1. Project title

Patients with traumatic brain injury: Mapping of traumatic axonal injuries in clinical neuroimaging modalities and their importance in predicting long-term outcome.

2. Background

Traumatic brain injury (TBI) is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force (1). It is a leading cause of disability and death among young adults and may lead to cognitive, emotional and psychosocial consequences (2, 3). TBI is a heterogeneous disease, and span from primary to secondary pathologies (4). The classic understanding of traumatic axonal injury (TAI) is histopathologically characterized by primary axotomy at injury time. Research the last decades show that more often a biochemical cascade is initiated at time of accident. This cascade may over time lead to either secondary axotomy or restoration of the axon, dependent on the degree of injury (5, 6). TAI is still overlooked by physicians, even though this injury type is shown in all degrees of TBI (7, 8)

Traditionally, in moderate and severe TBI, age, Glasgow Coma Scale (GCS) score, pupil reactivity and CT findings are considered important for outcome prediction (9), but recent studies have shown that also different MRI features are important for outcome prediction in all severities of TBI (10, 11). CT is still the primary imaging modality in TBI, since fast scanning time enables quick clarification on necessity of neurosurgery. But we know that CT underestimates the presence and burden of parenchymal injuries, especially TAI. This injury type is prevalent in moderate and severe TBI (7) and also important for patient outcome, especially if deeper parts of the brain are affected (11, 12). Standard clinical MRI is superior in detecting TAI (13), since these pathological processes can indirectly be detected in different MRI sequences (14). Advanced MRI post processing has enabled development of different brain templates and atlases (15), where individual segmented lesions can be mapped to a common reference brain, and all visualized lesions of interest displayed in a 3D brain model as a frequency / heat map. This approach has never been applied for TAI or other TBI lesions, but has recently been used in brain tumors (16).

Pathology detected in clinical MRI after TBI could represent coincident findings and not traumatic pathology. Age related white matter hyperintensities (WMHs) are the most frequent lesions in the general middle-aged population (> 50 years) (17) and this age group in general has poorer outcome after TBI than younger adults (18). It is of significant clinical interest to develop a method to differentiate between traumatic lesions and age-related WMHs.

3. Project aims

The overall aim for this PhD project is to increase the knowledge of the important injury type: TAI in TBI. In **paper 1** we aim to examine the different CT features in TAI patients compared to patients without TAI. As a secondary aim, findings will be related to patient outcome. In **paper 2** we aim to develop a new MRI scoring of TAI that better reflects outcome, as part of the international ERA-NET Neuron Consortium. In **paper 3** we aim to show the distribution / predilection site of different types of TAI lesions. As a secondary aim the findings will be related to global outcome. Finally, the aim in **paper 4** is to device a method to differentiate between age related WMHs and TAI lesions, either based on heat maps of age related WMHs alone or in combination with information from other MRI sequences (a multiparametric approach).

4. Material and methods

This PhD project will consist of cohort studies where the patients have been included prospectively. From September 2004 all patients with moderate and severe TBI have been included into a prospective database at St.Olavs University Hospital, referred to as the Trondheim TBI study. So far over 700 patients are registered in the ongoing database: approximately 50% have moderate TBI. In the MRI sub-studies we will include adults (16-70 years) and patients with early MRI (≤ 6 weeks), counting approximately 290 patients. The MRIs are either performed at St.Olavs University Hospital or at one of the local hospitals in the region using a harmonized MRI protocol. In the analyses of paper 2, 56 patients with severe TBI from Oslo University Hospital and 180 patients with mild TBI from St.Olavs Hospital will also be included (total 496 patients). A healthy, age-and sex matched control group from the large HUNT3 MRI project (n=1006) and Generation 100 (n=100), covering the age span 50-80 years, will be used in paper 4.

Predetermined demographic, prehospital and admission injury-related variables (including GCS scores, pupillary status, hypoxia, hypotension and laboratory status) are prospectively registered. Later, in-hospital variables (including intensive stay measures, medical and surgical treatments) are also registered into the database.

For consenting patients, functional outcome is assessed using the structured interview for the GOSE. This is an 8-category scale measuring a patient´s overall functioning (1=death, 8=upper good recovery). The interview is performed at both 6 and 12 months post-injury either by telephone or personal contact. The loss to follow-up is below 5%.

All patients will have at least one head-CT in the acute stage. A standardized structured reporting of the CT findings is already performed by radiologists or residents in radiology in cooperation with consultants. Quality checking of all CT images from the Trondheim TBI study and interrater assessments of n=100 CT scores is yet to be done.

Trondheim TBI group has led the development of a standardized reporting of traumatic findings in clinical MRI during fall 2017 in the ERA-NET Neuron TAI-MRI project. All standardized MRI reporting is done blinded to patient ID and clinical history, by five consultants in radiology (including the PhD candidate). A blinded interrater assessment is currently worked upon.

In cooperation with SINTEF the PhD candidate will use advanced post processing to create 3D heat maps where lesions from clinical MRI will be mapped to a normalized common brain (standard MNI space). Individual clinical MR images with annotated TAI lesions will be pooled and aligned to a standardized reference frame using the Advanced Neuroimaging Tools registration toolkit.

Heat maps of age-related WMHs derived from HUNT3 MRI and Generation 100 are already finalized. The WMHs heat maps will be overlaid with the TAI heat maps (all brains normalized to MNI space). Lesions most likely to be TAI and lesions most likely to represent age-related WMHs will be analysed for other MRI features such as fluid-attenuated inversion recovery (FLAIR) lesion intensity, apparent diffusion coefficient (ADC) values in and around the lesion

(from diffusion weighted imaging (DWI)) and correspondence with white matter hypointesities on the T1 volume.

Data will be analysed with SPSS, STATA or R. Descriptive statistics, group comparisons and regression analyses will be used. The threshold for significance will be set at $p < 0.05$. In the statistical analyses the PhD candidate we will cooperate with statistician and associate prof. Turid Follestad, who is already much involved in research in Trondheim TBI group.

5. Specification of papers

We plan to disseminate our results through 4 publications in international per-reviewed journals:

1. Paper 1: *Moderate and severe traumatic brain injury: CT findings in patients with and without traumatic axonal injury in early MRI.* **Flusund**, Vik, Skandsen, Follestad, Sandrød, Farnes, Vande-Vyvere, Moen.
2. Paper 2: *Trondheim clinical TAI-MRI scoring: relation to outcome in mild, moderate and severe TBI (EraNet study).* Moen, **Flusund**, Moe, Skandsen, Håberg, Olsen, Saksvoll, Kvistad, Røe, Anke, Einarsen, Abel-Grüner, Follestad, Vik
3. Paper 3: *Traumatic axonal injury lesions in clinical MRI after moderate and severe traumatic brain injury: a brain atlas approach.* **Flusund**, Reinertsen, Bøe, Solheim, Moe, Saksvoll, Follestad, Håberg, Vik, Moen.
4. Paper 4: *White matter hyperintesities in moderate and severe traumatic brain injury: how to differ traumatic axonal injuries from non-spesific, non-traumatic white matter changes?* **Flusund**, Moen, Reinertsen, Vik, Olsen, Abel-Grüner, Kvistad, Skandsen, Vangberg, Håberg.

In the **first paper** all data collection is completed, and only quality checking and interrater assessments remain for the candidate. The candidate will be first author, and the paper is planned for submission during early autumn 2021.

The **second paper** is an ERA-NET Neuron TAI MRI paper and represents a part of the international collaboration for Trondheim TBI group. The models proposed in this paper will later be tested in the large-scale CENTER TBI (www.center-tbi.eu). The candidate will be second author and write the paper in close collaboration with the main supervisor. All image analyses are completed. The candidate has during autumn 2018 analyzed n=63 of the patients and has just completed interrater assessments of another n=30 patients (50% employed Sept-18 – March-19, financed by Trondheim TBI group and ERA-NET Neuron TAI-MRI). This paper is planned for submission during summer 2019.

In the **third paper**, the PhD candidate will work together with researchers from SINTEF, to create 3D heat maps of TAI. The data analyses will begin during autumn 2019. The candidate will be first author and the paper is planned submitted autumn 2022.

In the **fourth paper,** the PhD candidate will work together with Trondheim fMRI group and HUNT, and compare 3D heat maps from a healthy normal population with 3D heat maps from a TBI population. The analyses will start during summer/autumn 2022 and the paper will be submitted during spring 2024.

6. Progress schedule and publishing plan

	2019			2020				2021				2022				2023				2024				2025
Complete interrater MRI and submission of paper 2																								
Advanced post processing. Paper 3 with SINTEF																								
Data-and interrater analyses, paper 1																								
Write paper 1																								
Finish and submit paper 1																								
Write paper 3																								
Finish and submit paper 3																								
Analyzing data, paper 4 (with fMRI group and HUNT).																								
Write paper 4																								
Finish and submit paper 4																								
Write thesis																								
Dissertation																								

7. Funding plan

The PhD candidate has received a standard PhD grant from the Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU), 50% for 6 years including operating funds. Application for additional costs is also granted (600.000 NOK for the whole study period), mainly for the study in collaboration with SINTEF. *The complete and more detailed project description approved by the Liaison Committee (funding application) can be made available on request.*

8. Ethical considerations

The Trondheim TBI study is already approved by the regional ethical committee (REK) (2009/2328). Use of data connected to paper 2 and 4 have also earlier been approved in the ERA-NET Neuron TAI-MRI study (2017/1214) and HUNT study (2011/456), respectively. At Thursday 07.02.19 the main supervisor contacted REK by telephone, and upon their request sent the funding project-description. If REK requires own approval of this particular PhD project beyond what is already approved, this will be handled according to REKs recommendations.

9. Attachments

Copy of the most essential ethical approvals (2009/2328 and 2017/1214). More information can be made available upon request.

References

1. Menon DK, Schwab K, Wright DW, Maas AI. Position Statement: Definition of Traumatic Brain Injury. Archives of Physical Medicine and Rehabilitation. 2010;91(11):1637-40.
2. Skandsen T, Finnanger TG, Andersson S, Lydersen S, Brunner JF, Vik A. Cognitive Impairment 3 Months After Moderate and Severe Traumatic Brain Injury: A Prospective Follow-Up Study. Archives of Physical Medicine and Rehabilitation. 2010;91(12):1904-13.
3. Carroll LJ, Cassidy JD, Cancelliere C, Côté P, Hincapié CA, Kristman VL, et al. Systematic Review of the Prognosis After Mild Traumatic Brain Injury in Adults: Cognitive, Psychiatric, and Mortality Outcomes: Results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Archives of Physical Medicine and Rehabilitation. 2014;95(3):S152-S73.
4. Saatman KE, Duhaime AC, Bullock R, Maas AI, Valadka A, Manley GT. Classification of traumatic brain injury for targeted therapies. Journal of neurotrauma. 2008;25(7):719-38.
5. Adams JH, Doyle D, Ford I, Gennarelli TA, Graham DI, McLellan DR. Diffuse axonal injury in head injury: definition, diagnosis and grading. Histopathology. 1989;15(1):49-59.
6. Johnson VE, Stewart W, Smith DH. Axonal pathology in traumatic brain injury. Experimental neurology. 2013;246:35-43.
7. Skandsen T, Kvistad KA, Solheim O, Strand IH, Folvik M, Vik A. Prevalence and impact of diffuse axonal injury in patients with moderate and severe head injury: a cohort study of early magnetic resonance imaging findings and 1-year outcome. Journal of neurosurgery. 2010;113(3):556-63.
8. Inglese M, Makani S, Johnson G, Cohen BA, Silver JA, Gonen O, et al. Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study. Journal of neurosurgery. 2005;103(2):298-303.
9. Murray GD, Butcher I, McHugh GS, Lu J, Mushkudiani NA, Maas AI, et al. Multivariable prognostic analysis in traumatic brain injury: results from the IMPACT study. Journal of neurotrauma. 2007;24(2):329-37.
10. Yuh EL, Mukherjee P, Lingsma HF, Yue JK, Ferguson AR, Gordon WA, et al. Magnetic resonance imaging improves 3-month outcome prediction in mild traumatic brain injury. Annals of neurology. 2013;73(2):224-35.
11. Moen KG, Brezova V, Skandsen T, Haberg AK, Folvik M, Vik A. Traumatic axonal injury: the prognostic value of lesion load in corpus callosum, brain stem, and thalamus in different magnetic resonance imaging sequences. Journal of neurotrauma. 2014;31(17):1486-96.
12. Skandsen T, Kvistad KA, Solheim O, Lydersen S, Strand IH, Vik A. Prognostic value of magnetic resonance imaging in moderate and severe head injury: a prospective study of early MRI findings and one-year outcome. Journal of neurotrauma. 2011;28(5):691-9.
13. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. The Lancet Neurology. 2008;7(8):728-41.
14. Parizel PM, Ozsarlak, Van Goethem JW, van den Hauwe L, Dillen C, Verlooy J, et al. Imaging findings in diffuse axonal injury after closed head trauma. European radiology. 1998;8(6):960-5.
15. Evans AC, Janke AL, Collins DL, Baillet S. Brain templates and atlases. NeuroImage. 2012;62(2):911-22.
16. Sagberg LM, Iversen DH, Fyllingen EH, Jakola AS, Reinertsen I, Solheim O. Brain atlas for assessing the impact of tumor location on perioperative quality of life in patients with high-grade glioma: A prospective population-based cohort study. NeuroImage Clinical. 2019:101658.
17. Haberg AK, Hammer TA, Kvistad KA, Rydland J, Muller TB, Eikenes L, et al. Incidental Intracranial Findings and Their Clinical Impact; The HUNT MRI Study in a General Population of 1006 Participants between 50-66 Years. PloS one. 2016;11(3):e0151080.
18. Hukkelhoven CW, Steyerberg EW, Rampen AJ, Farace E, Habbema JD, Marshall LF, et al. Patient age and outcome following severe traumatic brain injury: an analysis of 5600 patients. Journal of neurosurgery. 2003;99(4):666-73.