Department of Neurosurgery
Annual Research Report 2021

REGION H

Rigshospitalet

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Annual Research Report 2021

Rigshospitalet

Introduction

This is the first annual research report for the Department of Neurosurgery, Rigshospitalet.

For many reasons such a report has not been published earlier. First and most importantly, research in our department did not reach a level of impact that called for a need or a wish, to flash our efforts. Even though the research was there, was international, important and good, it was carried on very few shoulders that could not lift the research and development (R&D) alone.

The department is one of the largest neurosurgical departments in northern Europe for cranial procedures. The most important task for our department is making sure that our patients are provided with the highest international standard of treatment. As in other aspects of life, this capacity involves considerable responsibility. By this we mean that we hold a great responsibility to drive research and development towards better, safer and more evidence-based treatment, for our patients and relatives in the department and all neurosurgical patients in general. Therefore, it is with greatest pleasure, that we can proudly say that we through the last 5 years have reached this level of research which we have obligated ourselves to provide. This has come to life through a team-based-effort, where everybody in the department focus not only on the daily routines but constantly is aware of R&D by delivering everything from ideas, planning, collection of data to publication. Further and at least as important, we focus on early implementation of R&D results in clinical practice for the benefit for our patients. Our research is the effort and for the single researcher, but also the result of proud contributions from the entire department.

We would like to take the opportunity to congratulate and thank our professors Tiit Mathiesen and Marianne Juhler. The senior researchers, Rikke Guldager, Jane Skjøth-Rasmussen, Tina Nørgaard Munch, Kåre Fugleholm and Peter Birkeland. All the junior researchers. Our research coordinator Helle Bak Wilhjelm for putting everything on track. Our close collaborators internal as well as external, national as well as international, and finally but not least all the staff at the department for bringing our research to the next level.

It is always a joy to immerse oneself to one's job.

Yours sincerely

Janne Jakobsgaard and Morten Ziebell
Directors of Copenhagen neurosurgery

Research for clinical impact

Professor, Senior consultant, MD, Dr Med Sci, Dept. of Neurosurgery, Rigshospitalet

The department of neurosurgery has an annual caseload over 3300 cranial operations and is thereby the largest neurosurgical department devoted to cranial neurosurgery in northern Europe. This caseload warrants extensive research and development to meet healthcare needs, but the high numbers also create a unique opportunity to gather novel knowledge.

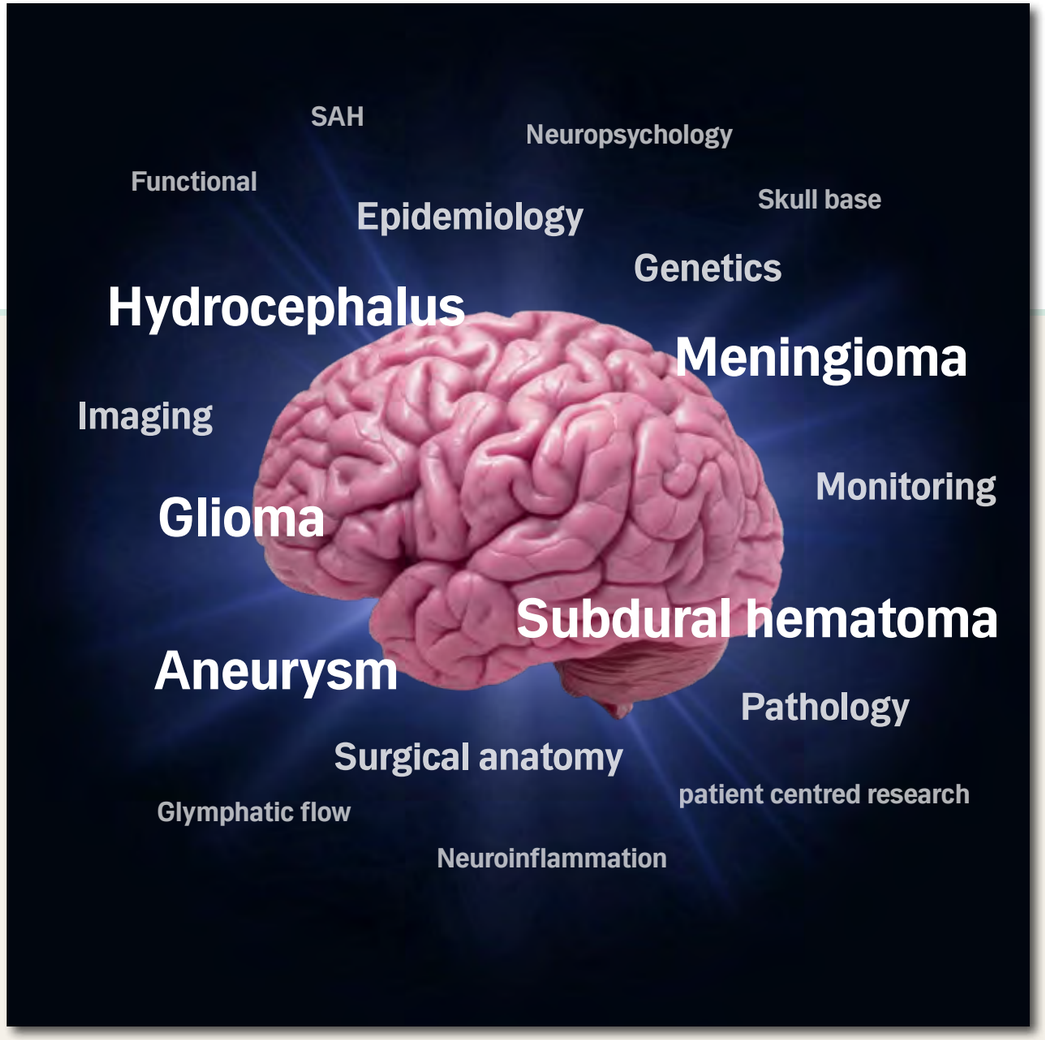
Departmental research covers clinical neurosurgery and forms a matrix of neurosurgical diseases crossed by research methods. The disease groups could be visualized as an x-axis of the matrix, while methodologies cross from the y-axis. This virtual matrix is PERNS, the personalized neurosurgery research group. PERNS is the overarching structure for clinical and translational research in neurosurgery and an integrated part of the Department of Neurosurgery. PERNS connects clinical neuroscience to preclinical sciences. Our strategy is ultimately dependent on two-way interaction with, among others, close collaborators at the departments of neuroradiology, nuclear medicine, neurology, pathology and preclinical sciences.

Pre- and postgraduate neurosurgeons interact with collaborators to cover clinical aspects, epidemiology, psychology, subjective suffering, and pre-clinical science relevant for each disease. The borders between groups are flexible and researcher collaborate to contribute skills and experience to combine efforts when needed to develop specific fields or address research questions.

The main disease entities comprise three major fields of neurosurgery. One is neuro-oncology with three different themes: gliomas, pediatric brain tumors and meningiomas along with skull base tumors and surgical anatomy. Another large group is cerebrospinal fluid related pathology and physiology including hydrocephalus and clinical aspects of glymphatic flow; much of this is studied within the CSF study group. Cerebro-vascular disease is the third, while a special theme of CNS-compartmentalization and blood-brain barrier function is linked to both previous groups. We develop research into neuro-trauma and functional neurosurgery, while spinal neurosurgery is covered by the department of degenerative spinal disease at Glostrup.

The main methodologies comprise clinical research, qualitative methodology, epidemiology, and neuropsychology which are primarily headed by departmental researchers while imaging, cellular, molecular and genetic studies, pathology and macro-anatomy are covered through integration of our collaborators in joint projects.

The major neurosurgical disease groups are addressed through structures such as the Copenhagen CSF Study Group, The personalized Meningioma Management Group, The Oncology Group, the Qualitative Research Group, The Danish Chronic Subdural Hematoma Study-group, and others to cover all aspects of trauma, vascular and functional disease in neurosurgery; structures that are either fixed or formed ad hoc to produce evidence and insight for management of neurosurgical patients.



Two professors, Marianne Juhler and Tiit Mathiesen, mainly cover CSF related disease and pediatric brain tumors or meningiomas and cerebrovascular disease, respectively. Of the senior researchers and associate professors, Morten Ziebell works on meningioma, imaging and functional; Tina Munch on epidemiology and genetics; Kåre Fugleholm on meningioma and trauma; Jane Skjøth on neuro-oncology; Peter Birkeland on CNS-compartmentalization and Rikke Guldager on subjective research with involvement of next-of-kin.

The Tandem grant from Novo Nordisk provide mayor support for CSF related research and the Lundbeck Foundation professor grant provides funding for 360° personalized meningioma research. Danmarks Frie Forskningsfonder support Tina Munch and the compartmentalization-project is a completely new model of collaborative development with Lundbeck A/S.

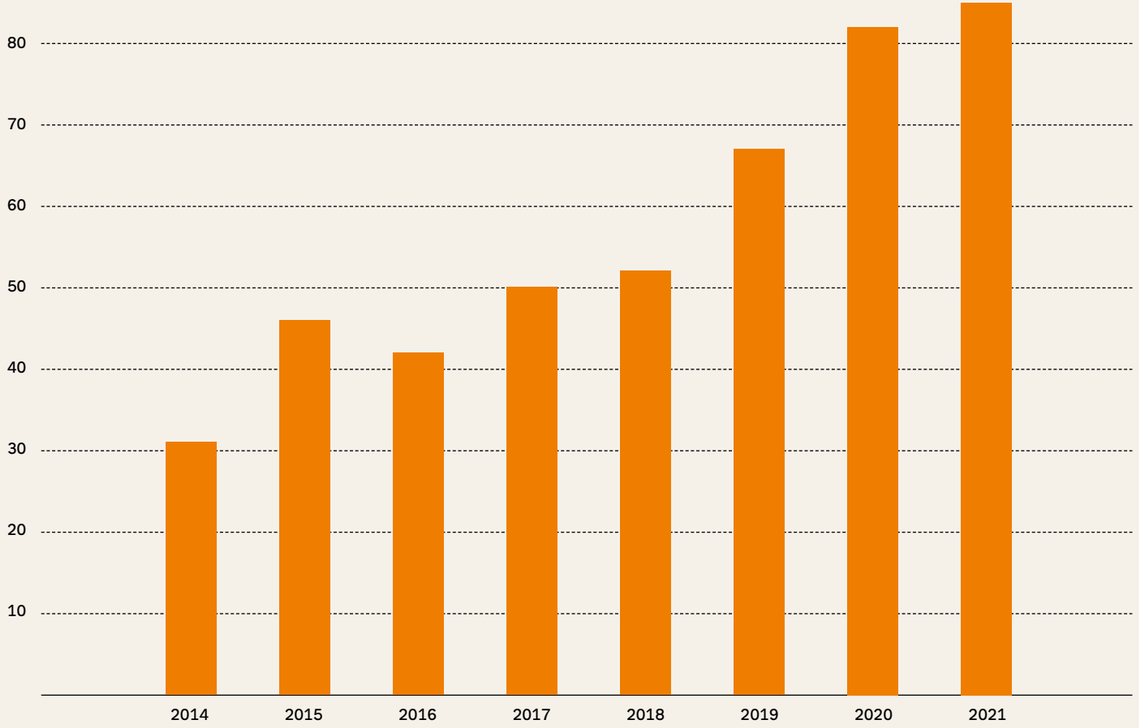
Neurosurgical research at Rigshospitalet
– a historical perspective

Kåre Fugleholm, Senior consultant, Associate professor, PhD, DrMed, FRCS(ENG), Dept. of Neurosurgery, Rigshospitalet

The Department of neurosurgery at Rigshospitalet has a long history of research. Looking back to the nineties, Flemming Gjerris, the professor at that time, together with Svend Erik Børgesen, established a hydrocephalus laboratory for development and research in which Niels Agerlin and Rachid Bech-Azeddine worked as research assistants. At that time, the PhD program was newly established at the University of Copenhagen, and the first neurosurgical PhDs were Kåre Fugleholm in 1994 followed by Birgitte Borgbjerg in 1995. The department also had an animal laboratory, in which Marianne Juhler and John Hauerberg investigated SAH and cerebral autoregulation. A rate of 0-10 publications per year reflected a primary focus on the clinical service commitments, and this was also true in the beginning of this century. In 2006, Bertil Romner replaced Flemming Gjerris as professor, and Marianne Juhler became an additional Professor to the chair. Loyal to the tradition, Marianne Juhler established a strong CSF study group, and as a consequence, the department started to have regular PhD's. Sadly, Bertil Romner passed away in 2013, before he was fully established, but he ignited a more general academic spirit at the department, and at the same time, he provided the funding for the Neurosurgical Research Fund at Rigshospitalet, which is still today instrumental in supporting research at the department. Funding is a real challenge in neurosurgical research, as the synergy with the industry does not fall as natural as for example in neurology, but the Lundbeck Foundation identified the need for support and established 1-year neurosurgical scholarships for medical students. After some years with an empty chair, Tiit Mathiesen became the new chair in 2017, bringing a wealth of expertise in ethics, inflammation and meningioma research, editorial experience, as well as the Personalized Neurosurgery (PERNS) strategy in research, and not least the famous pizza meetings, gathering researchers across generations for discussion and education, enhancing cross-talk and collaboration.

During the last decade, the academic activities have increased to an unprecedented level. We count 85 peer reviewed publications in 2021 (figure 1), and this impressive achievement rests on some of the previously mentioned relations, but additional factors have helped this development enormously. The clinical leads of the department, Janne Jacobsgaard, Jannick Brennum, and Morten Ziebell, have provided a constant supportive environment for research, both in the everyday work flow in the department, and with establishment of a departmental research council, to coordinate our efforts. A research office has been established, we have employed research coordinator Helle Bak, and we have supervised many medical students in their bachelor and master theses, feeding young researchers into the PhD program. The number of senior researchers has increased, and with that, the areas of research interests, with Jane Skjøth-Rasmussens acceleration of glioma research and Tina Munchs impressive epidemiological catalogue as perfect examples. We have introduced nurse-led research in the department, currently with postdoc Rikke Guldager as senior researcher. Finally, by this gazelle behavior, the department has been able to attract a better share of the research funding, both internally at Rigshospitalet, and externally, the last example being the new exciting research collaboration with the Lundbeck Foundation, with Peter Birkeland as the senior neurosurgical frontrunner.

Number of publication from 2014 - 2021

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Integrated research between **Neurointensive care, Anesthesia and Neurosurgery**

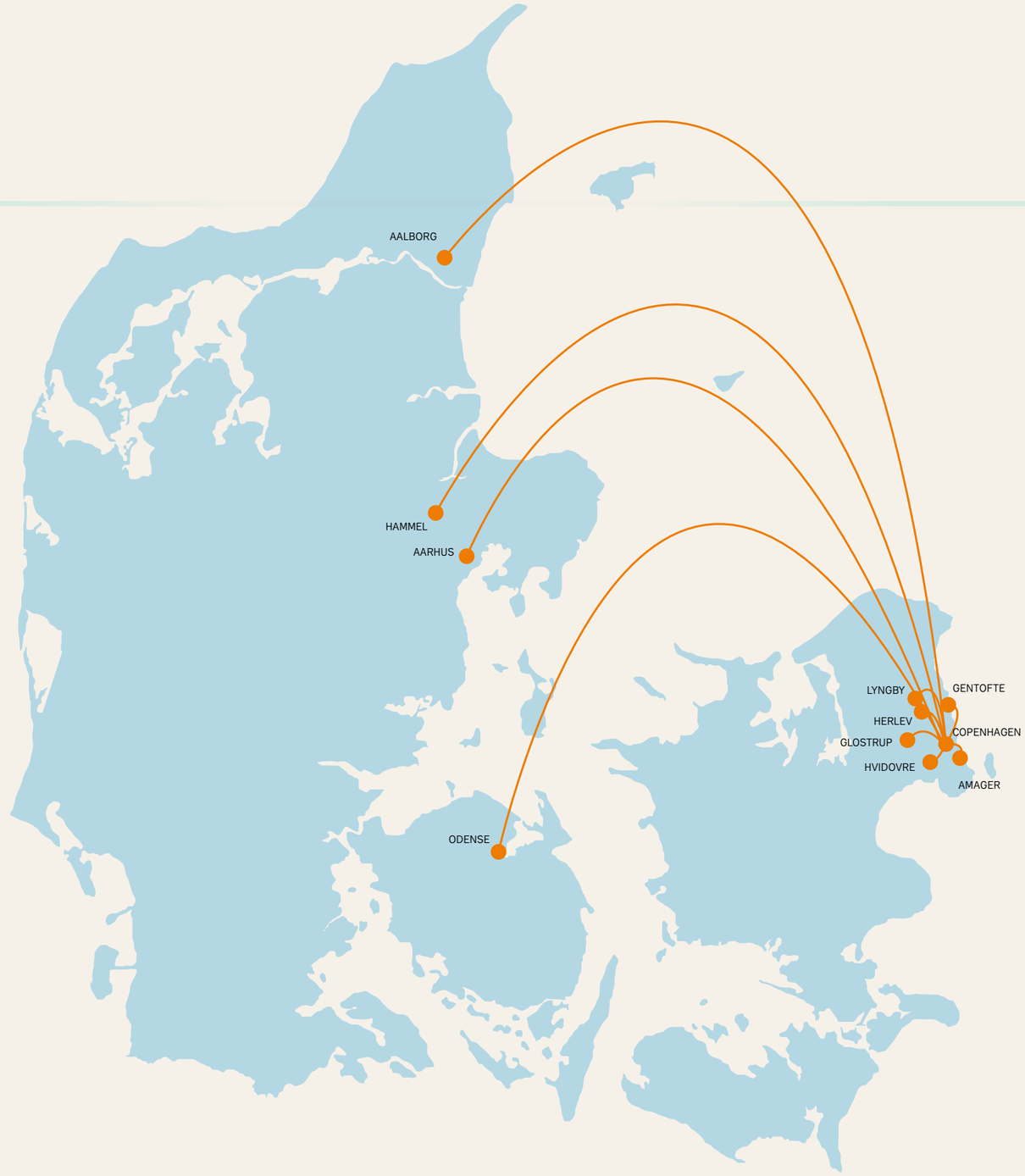
The mission of research at the Department of Neuroanaesthesiology is to improve the treatment of future patients, and because we collaborate clinically with the Department of Neurosurgery, we also have a close collaboration in research and have formed a joint structure to coordinate research. In 2021, we conducted collaborative studies of haemoglobin targets for blood transfusion in acute brain injury; weaning of external ventricular drainage, cerebrospinal fluid biomarkers of hydrocephalus, and measures of cerebral pressure autoregulation in patients with aneurysmal subarachnoid haemorrhage and other types of severe acute brain injury; ventriculostomy-related infection in patients with traumatic brain injury; imaging and electroencephalographic predictors of consciousness and outcome after traumatic and nontraumatic brain injury; nitrosative-oxidative stress in acute brain injury; and perioperative hyperlactataemia in patients undergoing tumour craniotomy.

Kirsten Møller,

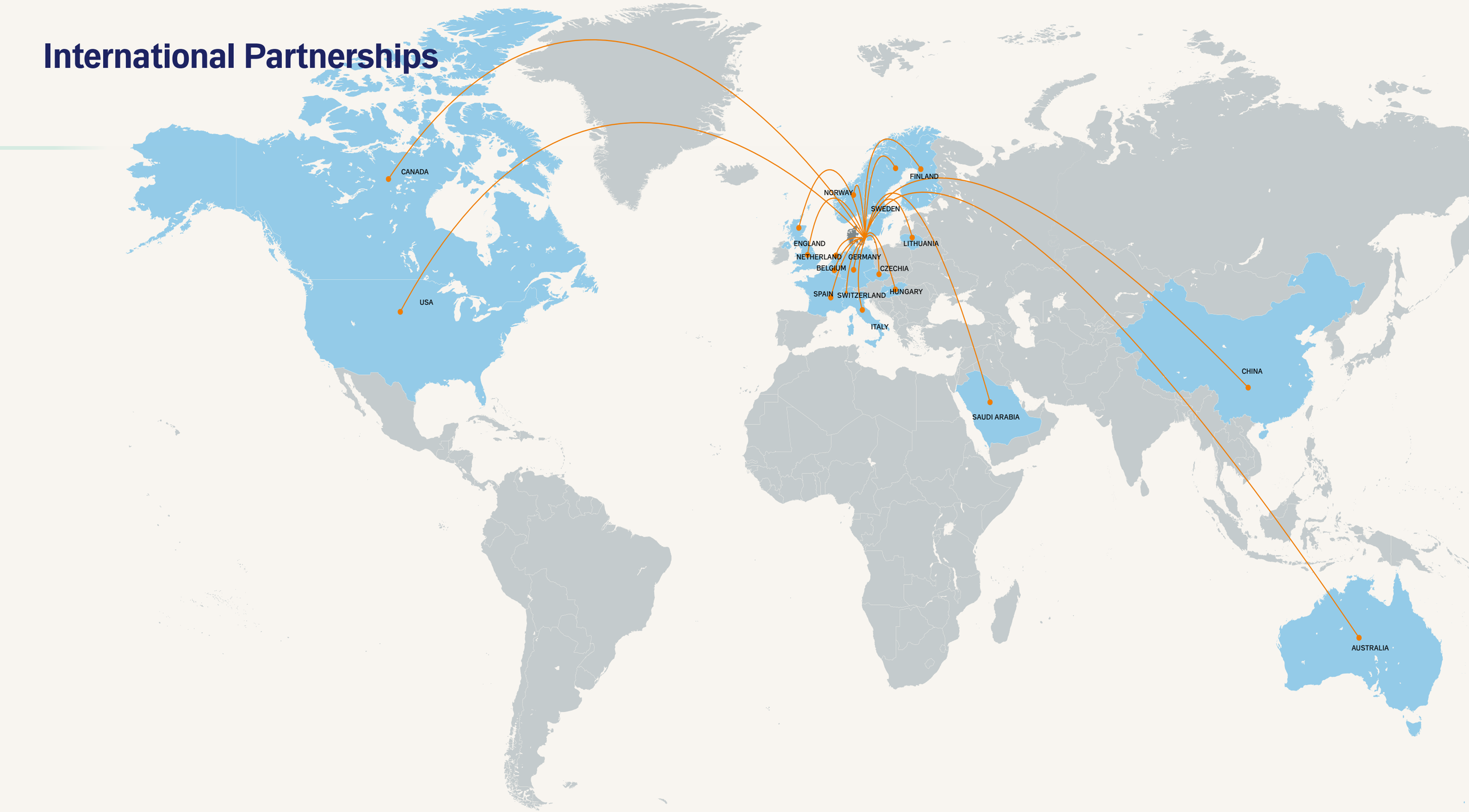
Professor of Neuroanaesthesiology, Rigshospitalet, University of Copenhagen

Danish Partnerships

- Biomedical Engineering, Technical University of Denmark (DTU), Lyngby
- Center for Clinical Metabolic Research, Herlev and Gentofte
- Clinical Experimental Research, Dept. of Rishospitalet, Glostrup
- Copenhagen Bio Science Park, COBIS, Copenhagen
- Danish Cancer Society, Copenhagen
- Danish Center for Sleep Medicine, Glostrup
- Danish Dementia Research Centre, Rigshospitalet, Copenhagen
- Danish Headache Research Centre, Rigshospitalet, Glostrup
- Dept. of Biology, University of Copenhagen, Copenhagen
- Dept. of Cellular and Molecular Medicine, Copenhagen University, Copenhagen
- Dept. of Clinical Genetics, Rigshospitalet Copenhagen
- Dept. of Clinical Immunology, Rigshospitalet, Copenhagen
- Dept. of Clinical Physiology, Nuclear Medicine and PET, Rigshospitalet, Copenhagen
- Dept. of Clinical Research, Amager og Hvidovre & Aarhus
- Dept. of Clinical Research, Odense University Hospital, Odense
- Dept. of Neuroanaesthesiology (OUH), Odense
- Dept. of Neuroanaesthesiology, Rigshospitalet, Copenhagen
- Dept. of Neurophysiology, Rigshospitalet, Copenhagen
- Dept. of Neurosurgery, Aalborg Univerity Hopsital, Aalborg
- Dept. of Neurosurgery, Aarhus Univerity Hopsital, Aarhus
- Dept. of Neurosurgery, Odense Univerity Hopsital, Odense
- Dept. of Oncology, Rigshospitalet Copenhagen and Aarhus University hospital
- Dept. of Ophthalmlogy, Rigshospitalet, Glostrup
- Dept. of Pathology, Rigshospitalet, Copenhagen
- Dept. of Paediatrics, oncology, Rigshospitalet, Copenhagen
- Dept. of Public Health, Aarhus University, Aarhus, Glostrup and Copenhagen
- Neuro- radiology/magnetic resonance imaging, Endovascular and interventional radiology, Dept. of Radiology, Rigshospitalet, Copenhagen
- Dept. of Spine Surgery, Copenhagen University Hospital, Glostrup
- H. Lundbeck A/S, Copenhagen
- Hammel Neurorehabilitation and Research Centre, Hammel
- Mental Health Centre Copenhagen, Copenhagen University Hospital, Copenhagen
- Neurobiology Research Unit, Rigshospitalet, Copenhagen
- Research unit for Epidemiology, Biostatistics and Biodemography, The University of Southern Denmark, Odense
- Section of Biostatistics, Copenhagen Universitet, Copenhagen
- Statens Serum Institute (SSI), Copenhagen



International Partnerships



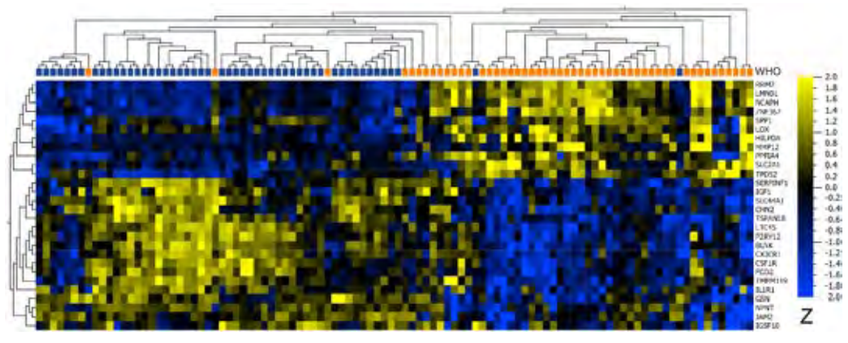
Personal, clinical, and biological analyses of WHO grade 3 meningioma

Andrea Daniela Maier, PhD fellow, Dept. of Neurosurgery, Rigshospitalet

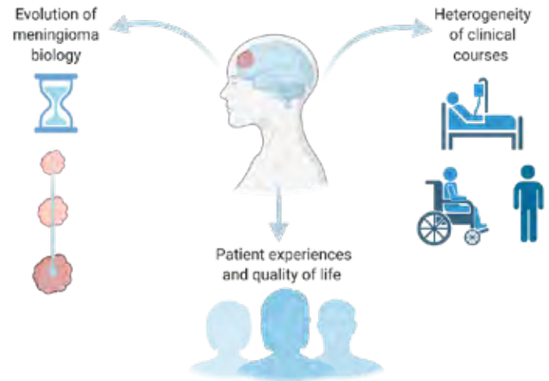
Malignant meningioma, or WHO grade 3 meningioma, is a primary cancer of the meninges surrounding the brain. Most meningiomas are benign, according to the WHO classification, which divides meningiomas into grade 1 meningiomas (80%), grade 2 (15-20%) and grade 3 (1-5%). Patients with malignant meningioma are rare, but the incidence of all meningiomas will increase with an aging population and an increasing number of incidental findings. Patients with malignant meningioma experience significant morbidity and mortality and dismal outcomes despite repeated surgery, radiation, and experimental therapies. Because of the rarity of malignant meningiomas, we lack knowledge of tumour biology, clinical courses, and patient perspectives. Moreover, the accelerated course and malignant transformation of benign meningiomas provide a model to understand biology and meet clinical challenges of all meningiomas.

The main objective of my PhD thesis is to investigate how these patients perceive their disease, how the disease course develops, and provide in-depth information on the biological profile of the tumour and its recurrences.

We retrospectively investigated a unique population based consecutive cohort of patients treated for malignant meningioma at Rigshospitalet during 2000-2020. Fifty-one patients underwent 151 surgeries for primary or recurrent tumours. Patients with a malignant meningioma had a substantial risk of undergoing multiple surgeries and they had a high risk of surgical complications. Very few operations were followed by an improvement of the neurological condition of patients, which must be factored into the decision making. Importantly, we identified potential benefits of early palliative care and explored how uncertainty of the clinical courses must be considered when communicating to the patient and relatives.



Example of results in the gene expression study. We see a heatmap and clustering showing 51 malignant meningioma (marked orange) and 51 benign meningioma (marked blue). Gene expression is visualized with a z-score, where a relatively higher expression is yellow and relative lower is blue (z-score). The genes involved in microglia regulation are listed on the right, and we see that the gene expression profile of these genes yields a near-perfect separation of benign and malignant meningiomas.



Next, we used semi-structured interviews to investigate a first-person perspective of quality of life and everyday life. Our preliminary analysis of recurrent themes in the material showed a fundamental change of roles and new restrictions in everyday life combined unawareness of prognoses and uncertainty of the future that deeply impacted quality of life. Unawareness of the gravity of their disease largely reflected adherence to the first-given pre-surgical information of having a benign brain tumour, a presumed grade 1 meningioma, in their personal disease narrative.

To investigate biology, we used a targeted gene expression panel from Nanostring with 787 genes involved in meningioma biology and neuroinflammatory processes. Our novel findings showed a pivotal role for the brain's immune cells in meningioma development. Surprisingly, neuroinflammatory microglial profiles differed between benign and malignant meningiomas, and a subset of transcripts also differed between benign meningiomas that remained benign and those histologically benign meningiomas that underwent malignant degeneration and recurred as malignant meningiomas. Importantly, we saw that benign tumours from patients that later developed a malignant meningioma, had upregulation of certain genes years before the meningioma recurred as a malignant meningioma, allowing for early identification and treatment of patients at high risk.

The project provided a model that accounts for personal, clinical and biological perspectives of individually targeted care.

- Patients were unlikely to improve neurologically after repeated surgeries
- Coping was difficult due to uncertainty of future
- RNA signatures could reveal meningiomas deemed to malignant transformation and recurrence

Clinical genetics in the diagnostic strategy and targeted treatment of congenital hydrocephalus

Tina Nørgaard Munch, Neurosurgical staff specialist, associate professor, Senior researcher, Dept. of Neurosurgery, Rigshospitalet

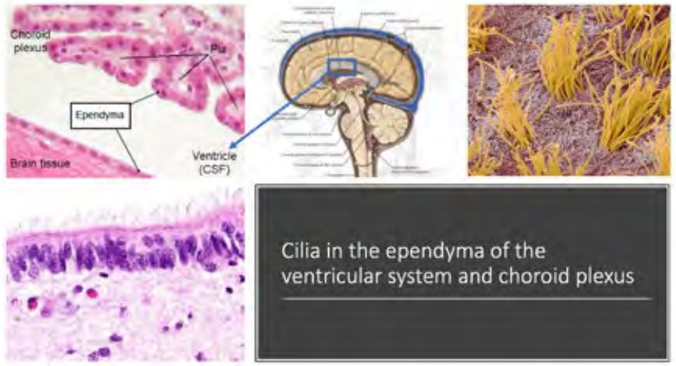
The project is a collaboration between Department of Neurosurgery and Department of Clinical Genetics, Rigshospitalet, Copenhagen. Supported by The Independent Research Fund Denmark.

Congenital hydrocephalus occurs in 0.62/1000 live born children in Denmark and the choice of surgical treatment relies on the radiologic presentation as either obstructive or communicating hydrocephalus. A plethora of surgical treatment options makes a highly individualized treatment possible, but the essential problem is, that these technical advances surpassed the knowledge of the underlying disease mechanisms. Thus, application of the most suitable treatment for the individual remains to be challenging, resulting in extremely high failure rates (cumulative 1-year risks of 44-50 %).

Clinical genetics has gained ground in predicting individual prognoses and treatment outcomes in several other diseases, but not hydrocephalus. A total of 100+ candidate genes for hydrocephalus have been described, including eight genes known to cause Mendelian inheritance. Recently, we performed the first population-based candidate gene study and it turned out that most of the patients were carriers of one or more variants likely to be disease-causing. Interestingly, these genes to a large extent involved the ciliome – the genes encoding function of the cilia, the antenna-like protrusions present in multiple organs, including the brain. In the brain, cilia are located at the inner surface of the brain ventricles, the choroid plexus and on the surface of cells lining the subarachnoid space (please, see the figure for illustrations). Thus, our findings, together with the emerging literature in this area, suggest that the genetic etiology of congenital hydrocephalus largely is attributable to ciliopathy-related genetic variants.

In the brain, motile cilia are crucial for the circulation of cerebrospinal fluid and the transport of signaling molecules and cells within the ventricular system and subarachnoid space. Thus, the motile cilia facilitate transport of cerebrospinal fluid within the fluid-filled spaces in the brain and the circulation around the brain hemispheres and spinal cord to the venous system where most of the cerebrospinal fluid is absorbed. Primary cilia play important roles in neurodevelopment. The primary cilia communicate with neuronal stem cells located right outside the ventricular system and they are involved in complex signaling cascades involved in the formation of the brain. The primary cilia are crucial for the activation of the stem cells and their differentiation into functional brain tissue as well as their migration to the correct locations in the mature brain, e.g., the wiring of the brain. Furthermore, some of the cilia are involved in regulation of protein content and composition of the cerebrospinal fluid by helping control the barrier between the lining of the brain ventricles and the cerebrospinal fluid.

Dysfunction of one or more of these ciliary functions can lead to hydrocephalus. The increasing knowledge of the genetic etiology of congenital hydrocephalus calls for being used for a more personalized diagnosis and treatment of



congenital hydrocephalus. Furthermore, ciliopathies may play a role in other congenital brain diseases such as epilepsy, autism spectrum disorder and brain tumors, conditions, which often co-occurs with hydrocephalus.

How can knowledge on ciliopathies be used in personalized diagnosis and treatment?

It is possible that the very high risk of failure, 44% within 1 year, of endoscopic third ventriculostomy (ETV) is explained by an undiagnosed motile ciliopathy in the ventricular system. In such cases the ETV would solve the internal outlet problem, but not the co-existing cerebrospinal fluid circulation problem. This leave the patients with a persistent "functional aqueductal stenosis", meaning that even though the outlet problem is solved by the ETV the circulation problem remains. Therefore, a shunt with low opening pressure may more likely be a successful first choice-treatment in these patients.

The prevailing cause of the very high 1-year risk of shunt failure, 50 % within 1 year, is a hitherto unexplained tendency to shunt obstruction in some patients. This tendency may be in some cases be caused by altered composition and/or increased protein content of the cerebrospinal fluid attributable to a primary ciliopathy. The revision rate may be reduced if this is accounted for in the choice of shunt type.

How can knowledge on ciliopathies be used in neuroscience?

The results of this project may furthermore elucidate the roles of ciliopathies in brain diseases in the broadest sense, as the hydrocephalus genes involving the ciliome affect the molecular genetic pathways involved in the fetal formation of the brain. Therefore, elucidating the role of ciliopathies in hydrocephalus and other brain diseases may pave the way for future development of medical and pharmacogenetic therapies targeted at restoring cilia dysfunction. Examples could be lentiviral gene therapy, as used in primary ciliary dyskinesia, and the use of melanin-concentrating hormone, that increase the ciliary beating frequency.

- Hydrocephalus has genetic roots
- Treatment can be targeted
- Is hydrocephalus a ciliopthy?

FG001: first-in-human study of a novel upar-targeted imaging agent for visualization of malignant glioma during surgery

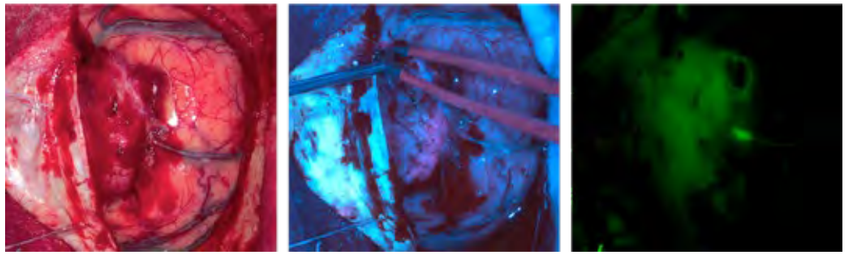
Jane Skjøth-Rasmussen, Senior consultant, PhD, Dept. of Neurosurgery, Rigshospitalet

We investigate a new fluorescent agent as a surgical aid for neurosurgery. The project was initiated with inclusion of the first patient November 4th 2020.

In over a year we managed to include and surgically evaluate the new Upar-targeted optical probe called FG001 in more than 33 patients. Requirements for a first-in -man study are high and the team needed to meticulously plan and monitor every little detail from drug-storage to registration of EKG-equipment detailed monitoring of any adverse event during the 48 hours of trial in every patient. And already now we can conclude that the drug is safe and capable to delineate tumor-infiltrated tissue and distinguish it from healthy brain. Translation from bench to bedside is important in science and a First-in-Human study is not only laborious but requires a high degree of trust in care processes and quality of management.

Due to the great effort of our team, we are now close to completion of Phase I and results will be presented at the upcoming SNS 2022 in Bergen. We have, however, already published a serendipitous observation. In one case, the expected malignant glioma turned out to be a meningeoma. To our surprise, we found compelling fluorescence that did not only light up the tumor but also the dural attachment. The case made the cover of Acta Neurochirurgica and was published under the title: "*A new uPAR-targeting fluorescent probe for optical guided intracranial surgery in resection of a meningioma – a case report*".

The substance "FG001" was developed by Prof. Andreas Kjær, Clinical Physiology and Nuclear Medicine. Our results are encouraging, and we are planning a multicenter Phase II trial and extension of indications to determine the capability of FG001 to visualize other types of brain tumors and grades. Moreover, Upar appears to be specific for neoplastic tissues and targeting Upar has potential future therapeutic applications in addition to offering a completely new principle for fluorescence guided resections.



The image illustrates tumor in white light and the corresponding images with fluorescence using blue light 405 nm (from 5-ALA) or NIR green color enhanced (from FG001).

Involvement of relatives in patients with acquired brain injury or malignant brain tumor – a nursing intervention study

Rikke Guldager, Registret Nurse, MSci, PhD, Postdoc/Clinical Nurse Specialist, Dept. of Neurosurgery, Rigshospitalet

Relatives of patients with severe acquired brain injury or malignant brain cancer (WHO grade 3 and 4) are burdened and exposed to a high risk of anxiety and depression. Their life situation has changed, and they are faced with a new role as informal caregivers for the affected. Despite the burden that many relatives experience, several qualitative studies have identified that relatives to patients with severe acquired brain injury or malignant brain cancer want to be involved in care and treatment. No Danish tool is yet developed to identify relatives' diverse needs for involvement during the patients' course of disease – or taking relatives' resources into account. However, current practice is neither systematic, nor evidence based despite that relatives' need for support and the importance of involvement of relatives are widely acknowledged

We develop, test, validate, implement a tool for systematic involvement of relatives in the patients' course of disease and treatment trajectory; and we evaluate the tool to ensures scientific validity.

Our project involves the Department of Neurology and Department of brain injury at Rigshospitalet and the Hammel Neurorehabilitation Center for in a national multicenter study based on complex intervention in four phases. The target group of the project is relatives (> 18 years) to patients with acquired brain injury or malignant brain cancer (WHO grades 3 and 4).

We conduct scoping reviews related to three research questions in the development phase and have identified a knowledge gap concerning the involvement of relatives in the patient with malignant brain cancer; many relatives express a wish to participate in care processes but such preferences have not been met.

We anticipate that a standardized tool can ensure that relatives' resources and needs are systematically identified. to the tool will support relatives' involvement and epitomize on opportunities of the individual in the new life situation. A targeted intervention will create better collaboration and communication between the relatives and professional caregivers, with higher satisfaction, and ultimately a better pathway for the patient.

- Relatives to patients with severe acquired brain injury og malignant brain cancer want to be involved in care and reatment
- Develop standardized tool

CSDH – a challenge in quantity and quality

Kåre Fugleholm, Senior consultant, Associate professor, PhD, DrMed, FRCS(ENG), Dept. of Neurosurgery, Rigshospitalet
Thorbjørn Søren Rønn Jensen, Senior House Officer, PhD fellow, Dept. of Neurosurgery, Rigshospitalet

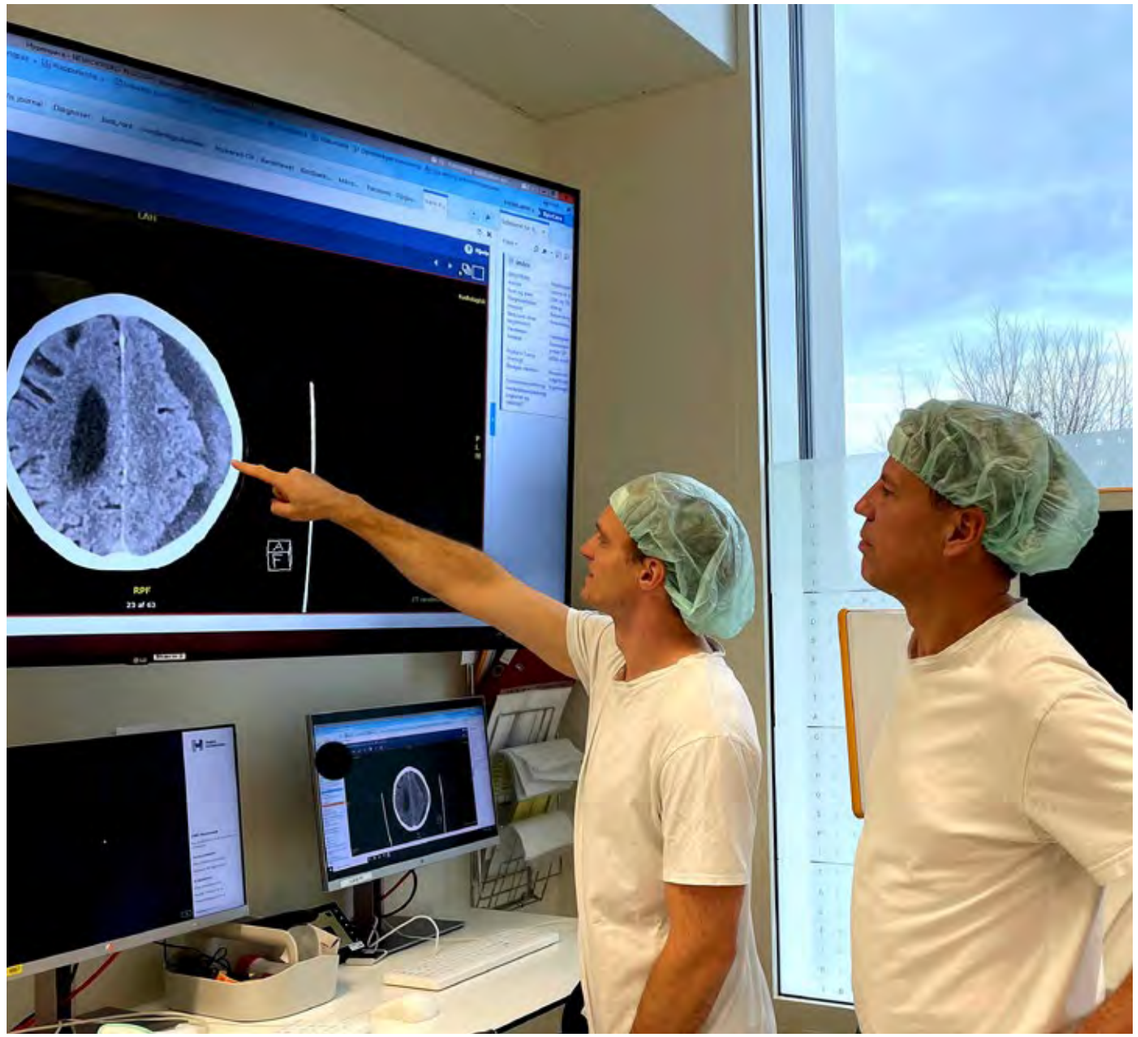
Surgery for chronic subdural hematoma (CSDH) has now become the most frequent neurosurgical procedure, largely due to an ageing population on anticoagulants. Consequently, the patients and the health sector are increasingly challenged by this disease, for which the cause and mechanism are still largely unknown. In essence, the hematoma comprises a balloon-like structure in the space between the brain and skull, which is insidiously inflated with fluid over a timespan of weeks to months, sometimes on both sides simultaneously. This highly imaginable process causes dysfunction of the compressed brain with a sneaking loss of mobility and function, often leading to a run of misdiagnoses before the patient is finally scanned and the culprit is identified. To make things worse, treatment strategies have a weak evidence base, and recurrence is commonplace. This scenario has spurred vivid activity in CSDH research and search for evidence supported CSDH management.

The CSDH research team at Rigshospitalet was established in 2012 as a parallel to a national steering group, with participants from all neurosurgical departments in Denmark. In a close national collaboration, we now coordinate CSDH management and research including publication of world first national guidelines for CSDH treatment in 2018. This national collaboration has created a unique platform for research, and for clinical implementation of findings, in a unique national standardized approach for CSDH patients for preoperative evaluation, surgical strategy, and postoperative care.

We attack the CSDH challenge from all angles with local, national and international collaborations, focusing on prevention and personalized treatment. Currently, we cover operative technique, postoperative care and observation, outcome, epidemiology, genetics, histology, and pathophysiology in clinical and basic-science projects. Our results are continuously and directly implemented, not only at Rigshospitalet, but also nationally and internationally.

The CSDH-research group has published 11 peer reviewed papers since 2016, of which two publications in Journal of Neurosurgery have led to immediate change of treatment strategy. One study based on a national 3-year cohort, found that bilateral CSDH should be treated bilaterally, and a more recent national randomized controlled trial (RCT), showed that 48 hours drainage time is not superior to 24 hours. We now conduct a further national RCT to clarify if we can reduce the drainage time (Draintime 2), and consequently shorten length of stay further. In a concerted effort with molecular, genetic and epidemiological research, we explore pre-symptomatic diagnosis of CSDH, based on individual risk assessment. Anti-inflammatory treatment can provide a window to non-surgical and personalized treatment of CSDH, even before the patients gets symptoms or realize the danger of a hematoma.

- Skyrocketing incidence of chronic SDH with aging population
- Need mechanistic science and individual risk assessment
- Need evidence based treatment



PhD Thesis: Characterization of intracranial pressure (ICP) signals

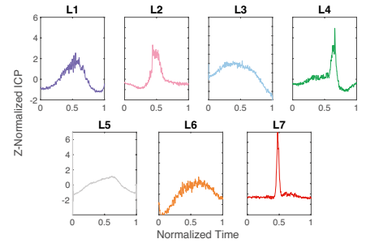
Isabel Martinez Tejada

With the development of telemetric monitoring devices in the last decade, ICP monitoring has become feasible in a broader clinical setting, with patients undergoing ICP monitoring with mobile equipment either in-hospital or in the home setting, where a larger variety of ICP waveforms exist. Currently, the identification of these waveforms, the so-called macro-patterns lasting seconds to minutes, is primarily based on visual inspection. The need for objective and more automated identification of these variations emerges as a potential tool for better understanding the physiological underpinnings of the patient's clinical state.

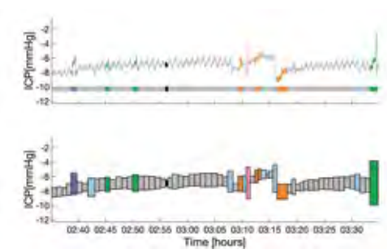
During my PhD thesis, we investigated a new methodology that could serve as a foundation for future objective and reproducible macro-pattern identification in the ICP signal with the hope to better understand the morphological characteristics and distribution of these macro-patterns in the ICP signal and their clinical significance.

First, we showed that the current terminology and descriptions of B-waves no longer adequately address the ICP waveforms found in the clinical practice today. Their origin is also unclear. Our results found that ICP B-waves, also observed in healthy subjects during sleep, are associated both with respiratory disturbances and vascular contribution of flow velocity in a limited frequency range.

Second, a new data quality pipeline was designed to integrate all data validation checks to ensure high data quality. The method was applied to ICP signals before macro-pattern identification, to mitigate the possibility of artefacts masking the true signal.



Finally, a method based on k-Shape clustering was developed to identify the most encountered macro-patterns in ICP signals. We found a total of seven macro-patterns—with varying occurrence and distribution—that described our ICP signals.



In conclusion, we proposed a new, objective, and more automated method to identify macro-patterns in ICP signals. Thanks to this method, disease entities are likely to be identifiable based on the internal distribution and weighting of specific ICP macro-patterns. This information aims at optimizing both disease and treatment identification.

- Individual pathophysiology reflects ICP waveforms
- Automated analysis identifies macro patterns
- Signal analysis can support treatment

PhD fellow list

PHD STUDENT	PROJECT	SUPERVISORS	START DATE	END DATE
Aleena Azam	Preclinical and clinical validation of new imaging biomarkers and treatment modalities in gliomas	Andreas Kjær Jane Skjøth-Rasmussen	01.12.2021	01.12.2024
Andrea Daniela Maier	Malignant meningioma: Clinical, spatial and temporal heterogeneity	Tiit Mathiesen David Scheie	01.10.2018	01.10.2022
Aske Foldbjerg Laustsen	Nordic-European Study of the cerebellar mutism syndrome (CMS) in children with brain tumors of the posterior fossa	Marianne Juhler A. Kjeld Schmiegelow Astrid Sehested René Mathiasen Jonathan Kjær Grønbæk	01.01.2022	31.01.2024
Casper Schwartz Riedel	the Glymphatic System in Humans - Sleep-disordered breathing and intracranial pressure B-waves	Marianne Juhler Poul Jennum	01.05.2017	07.04.2022
Jeppe Lohfert Haslund-Vinding	Neuroinflammation in Relation to Elective Meningeoma Surgery	Tiit Mathiesen Morten Ziebell	01.05.2021	30.04.2025
Jesper Peter Bömers	Delayed cerebral ischemia in subarachnoid hemorrhage - Towards a novel pharmacological intervention	Tiit Mathiesen Lars Edvinsson	01.04.2020	01.04.2023
Jon Foss-Skiftesvik	Genetic predisposition to central nervous system tumors in children	Kjeld Schmiegelow René Mathiasen Jane Skjøth-Rasmussen Karin Wadt	01.06.2020	01.06.2023
Jonathan Kjær Grønbæk	Clinical risk factors for speech impairment after posterior fossa tumour surgery in children	Marianne Juhler Kjeld Schmiegelow Astrid Marie Sehested René Mathiasen Karsten Nysom Morten Arnberg Wibroe	01.01.2019	01.01.2022
Laura Giraldi	Meningioma – hormonal influence and risk of post-craniotomy de novo epilepsy	Tina N Munch Kåre Fugleholm Mads Melbye	01.02.2018	01.02.2022
Sarah Skovlunde Hornshøj Pedersen	Long-term prognosis following Paediatric Traumatic Brain Injury – the cognitive function, rehabilitation and intracranial pressure	Marianne Juhler Tina Munch Morten Ziebell Morten Andresen Alexander Lilja-Cyron	01.05.2020	31.04.2024
Tenna Capion	Choice of strategy for EVD cessation in adult patients with hydrocephalus following aneurysmal subarachnoid haemorrhage	Tiit Mathiensen Marianne Juhler Alexander Lilja-Cyron Kirsten Møller	01.09.2019	01.10.2023
Thorbjørn Søren Rønn Jensen	The pathophysiology of chronic subdural hematoma: molecularly, epidemiological and genetically	Kåre Fugleholm Tina Munch Tina Binderup	01.10.2000	01.10.2023
Trine Hjorslev Andreasen	S-ketamine for cortical spreading depolarisation in patients with severe acute brain injury	Kirsten Møller Marianne Juhler Martin Fabricius	01.01.2021	01.07.2024

Researcher PhD

Aleena Azam
MD, PhD fellow

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet
Dept. of Clinical Physiology, Nuclear Medicine and PET, Rigshospitalet
Cluster for Molecular Imaging, University of Copenhagen

RESEARCH FIELDS
Strong interest in the field of gliomas with focus on glioblastoma multiforme aiming towards the development of new preclinical and clinical imaging biomarkers as well as new treatment modalities against gliomas.

aleena.azam@regionh.dk

Casper Schwartz Riedel
MD, M.Sc., PhD fellow

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet

RESEARCH FIELDS
- Cerebral hemodynamics and sleep, with a special interest in ICP and sleep-disordered breathing
- Glymphatic system in humans and CSF circulation

casper.schwartz.riedel@regionh.dk

Jon Foss-Skiftesvik
MD, senior resident in neurosurgery, PhD fellow

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet
Dept. of Pediatric Oncology Research Laboratory, Rigshospitalet
Dept. of Neonatal Genetics, Statens Serum Institut

RESEARCH FIELDS
Pediatric neurosurgery; pediatric neuro-oncology; genetics; epigenetics; biobanking

Jon.foss-skiftesvik@regionh.dk

Sarah Skovlunde Hornshøj Pedersen
PhD fellow

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet

RESEARCH FIELDS
Pediatric neurosurgery, Pediatric head trauma, Monitoring and Measurement of Intracranial pressure in children

sarah.skovlunde.hornshoej.pedersen.01@regionh.dk

Andrea Daniela Maier
PhD fellow

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet
Dept. of Pathology, Rigshospitalet

RESEARCH FIELDS
My main research focus is the integration of clinically relevant molecular markers into meningioma diagnostics and prognostication. Specifically, I am working on a cohort of WHO grade III meningiomas (malignant meningiomas) where I explore the gene expression profile across recurrences and clinical characteristics of the patient group.

andrea.maier@regionh.dk

Jeppe Lohfert Haslund-Vinding
MD, Neurosurgical Resident, PhD fellow

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet

RESEARCH FIELDS
My field of interest revolve neuroinflammation, epilepsy and psychological morbidity in patients undergoing surgery for intracranial meningioma.

jeppe.lohfert.haslund-vinding.01@regionh.dk

Jonathan Kjær Grønbæk
MD, PhD fellow

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet
Dept. of Paediatrics and Adolescent Medicine, Rigshospitalet

RESEARCH FIELDS
- Posterior fossa tumour surgery in children
- Paediatric neurosurgery
- Cerebellar Mutism Syndrome

Jonathan.kjaer.groenbaek@regionh.dk

Silas Haahr Nielsen
MD, PhD fellow

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet

RESEARCH FIELDS
- Minimally invasive treatment of brain tumors and epilepsy with MR-guided Laser Interstitial Therapy.
- Blood-brain barrier.
- Neurooncology.
- Neuroimaging.
- Stereotactic surgery.
- Randomised controlled trials (RCT).
- Teaching.

Silas.haahr.nielsen@regionh.dk

Aske Foldbjerg Laustsen
MD, PhD fellow

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet
Dept. of Paediatric and Adolescent Medicine, Rigshospitalet
University of Copenhagen

RESEARCH FIELDS
Cerebellar Mutisme Syndrome after Posterior Fossa tumour surgery in children.

aske.foldbjerg.laustsen@regionh.dk

Jesper Peter Bömers
MD, PhD fellow

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet

RESEARCH FIELDS
Subarachnoid hemorrhage, brain metabolism

Jesper.peter.boemers@regionh.dk

Laura Giraldi
MD, PhD fellow

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet
Dept. of Epidemiology Research, Statens Serum Institut

RESEARCH FIELDS
- Meningioma
- Craniotomy
- Epilepsy

Lvmfg89@gmail.com

Tenna Capion
PhD fellow

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet

RESEARCH FIELDS
Vascular Neurosurgery, Neurosurgical Procedures, Aneurysmal subarachnoid haemorrhage, Extra ventricular drainage

tenna.baek.capion@regionh.dk

Research 2021

Thorbjørn Søren Rønn Jensen
Senior House Officer, PhD fellow

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet

RESEARCH FIELDS
- Chronic subdural hematoma pathogenesis from a molecular, epidemiological and genetic perspective.
- Chronic subdural hematomas management investigated in collaboration with the national DAnish Chronic SUbdural Hematoma Study (DACSUHS)

Tjens07@gmail.com
Thorbjoern.soeren.roenn.jensen.01@regionh.dk

Trine Hjorslev Andreasen
MD, PhD fellow

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet,
Dept. of Clinical Physiology and Nuclear Medicine and PET, Rigshospitalet

RESEARCH FIELDS
Neurosurgery, cortical spreading depolarisation, acute brain injury

Trine.hjorslev.andreasen@regionh.dk

Emma Anemone Kofoed Lauridsen
Medical Student

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet
Faculty of Health & Medical Sciences, University of Copenhagen

RESEARCH FIELDS
Research in meningiomas, Health-Related Quality of Life and skullbase surgery

emma.lauridsen@regionh.dk

Sara Nordentoft
RN, MSc.

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet

RESEARCH FIELDS
Primary scope of interest is patients diagnosed with high-grade glioma and their family caregivers, including needs and preferences for support during the disease- and treatment trajectory and quality of life.

Sara.marie.juel.nordentoft@regionh.dk

Researcher

Alexander Lilja-Cyron
MD, PhD

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet

RESEARCH FIELDS
- Intracranial pressure dynamics
- Traumatic brain injury
- Hydrocephalus

alexander.lilja-cyron@regionh.dk

Christian Mirian
MD, Research assisstant

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet

RESEARCH FIELDS
Meningioma. Epidemiological and clinical research, with primary interest in application of peptide receptor radionuclide therapy

Christian.mirian.larsen@regionh.dk

Markus Engebæk Krogager
Research assistent (pre-PhD former scholarship researcher)

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet

RESEARCH FIELDS
An original, multimodal (radiological-, cadaveric-, mathematical-) research approach for analysis and diagnosis of surgical relevant posterior fossa veins

markus.engebaek.krogager@regionh.dk

Victoria Emilie Neesgaard
Medical student

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet
Dept. of Neurosurgery, Odense University Hospital, Denmark
University of Southern Denmark

RESEARCH FIELDS
- The symptomatology and mechanisms of arachnoid cysts.
- The interrelations between infectious burden and Alzheimer's Disease.

vinee16@student.sdu.dk

Axel Forsse
MD, PhD

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet

RESEARCH FIELDS
Neurosurgery, cerebrovascular disease, cerebral metabolism, neuromonitoring

Jon.axel.forsse@regionh.dk

Christian Baastrup Søndergaard
Neurosurgical registrar, junior research assistant

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet

RESEARCH FIELDS
- Decompressive craniectomy and decompressive hinge craniotomy
- Neurooncology
- Peripheral nerve surgery

Christian.baastrup.soendergaard.01@regionh.dk

Michael Karl Karlsson
MD, PhD

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet

RESEARCH FIELDS
Acute cerebral mitochondrial dysfunction as a pathophysiological mechanism following ischemic and traumatic brain injury and exploring this as a therapeutic target.

michael.karl.karlsson@regionh.dk

Senior researcher

Jane Skjøth-Rasmussen
Senior consultant, PhD

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet
Dept. of Clinical Medicine, University of Copenhagen

RESEARCH FIELDS
Neuro oncology

Jane.skjoeth-rasmussen@regionh.dk

Morten Ziebell
Senior Consultant, PhD
Head of Copenhagen Neurosurgery

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet

RESEARCH FIELDS
- Imaging and anatomy
- Meningioma
- Neuroinflammation
- Neuro oncology

Morten.ziebell@regionh.dk

Rikke Guldager
Registret Nurse, MSci, PhD, Postdoc/Clinical Nurse Specialist

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet

RESEARCH FIELDS
- Patient and relatives involvement (PPI, Patient and public involvement)
- Pain assessment (in patients with disorders of consciousness)
- Ethical issues in research
- Experiences with everyday life after illness

Rikke.guldager.01@regionh.dk

Kåre Fugleholm
Senior consultant, Associate professor, PhD, DrMed, FRCS(ENG)

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet

RESEARCH FIELDS
- Skull base surgery
- Peripheral nerve
- Chronic subdural hematoma
- Meningioma
- Decompressive ranial procedures

kaare.fugleholm@regionh.dk

Nina Rostgaard
Postdoc, MSC Human Biology, PhD

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet
guest researcher at Dept. of Neuroscience, Faculty of Health and Medical Sciences, University of Copenhagen

RESEARCH FIELDS
- Molecular neurobiology
- I am part of the CSF Study Group analyzing biomarkers in CSF from patients with hydrocephalus and studying molecular mechanisms of CSF production in laboratory experimental setups.

Nina.rostgaard@regionh.dk

Tiit Mathiesen
Professor, Senior consultant, MD, Dr Med Sci

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet
Dept. of Clinical Medicine, University of Copenhagen

RESEARCH FIELDS
- Neuroinflammation
- Meningioma
- Vascular
- Ethics
- Anatomy

Tiit.illimar.mathiesen@regionh.dk

Marianne Juhler
Professor, Senior consultant, Dr Med Sci
Head of Copenhagen CSF Study Group

ASSOCIATION WITH
Dept. Neurosurgery, Rigshospitalet
Dept. of Clinical Medicine, Copenhagen University

RESEARCH FIELDS
- ICP physiology and regulation.
- ICP signal analysis and technology
- Clinical research on hydrocephalic and ICP disorders
- Pediatric neurosurgery

Marianne.juhler@regionh.dk

Peter Birkeland
Consultant neurosurgeon, Postdoc

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet

RESEARCH FIELDS
- Blood-brain barrier
- Vascular neurosurgery
- Moyamoya disease

Peter.Fryd.Birkeland@regionh.dk

Tina Nørgaard Munch
Neurosurgical staff specialist, associate professor, Senior researcher

ASSOCIATION WITH
Dept. of Neurosurgery, Rigshospitalet
Dept. of Epidemiology Research, Statens Serum Institut
Dept. of Clinical Medicine, University of Copenhagen

RESEARCH FIELDS
- Epidemiology and genetics
- Meningioma
- Cerebrospinal fluid dynamics
- Chronic subdural hematoma

tina.noergaard.munch@regionh.dk

Publications 2021

PhD dissertation

Characterization of intracranial pressure (ICP) signals | Tejada, I. M., 2021

Papers in peer-reviewed journals

Alternative route to a hypoglossal canal dural arteriovenous fistula in case of failed jugular vein approach | Dahl, R. H., Biondi, A., Caterino, F. D., Vitale, G., Poulsgaard, L. & Benndorf, G., apr. 2021, I: Interventional neuroradiology : journal of peritherapeutic neuroradiology, surgical procedures and related neurosciences. 27, 2, s. 275-280 6 s.

Børn med iskæmisk apopleksi | Bindslev, J. B., Truelsen, T., Gyhrs, M., Kondziella, D., Hoffmann, M., Stensballe, J., Hauerberg, J., Stavngaard, T., Lundstrøm, K., Born, A. P., Larsen, V. A., Hansen, K. & Hoei-Hansen, C. E., 14 jun. 2021, I: Ugeskrift for Laeger. 183, 24, V11200890.

Burr hole craniostomy versus minicraniotomy in chronic subdural hematoma: a comparative cohort study | Zolfaghari, S., Bartek, J., Strom, I., Djärf, F., Wong, S-S., Ståhl, N., Jakola, A. S. & Nittby Redebrandt, H., nov. 2021, I: Acta Neurochirurgica. 163, 11, s. 3217-3223 7 s.

B-waves are present in patients without intracranial pressure disturbances | Riedel, C. S., Martinez-Tejada, I., Norager, N. H., Kempfner, L., Jennum, P. & Juhler, M., aug. 2021, I: Journal of Sleep Research. 30, 4, s. e13214 e13214.

Causal relationship between slow waves of arterial, intracranial pressures and blood velocity in brain | Martinez-Tejada, I., Czosnyka, M., Czosnyka, Z., Juhler, M. & Smielewski, P., 27 okt. 2021, I: Computers in Biology and Medicine. 139, s. 104970 104970.

Central and peripheral nervous system complications of COVID-19: a prospective tertiary center cohort with 3-month follow-up | Nersesjan, V., Amiri, M., Lebech, A-M., Roed, C., Mens, H., Russell, L., Fonsmark, L., Berntsen, M., Sigurdsson, S. T., Carlsen, J., Langkilde, A. R., Martens, P., Lund, E. L., Hansen, K., Jespersen, B., Folke, M. N., Meden, P., Hejl, A-M., Wamberg, C., Benros, M. E. & Kondziella, D., sep. 2021, I: Journal of Neurology. 268, 9, s. 3086-3104 19 s.

Co-occurring hydrocephalus in autism spectrum disorder: a Danish population-based cohort study | Munch, T. N., Hedley, P. L., Hagen, C. M., Bækvad-Hansen, M., Bybjerg-Grauholm, J., Grove, J., Nordentoft, M., Børglum, A. D., Mortensen, P. B., Werge, T. M., Melbye, M., Hougaard, D. M. & Christiansen, M., 28 apr. 2021, I: Journal of Neurodevelopmental Disorders. 13, 1, s. 19 19.

Correction to: Symptoms presented during emergency telephone calls for patients with spontaneous subarachnoid haemorrhage | Sonne, A., Egholm, S., Elgaard, L., Breindahl, N., Jensen, A. H., Eskesen, V., Lippert, F., Waldorf, F. B., Lohse, N. & Rasmussen, L. S., 14 okt. 2021, I: Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine. 29, 1, s. 149 1 s.

Criteria-based dispatch of emergency medical services in non-traumatic subarachnoid haemorrhage | Sonne, A., Andersen, J. B., Eskesen, V., Lippert, F., Waldorff, F. B., Bang, C. W., Siersma, V., Lohse, N. & Rasmussen, L. S., 17 aug. 2021, I: Danish Medical Journal. 68, 9, A02210152.

Dansk Neuro Onkologisk Register (DNOR): - Resumé af Årsrapport 2019-2020 | Hansen, S., Laursen, R. J., Skjøth-Rasmussen, J., Rasmussen, B. K., Lucacova, S., Scheie, D., Ragner, A. Z. K., Gam-Jensen, K. & Engberg, H., 2021, 2 s. Ugeskrift for Læger.

Depression and ability to work after vestibular schwannoma surgery: a nationwide registry-based matched cohort study on antidepressants, sedatives, and sick leave | Thurin, E., Förander, P., Bartek, J., Gulati, S., Rydén, I., Smits, A., Hesselager, G., Salvesen, Ø. & Jakola, A. S., aug. 2021, I: Acta Neurochirurgica. 163, 8, s. 2225-2235 11 s.

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Diagnostic Accuracy and Clinical Impact of [18F]FET PET in Childhood CNS tumors | Marner, L., Lundemann, M., Sehested, A., Nysom, K., Borgwardt, L., Mathiasen, R., Wehner, P. S., Henriksen, O. M., Thomsen, C., Skjøth-Rasmussen, J., Broholm, H., Østrup, O., Forman, J. L., Højgaard, L. & Law, I., 1 dec. 2021, I: Neuro-Oncology. 23, 12, s. 2107-2116 10 s.

Diagnostics with clinical microbiome-based identification of microorganisms in patients with brain abscesses - a prospective cohort study | Hartung Hansen, K., Stenz Justesen, U., Kelsen, J., Møller, K., Helweg-Larsen, J. & Fuursted, K., nov. 2021, I: APMIS - Journal of Pathology, Microbiology and Immunology. 129, 11, s. 641-652 12 s., 13181.

Early Orthostatic Exercise by Head-Up Tilt With Stepping versus Standard Care After Severe Traumatic Brain Injury Is Feasible | Riberholt, C. G., Olsen, M. H., Søndergaard, C. B., Gluud, C., Ovesen, C., Jakobsen, J. C., Mehlsen, J. & Møller, K., 14 apr. 2021, I: Frontiers in Neurology. 12, s. 626014 626014.

Elevated CSF inflammatory markers in patients with idiopathic normal pressure hydrocephalus do not promote NKCC1 hyperactivity in rat choroid plexus | Lolansen, S. D., Rostgaard, N., Andreassen, S. N., Simonsen, A. H., Juhler, M., Hasselbalch, S. G. & MacAulay, N., 4 dec. 2021, I: Fluids and Barriers of the CNS. 18, 1, s. 54 54.

Empirical Mode Decomposition-Based Method for Artefact Removal in Raw Intracranial Pressure Signals | Martinez-Tejada, I., Wilhjelm, J. E., Juhler, M. & Andresen, M., 2021, I: Acta Neurochirurgica, Supplement. 131, s. 201-205 5 s.

Endoskopisk behandling af hydrocefalus | Jensen, T. S. R., Tefre, S., Holst, A. V., Hansen, T. S. & Juhler, M., 30 aug. 2021, I: Ugeskrift for Laeger. 183, 35, V03210290.

Erratum: Hagen et al. Unilateral Optic Nerve Sheath Fenestration in Idiopathic Intracranial Hypertension: A 6-Month Follow-Up Study on Visual Outcome and Prognostic Markers. Life 2021, 11, 778 | Hagen, S. M., Wegener, M., Toft, P. B., Fugleholm, K., Jensen, R. H. & Hamann, S., 27 sep. 2021

Expression of the stem cell marker CD133 in malignant meningioma | Maier, A. D., Mirian, C., Bartek, J., Juhler, M., Bartkova, J., Broholm, H. & Mathiesen, T. I., 2021, I: Clinical Neuropathology. 40, 3, s. 151-159 9 s.

Family involvement in the treatment of patients with an acquired brain injury or malignant brain tumor: a scoping review protocol | Guldager, R., Poulsen, I., Aadal, L., Nordentoft, S. & Loft, M. I., 14 jun. 2021, I: JBI evidence synthesis. 19, 11, s. 3190-3197 8 s.

Frakturer i rygsøjlen | Bech, R. D., Zielinski, O., Morgen, S. S., Tøndevold, N., Hansen, L. V., Kelsen, J. & Gehrchen, M., 5 jul. 2021, I: Ugeskrift for Laeger. 183, 27, s. V08200628

Genome-wide association study across pediatric central nervous system tumors implicates shared predisposition and points to 1q25.2 (PAPPA2) and 11p12 (LRRC4C) as novel candidate susceptibility loci | Foss-Skiftesvik, J., Hagen, C. M., Mathiasen, R., Adamsen, D., Bækvad-Hansen, M., Børglum, A. D., Nordentoft, M., Werge, T., Christiansen, M., Schmiegelow, K., Juhler, M., Mortensen, P. B., Hougaard, D. M. & Bybjerg-Grauholm, J., mar. 2021, I: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery. 37, 3, s. 819-830 12 s.

Haemodynamic-directed cardiopulmonary resuscitation promotes mitochondrial fusion and preservation of mitochondrial mass after successful resuscitation in a pediatric porcine model | Senthil, K., Morgan, R. W., Hefti, M. M., Karlsson, M., Lautz, A. J., Mavroudis, C. D., Ko, T., Nadkarni, V. M., Ehinger, J., Berg, R. A., Sutton, R. M., McGowan, F. X. & Kilbaugh, T. J., jun. 2021, I: Resuscitation plus. 6, s. 100124

Health-Related Quality of Life and Return to Work after Surgery for Spinal Meningioma: A Population-Based Cohort Study | Pettersson-Segerlind, J., von Vogelsang, A-C., Fletcher-Sandersjöö, A., Tatter, C., Mathiesen, T., Edström, E. & Elmi-Terander, A., 19 dec. 2021, I: Cancers. 13, 24, 6371.

Hovedpine og ansigtssmerter | Bendtsen, L., Schytz, H. W., Jensen, R. H., Bach, F. W., Kasch, H., Hansen, J. M., Ashina, M., Antic, S., Scheuer, K. H., Thimsen Pedersen, A., Beier, D., Ægidius, K. L., Vukovic Cvetkovic, V., Lund, N., Hvedstrup, J., Madsen, B. K., Carlsen, L. N., Munksgaard, S. B., Maarbjerg, S., Jensen, T. S., Rochat, P. B. & Amin, F. M., 2021

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Rigshospitalet / Neuroscience Centre
Department of Neurosurgery
Section 6031, entrance 6, 3rd floor
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