedSci



Peter Schmidt-Hansen
MD



Messoud Ashina
MD, Ph.D., DrMedSci



Thue Hjortkær Nielsen
MD



Lars Bendtsen
MD, Ph.D., DrMedSci



**Secretaries:**

Helle Jensby (Team leader)
Katrine Kristensen
Karin Aagaard
Pernille Sellebjerg-Andersen
Jane Sandby
Dorte Helmundt
Birgitte Suhr
Lis Jønsson
Tina Kærgaard

Nurses

Anne-Margrethe Manniche
Annette Vrangaa Rasmussen
Hjørdis Rasmussen (assistent)

Psychiatrist

Marianne Nilsson
Department of Psychiatry P
Glostrup Hospital

Physio-therapists

Karin Gøse
Bjarne Madsen

Gynecologist

Birgit Hansen
Department of Gynecology
Glostrup Hospital

Psychologists

Jakob Sander Haneen
Dorthe Kjeldgaard Nielsen

Dental expertise

Professor, dr. odont Peter Svensson
Aarhus Dental School

**Teaching activities, Guest lectures and visitors**

International Headache Teaching course organized by Dr Messoud Ashina, DHC and Hayrunnisa Bolay, Turkey
Dr Aleksandra Radjonovic, University of Belgrade, Serbia
Professor Jens Ellrich, Aachen, Germany
Dr.med Anna Makovski, Aachen, Germany
Professor Carl Dalhof, Göteborg Migraine Clinic, Sweden
Dr Tine Poole, Oslo, Norway
Dr Rawi Rawishankar, Mombay, India
As well as numerous Danish colleagues

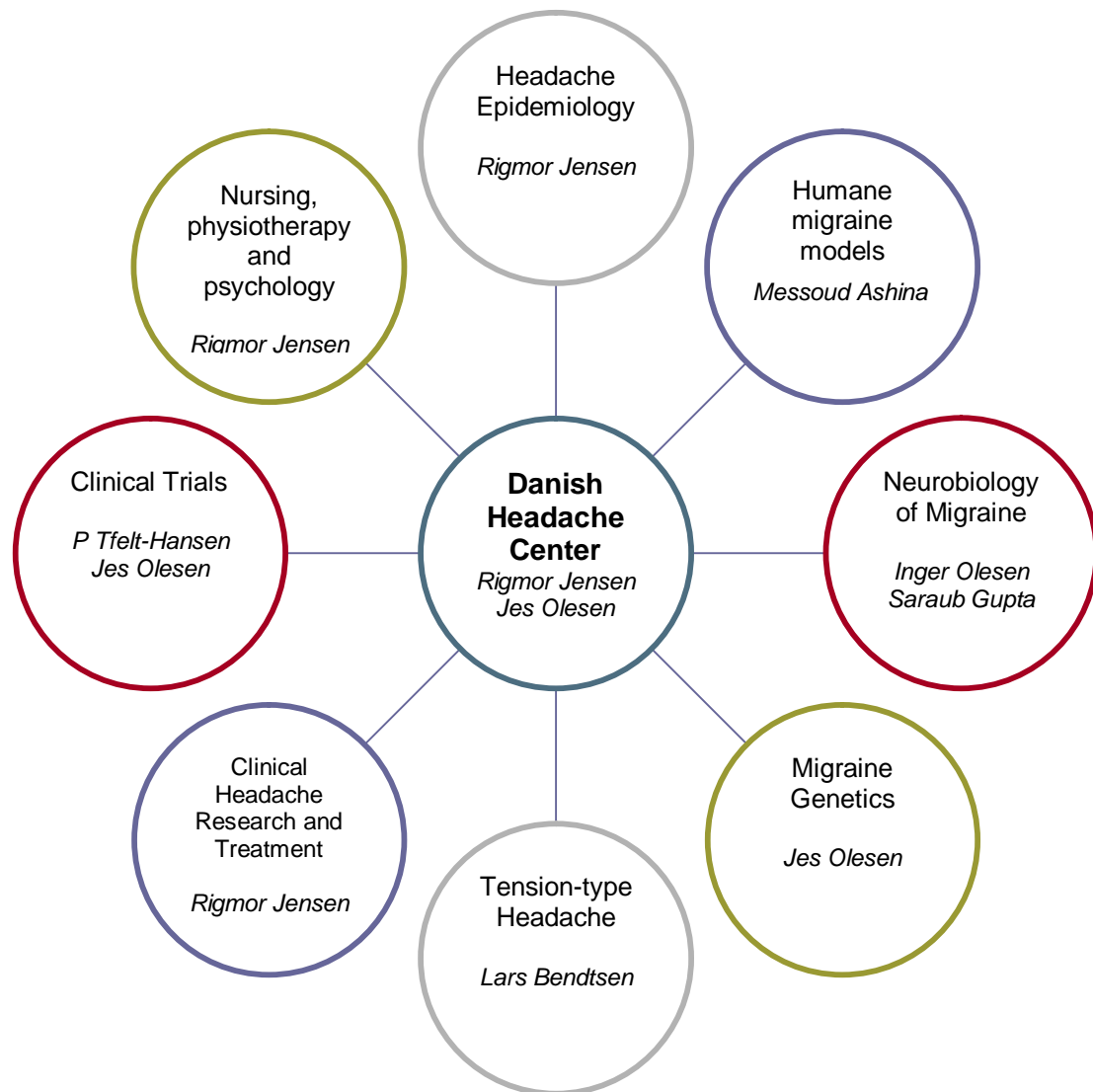




Research

Danish Headache Center has a vigorous research group including 6 senior researchers, 11 Ph.D. students mostly MD's and medical students. The organization of research is shown in figure 3.

Figure 1. Organization of Research





Research Staff

Senior scientists:

Jes Olesen
Rigmor Jensen
Lars Bendtsen
Messoud Ashina
Inger Jansen Olesen
Christina Kruuse
Saraub Gubta

Associate senior researchers:

Lise Lykke Thomsen
Peter Schmidt-Hansen
Malene Kirchmann

Technologists:

Hanne Andresen
Lene Elkjær
Kirsten Brunsgaard

Administrative assistants:

Kirsten Hjelm
Hanne Aggergaard

Ph.D.students:

Alexandra Rahmann
Henrik Winther Schytz
Lars Schack Kruuse
Sohail Agshar
Peter Zeeberg
Line Buchgreitz
Kim Lindelof
Louise Susanne Juhl
Kenneth Beri Plough
Jakob Møller Hansen
Troels Wienecke
Anne Werner Hauge
Lena Raffn
Maren Skau
Helle Wulf
Michael Baun

Research and clinical collaborations

Departments within Glostrup Hospital

- Department of Neurosurgery
- Department of Clinical Experimental Research
- Department of Clinical Physiology
- Department of Clinical Biochemistry
- Department of Pediatrics
- Department of Radiology
- Department of Gynecology
- Department of Anesthesiology
- Department of Oral and Maxillo-Facial Surgery
- Department of Clinical Neurophysiology

External collaborators

- Center for Health and Preventive Medicine, Copenhagen County
- DeCode, Reykjavik, Iceland
- The Headache Clinic, Kiel University, Germany
- The Headache Center, Thomas Jefferson University, Philadelphia, USA
- The Pain Clinic, Herlev University Hospital, Copenhagen, Denmark
- Department of Ophthalmology, Herlev University Hospital, Copenhagen, Denmark
- The Pain Clinic, The National University Hospital, Rigshospitalet, Copenhagen, Denmark
- Department of Neurology, Frederiksborg Amts Sygehus Hillerød, Denmark
- Center for sensory-motor integration, AUC, Aalborg, Denmark
- Institute of Anatomy, Panum Institute, University of Copenhagen, Denmark
- Department of Medical Physiology, Royal School of Veterinary Medicine, Denmark
- NeuroSearch A/S, Denmark





- Department of Experimental Research, University of Lund, Sweden
- Institute of Pharmacology, University of Pharmacology, Copenhagen, Denmark
- Department of Neurology, Parma University Hospital, Parma, Italy
- Institute Neurologico C Mondino, University of Pavia, Italy
- Institute for Physiology, Johannes Gutenberg University in Mainz, Germany
- Department of Pharmacology, University of Washington, Seattle, USA

Present research Areas

Human migraine models

Members:

Messoud Ashina, Sohail Asghar, Jakob Møller Hansen, Henrik Schytz, Troels Wienecke, Jes Olesen.

Background:

Experimental headache models offer unique possibilities to study mechanisms responsible for migraine. Using the nitric oxide (NO) and calcitonin gene-related peptide (CGRP) model of experimental headache, our group demonstrated that NO- or CGRP-induced a biphasic response with an immediate and a delayed headache identical to migraine.

These provocation experiments show the importance of NO and CGRP in spontaneous migraine attacks. The efficacy of the NO synthase inhibitor and a CGRP antagonist are final proof of this relation

Current projects:

The aims of current studies are to study human migraine models in patients with genetically explained hemiplegic migraine, to explore the possible role of the parasympathetic nervous system and prostanoids in migraine pathophysiology, and to study activation of trigeminal pain pathways by fMRI during different sequences of a headache attack

Collaboration:

Henrik Larsson and Adam Espe Hansen (Department of Clinical Physiology), Vibeke Andre Larsen (Department of Radiology), EUROHEAD (www.eurohead.org), David Borsook and Lino Becerra, PAIN Group, Mclean Hospital, Harvard University Boston USA

Tension-type headache

Members:

Rigmor Jensen, Line Buchgreitz, Sait Ashina, Messoud Ashina, Peter Schmidt-Hansen, Lars Bendtsen.

Background:

Increased understanding of the relative importance of peripheral factors (mainly muscular) and central factors (mainly central pain processing) in the pathophysiology of tension-type headache are crucial for the development of more effective treatment options for this disorder. Experimental models studying muscular factors, e.g. muscle pain sensitivity, and central factors, e.g. degree of wind-up, and the interaction between these factors are needed to explore the cause/effect relationship between the various peripheral and central abnormalities reported in tension-type headache. Previous studies from our group have, e.g., demonstrated abnormal tenderness and pain perception indicating central sensitization.

Current projects:

Investigations of muscular pain sensitivity, processing, and modulation of peripheral nociceptive input in the central nervous system.





Collaboration:

Lars Arendt Nielsen, Center for Sensory-Motor Interactions, Department of Health Science and Technology, Aalborg University, Denmark. Walter Magerl, Institute of Physiology and Pathophysiology, Johannes Gutenberg University Mainz, D-55099 Mainz, and Professor Jens Elrich; Institute of Physiology, Achen University Hospital, Germany.

Epidemiology

Members:

Line Buchgreitz, Lena Raffn, Ann Lyngberg, Peter Zeeberg, Rigmor Jensen.

Background:

Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations. The Glostrup County population study from 1989 was the first prevalence study of specific headache entities in a representative general population, based on a structured interview and examination by a physician. This study demonstrated the huge impact headache has on individuals and society. In 2001, a new study of the epidemiology of primary headaches in a general population was conducted. The study combined a 12 years follow-up of the 1989 cohort and a new cross-sectional survey of young adults. This study showed an increase in frequency and health care utilisation and thereby indicated a higher impact of headache in 2001 than in 1989. Risk factors for migraine were young age, female gender, familial disposition, no vocational education, high work load and frequent tension-type headache. For tension-type headache risk factors were young age, female gender, poor self-rated health, inability to relax after work, and sleeping fewer hours per night. In general migraine and tension-type headache had a favourable prognosis with increasing age and only a minority of subjects had increased headache frequency. Prognostic factors were identified.

Current projects:

A large clinical study of patients treated at the Danish Headache Center has already been conducted with main focus on medication overuse headache. It has been demonstrated that detoxification have a very positive outcome, especially in migraineurs and that these patients becomes reactive to migraine prophylactics again. Data are presently under evaluation, and several new projects focusing on specific treatment results and neurobiological mechanisms underlying medication overuse headache are planned.

Genetics

Members:

Malene Kirchmann, Lise Lykke Thomsen, Anne Hauge, Jes Olesen.

Background:

Family studies and twin studies show that migraine is an inherited disorder. The genes involved in migraine have not been identified except for some families presenting a rare subtype of migraine with aura, familial hemiplegic migraine. The identification of genes involved in migraine may give clues to underlying pathophysiological mechanisms.

Current projects:

The aim of our studies is to identify the genes involved in migraine with aura, familial hemiplegic migraine, and migraine without aura. To date we have collected blood from more than 1400 migraine patients and the molecular genetic analyses have been initiated.





Molecular mechanisms in migraine

Members:

Christina Kruse, Lars Schack Kruse.

Background:

Studies in humans help to explore possible migraine and headache provoking factors, as well as shed light on some of the pathophysiological mechanisms behind these disease syndromes. However, the natural limitations of these studies are the difficulty in looking into the more detailed molecular mechanisms in the cellular systems involved and the difficulties of applying certain drugs to humans. Thus, studies on isolated tissues are warranted for localizing and investigating function of tissue and cells assumed relevant in initiation of the pain process in order to investigate potential treatment targets. In collaboration with dept. of clinical biochemistry, we have described the presence of some of the intracellular enzymes involved in the pain process and the possible effect of modulating the signalling cascade in pain and regulation of cerebral artery diameter.

Current projects:

The future focus will be on these signalling mechanisms and how they may relate to the pain sensing structures in the brain and play a part in the induction and possible maintenance of headache and migraine.

Pharmacological and molecular studies of the cranial circulation

Members:

Inger Jansen Olesen, Louise Juhl, Kenneth Beri Ploug, Jes Olesen.

Background:

We have during the last 20 years studied the pharmacology of isolated cranial blood vessels from animals and humans in vitro. This work has led to several publications on the characterization of cerebrovascular receptors for 5-hydroxytryptamine and the sensory neuropeptides calcitonin gene-related peptide and substance P. During the last 5-8 years we have introduced new techniques, giving us the ability to study the expression of mRNA and proteins for specific receptors in migraine relevant tissue. In addition, we have introduced the genuine closed cranial window technique. This method allows us to perform in vivo measurements of the effect of a drug on pial and dural arteries when administered intravenously.

Current projects:

The episodic nature of migraine attacks suggests that ion channels are involved in its pathophysiology. This is confirmed by finding the mutation in patients suffering from familial hemiplegic migraine within three different ion channel genes identified to date. Potassium channels have an important role in the regulation of vascular tone and an opener of Katp channels has in clinical trials been found to induce headache. The aim of the current project is to explore the subunit composition and role of ion channels in pial and meningeal arteries. This will give us an understanding of which channels and subtype compositions this is present in these arteries. Thus, giving us information to further understand the pathophysiology of migraine and to define new targets for the pharmacological treatment of migraine.

Collaboration:

Lars Edvinsson (Department of Experimental Clinical Research) Anders Hay-Schmidt (Panum Institute, Copenhagen), Dan Klærke (The Royal Veterinary and Agricultural University, Copenhagen).





Idiopathic intracranial hypertension

Members:

Rigmor Jensen, Maren Skau.

Background:

Idiopathic intracranial hypertension (IIH) is an intriguing, clinical condition of increased intracranial pressure without pathological, laboratory or radiological evidence of intracranial pathology in young, obese individuals. The clinical symptoms are severe headache, pulsatile tinnitus, transitory visual obscurations and diplopia. Demographic studies report a rapidly increasing incidence of IIH in obese young females and with the global epidemic increase of obesity a significant increase in the number of IIH patients in Denmark can be predicted. Severe obesity is closely related to a number of neuroendocrinological changes which has still not been evaluated in IIH.

Untreated IIH may lead to severe visual loss and blindness resulting from damage to the optic nerve. The mechanism whereby IIH leads to optic nerve dysfunction is poorly understood but it seems to be closely linked to edema of the optic nerve head and the associated elevation of hydrostatic pressure inside the optic nerve.

The multidisciplinary study of IIH comprising neurobiological and ophthalmological aspects is a unique study of still unsolved aspects in IIH. Read more about IIH on www.danishheadachecenter.com

Current projects:

Investigations of ophthalmological and neurobiological aspects in Idiopathic intracranial hypertension

Collaboration:

Dan Milea, Department of Ophthalmology, Glostrup Hospital, Denmark

Jens Peter Gøtze, Department of Clinical Biochemistry, Danish National Hospital, Copenhagen, Denmark

Future Research Areas

In 2007 the scientific focus is directed towards:

- Neurovascular signalling in LUCENS center,
- Experimental humans models of migraine with implementation of the new imaging techniques
- Idiopathic intracranial hypertension
- The clinical division in The Headache Center.





Publications 2006

In reviewed scientific journals (48)

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- (12) Jensen R, Bendtsen L. *Tension-type headache: why does this condition have to fight for its recognition?* *Current pain and headache reports* 2006;10:454-458.
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- (14) Jensen RH. *Hovedpine*. *Ugeskr Laeger* 2006;168:1950-1953.
- (15) Juhl L, Petersen KA, Larsen EH, Jansen-Olesen I, Olesen J. *The in vivo effect of adrenomedullin on rat dural and pial arteries*. *Eur J Pharmacol* 2006;538:101-7.
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- (17) Kirchmann M. *Migraine with aura: new understanding from clinical epidemiologic studies*. *Curr Opin Neurol* 2006;19:286-293.
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Textbook

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Clinical Activities

The clinical activity in DHC consists of a multidisciplinary out-patient service and an in-patient service. In 2006, some of our experienced members of the staff sought new positions, leading to replacements and new colleagues in the teams. At the end of 2006 the staff consisted of 2.5 psychologists, 2 physical therapists, 3 nurses and 7 secretaries (several part time jobs). In 2006, the service was significantly improved with 2 very experienced specialists, a psychiatrist Marianne Nilsson (one day per week) and a dental specialist, professor, DDS Peter Svensson, with specific focus on patients with temporomandibular dysfunction and facial pain (one day per month).

The multidisciplinary out-patient activities in 2006 are shown in figure 2. The total number of contacts/visits in the out-patient center was 7653. The intake was 1058 new patients and only 546 patients were discharged from the out-patient service. A total of 1638 patients were in active treatment at the center.

The regional distribution of patients is similar to prior years where the vast majority (70%) are from the county of Copenhagen, the City of Copenhagen and Northern Sea land, and those from other areas that in future will be outside of the new hospital region (Figure 3).

The male/female ratio is also unchanged 1/2 and the mean age of our patients are 43 years with a range from 11 to 89 years. The general impact of headache in our patients is significant with a mean frequency of headache on 20 days per month leading to a very high number of absence days from work 5 days per month or reduced working capacity or limited career as illustrated in Figure 4 and 5.

Figure 2
The patient flow in the Danish Headache Center in 2006.

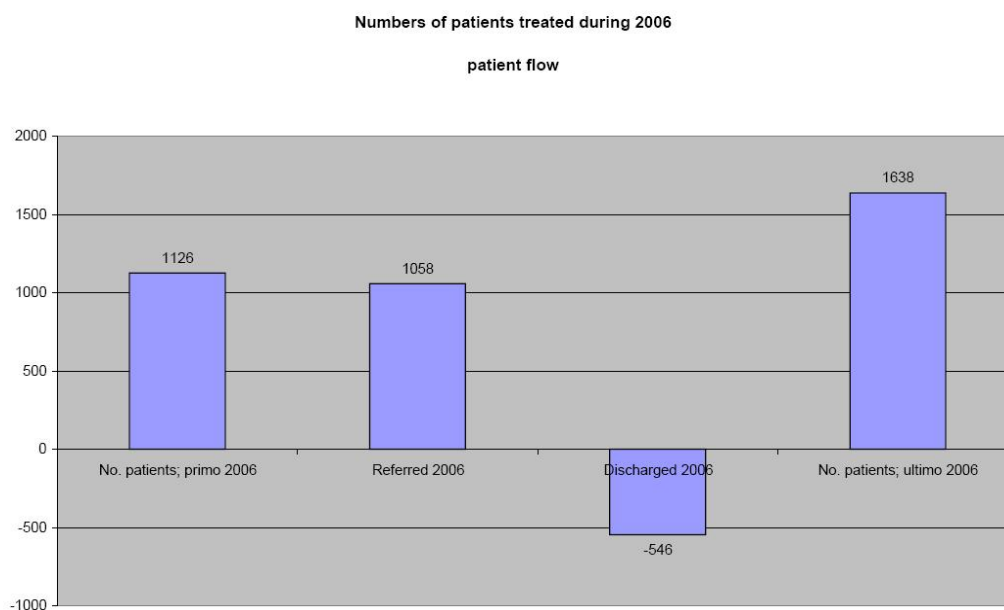




Figure 3 Geographical distribution of referred patients in 2006

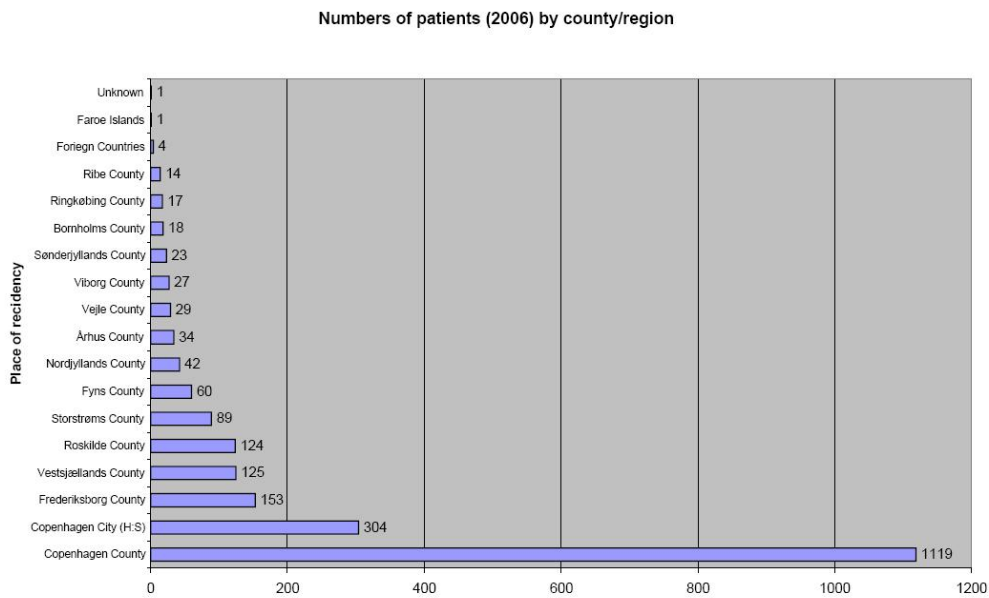


Figure 4 Work Effectiveness – working with headache (from Vinding G, Zeeberg P, Lyngberg A, Petersen R, Jensen R. The burden of headache in a patient population from a specialized headache center, in press)

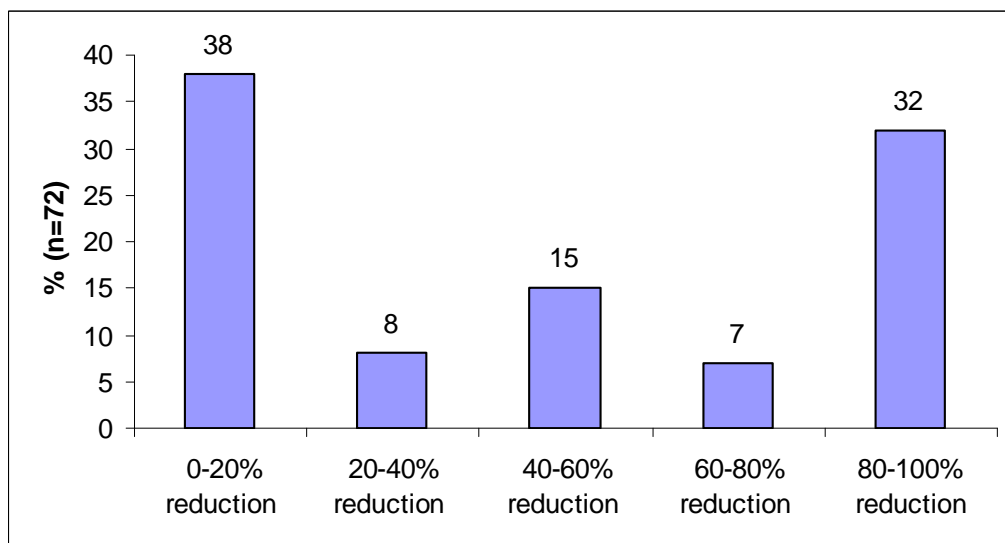
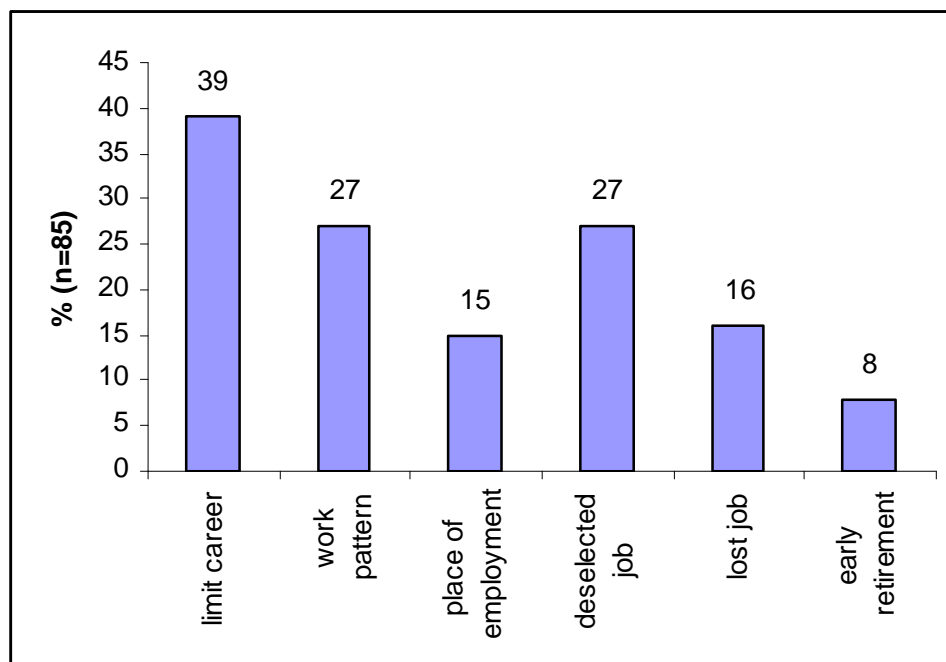




Figure 5. General impact of headache on the patients working capacity and other activities (from Vinding G, Zeeberg P, Lyngberg A, Petersen R, Jensen R. The burden of headache in a patient population from a specialized headache center, in press)



The in-patient headache service

The in-patient programme with 6 beds was implemented from September 2005 and the patients which mainly were patients with medication overuse headache followed a structured regime. All 6 patients arrive on a Tuesday where they are given a structured introduction by a nurse and a chart is written. The next day a senior doctor, who is in charge of all 6 patients for the entire 14 days, carefully reviews the history and examines the patients and then tailors the standard program to the individual needs of the patient. Following this, patients are screened by a psychiatrist with special interest in headache, receive daily therapeutic talks with a nurse and physiotherapy and psychological therapy are offered either individually or in groups. After week 1 and just before discharge, the patient meets their health care providers together for a multidisciplinary talk. Following discharge, patients are seen at regular intervals by a nurse and a doctor as well as physiotherapist and psychologist as needed. Usually the in-patient course is followed by a 1-2 year course as an out-patient with consultation every 3-4 month. Unfortunately, due to a temporary lack of staff the headache beds were closed for headache patients in a 5 months period and used for other neurological patients from October 2006.

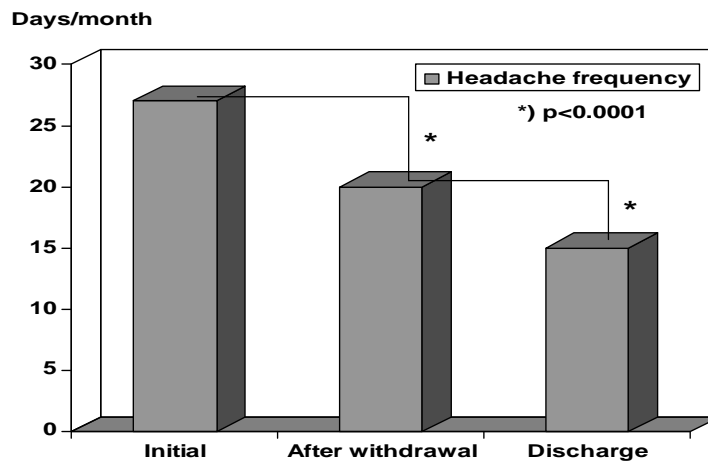
The treatment outcome of medication-overuse headache is rewarding and although patients are categorized and referred as refractory headache patients the effect of the detoxification and the additional treatment programme is very promising. Among 1326 patients analysed, 337 (25%) had medication overuse headache. All diagnostic groups had a significant reduction in headache frequency from the initial visit to discharge, with an overall mean relative reduction of 46% ($p < 0.0001$). Patients without improvement 2 months after complete drug withdrawal, subsequently responded to pharmacological and non-pharmacological prophylaxis with a 26% decrease in headache frequency as measured from the end of withdrawal to discharge ($p < 0.0001$).

In this study, 47% were on prophylaxis at discharge. Former non-responders to medical prophylaxis had a 49% decrease in headache frequency from first visit to discharge ($p < 0.0001$), while those who never had received prophylaxis had a 56% reduction ($p < 0.0001$). This important study confirm the clinical impression that almost all patients with medication overuse benefit from drug withdrawal, either directly or by transformation from therapeutic non-responsiveness to responsiveness. (Zeeberg et al. Cephalalgia 2006; 26:1192-98 and Zeeberg et al. Neurology 2006; 66:1894-8).





Figure 6. The treatment outcomes after discontinuation of medication overuse in a 2 months withdrawal period and after multidisciplinary treatment modalities in The Danish Headache Center. (From Zeeberg et al., Cephalalgia 2006)



Facilities

When the Danish Headache Center at short notice was moved to its current premises several rooms were not optimal for the intended function. Particularly rooms for psychologists and physiotherapists were too small to allow optimal patient contact. Furthermore, the recent expansion of staff in association with the opening of The Headache Center for Children and Adolescents did not result in any increase of available space, because of the lack of space in general caused by its ongoing renovation. It is our sincere hope that this situation may be solved in 2007.

Perspectives

Although it may be extremely difficult to find the time in a busy clinical setting it is absolutely mandatory for the clinical work to have the scientific platform and in addition it is very rewarding and productive to combine basic experimental research with clinical experience on a daily basis to provide the evidence for future strategies. In addition, we aim to continue our analysis of treatment results, to make quality assurance, and to optimize the present strategies in order to develop new therapeutic avenues.

We are optimistic and hope to continue our goal to be in front for the headache patients and the entire society.



