ADVANCED IMAGING IN TRAUMATIC BRAIN INJURY

PhD Thesis

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I. INTRODUCTION

Traumatic brain injury (TBI) constitutes a public health problem worldwide, because of its high incidence, morbidity and mortality. TBI is a leading cause of death and disability in the young, otherwise healthy, employed population that does not only mean a personal, or family-wise disaster, but a social burden as well.

TBI is a very heterogeneous disease and affects the most complex organ of the body. The underlying pathomechanisms are still poorly understood. The present diagnostic tools might only reveal the "tip of the iceberg", the proper therapeutic methods are equivocal and the protocols largely differ among the TBI centers. Hippocrates is said to have remarked in 400 BC that "No head injury is too severe to despair of, nor too trivial to ignore". This statement briefly underscores the difficulties regarding the diagnosis and prognosis of TBI. Unfortunately, his words are relevant even today.

Diffuse axonal injury (DAI) is one of the most important pathological components of TBI, as a result of traumatic acceleration/deceleration or rotational shear-strain forces leading to axonal/myelin stretching or disruption. Previously, DAI has been considered a primary-type injury, with the damage occurring at the time of the accident. Research has shown that the delayed mechanisms (secondary components of DAI) are generally more important. Originally DAI was suggested upon an inferential basis, in any patient who demonstrated clinical symptoms disproportionate to his or her CT-scan findings. This category was generally restricted for comatose patients, whose vast majority (>90%) remained in a persistent vegetative state. Recently, however the term DAI (or the synonym traumatic axonal injury) has been more widely used, applying to the entire severity range of TBI, including a spectrum of axonal damage from a subtle, reversible functional disorder to the true disconnection.

The extent and severity of DAI is highly related to the clinical severity and outcome. However, clinical diagnostic tools including conventional imaging (clinical CT, MRI) fail to detect DAI due to its microscopic range. The role of the present routine imaging in TBI is limited to the recognition of pathologies that require surgical intervention (e.g. intracranial bleeding, fractures).

In contrast, advanced imaging, due to high sensitivity may provide an insight into the microstructural and functional pathomechanisms of TBI. These methods may also aid the evaluation and prognosis assessment of TBI.

Here we define advanced imaging as quantitative modalities and/or post processing methods that are available in research, but yet have not been widely applied in clinical environments. In the field of mild TBI, advanced imaging mainly means advanced MRI methods, as diffusion tensor imaging (DTI) –for white mater microstructure examination, functional MRI (fMRI) – for objective measurement of functional abnormalities, volumetric analysis – for the detection of subtle edema or

atrophy, and susceptibility weighted imaging (SWI) – for the depiction of microscopic bleedings. Though a large set of studies have conducted advanced MRI investigations in severe TBI as well, their feasibility in severe TBI is clearly limited, not merely because of the issues related to patient management (anesthesia, MRI safety issues), but also because the major pathologies such as bleedings, fractures and distortions constitute MRI artifacts and post-processing challenges.

In severe TBI, advanced imaging offering novel insights into diagnosis and prognosis assessment mainly involves quantitative CT analysis. Presently the CT signs are assessed qualitatively, quantitative evaluation (e.g. midline shift) is restricted to the use of linear (1 dimensional) measurements. Semi-automated 3-dimensonal, volumetric based assessment might enhance the evaluation of traumatic CT signs.

II. AIMS

The aim of the present thesis is to test if advanced neuroimaging can provide better insights into TBI induced alterations, thus aiding TBI diagnosis.

Advanced MRI techniques were applied in mild TBI patients where conventional imaging completely fails to detect any pathology. Quantitative CT was applied in severe TBI patients for whom MRI is often not applicable because of practical factors, however objective parameters might provide important additional information that may be missed during conventional CT reading.

Specific aims:

1. To clarify if advanced MRI such as DTI, volumetric analysis, fMRI, SWI are able to detect any brain alterations in the acute to subacute phase after injury in mild TBI patients with completely negative CT and routine MRI (T1W, T2W, FLAIR) scans (="uncomplicated mild TBI" patients).

2. To develop a quantitative assessment method of lateral ventricle asymmetry and test if lateral ventricle volume asymmetry might precede midline shift and so might be an earlier marker of hemispherical pressure increase.

III. ADVANCED MRI IN MILD TRAUMATIC BRAIN INJURY

3.1 Subjects and methods

Subjects

Fourteen patients (five females) from the outpatient unit of the department of Neurosurgery with mild TBI participated in this study. Patients fulfilled the criteria of "uncomplicated" mild TBI. Patients had a Glasgow Coma Scale of 15, loss of consciousness for less than one minute, amnesia for less than 30 minutes and negative posttraumatic CT. A control group of 14 age- and sex-matched healthy volunteers was also involved in the study. All subjects gave a written informed consent under a protocol approved by the local ethical committee.

Image acquisition

Initial MRI data of patients were acquired within 72 hours after injury (mean: ~2 days, ranging from 12 h to 72 h, referred to as 72h). The second acquisition was performed approximately one month later (mean: 35 days ranging from 28 days to 43 days after injury, referred to as one month). The control group also underwent the two time point acquisition with a similar time frame (average 30 days difference ranging from 27 to 36).

Magnetic resonance imaging was carried out on a Siemens Magnetom TIM Trio 3 Tesla scanner (Enlargen, Germany) with a 12 channel standard head coil. The protocol consisted of high resolution T1-weighted scan (MPRAGE) T2-weighted scan, FLAIR, DTI and SWI which were applied on all subjects.

A subset of the subjects (10 patients and 10 control subjects) also underwent fMRI at both time points using hometown walking and covert word generation task.

Data processing

Diffusion tensor imaging and Tract-Based Spatial Statistics (TBSS)

Initial diffusion image processing was carried out to generate Tract-Based Spatial Statistics (TBSS) input data using the FDT tools (FMRIB's Diffusion Toolbox), part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Diffusion data was then fed into DTIFit to calculate the diffusion tensor model for each brain voxel and subsequently to compute fractional anisotropy (FA) and mean diffusivity (MD) values from the tensor's three eigenvalues.

Voxelwise statistical analysis of the FA data was carried out using TBSS, part of FSL. TBSS projects all subjects' FA data onto a mean FA tract skeleton in standard space, before applying voxelwise cross-timepoint or cross-group statistics. We run TBSS for

other diffusion-derived data, MD as well. The voxelwise statistics were performed on skeletonized data using the permutation-based non-parametric Randomize analysis, involved in FSL. The two time point FA and MD data from both mild TBI and control groups were compared by non-parametric paired t-test to maximize statistical power. We compared the mild TBI to control group by non-parametric unpaired t-test, in both first and second time points. Results were considered significant for p < 0.05, corrected for multiple comparisons using „threshold-free cluster enhancement".

Volumetric analysis

T1-weighted high resolution images were fed into volumetric segmentation that was performed with the FreeSurfer image analysis suite (Athinoula A. Martinos Center for Biomedical Imaging, 2005). The output volumes of cortex, white matter, corpus callosum, ventricles, extracerebral CSF, hippocampus, amygdala, pallidum, caudate nucleus, thalamus, and nucleus accumbens were statistically compared between first and second time point by simple paired t-test, both in traumatic and control groups. Analysis between patient and control groups was carried out using unpaired t-test on volumes normalized to intracranial cerebral volume.

Susceptibility weighted imaging

Susceptibility weighted images were searched for hemorrhagic lesions by a board-certified neuroradiologist.

Functional MRI

Pre-processing and statistical analysis were performed using FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL. Whole brain general linear model (GLM) time-series statistical analyses of individual data sets were carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction. To model the BOLD response a box-car function with "task" vs. "rest" conditions was convolved with the FSL's canonical gamma haemodynamic response function (HRF). Single session data sets were registered into standard space using a three-step process. The resulting linear and non-linear deformations were combined mathematically and applied to the first-level statistical maps to take them into standard space. Second-level mixed effects analysis was carried out using the first level statistical maps to test for mean group activations within group changes over the one-month period and differences between the control and mild TBI groups. To calculate group average activation maps (e.g. < 72h acquisition in mild TBI group) the "single group average" model was set up. When calculating extraction based

contrast maps between time points of one group (e.g. < 72h data minus 1 month data and vice versa in mild TBI group) the "two groups, paired" design was applied (paired t-test). When calculating contrast maps between groups (control group minus mild TBI group and vice versa at both < 72h and 1 month) the "two groups, unpaired" design was selected (unpaired t-test). Average activation maps for both groups at both time points and contrast maps of all possible variations were calculated.

Statistical map thresholds were set using clusters determined by $Z > 2.3$ and a corrected cluster significance of $p < 0.05$.

3.2 Results

Structural images and SWI

T1- and T2-weighted and FLAIR structural images were found to be free of trauma related pathology.

No low-signal foci referring to microhemorrhages were apparent on the SWI in the traumatic or in the control group.

Diffusion tensor imaging and Tract-Based Spatial Statistics

Longitudinal analysis:

TBSS analysis between 72h and one month acquisition of traumatic patients showed significant difference (corrected $p < 0.05$) in voxels of anterior corpus callosum, right corona radiata and internal capsule for both FA and MD values. FA was lower, while MD was higher at 72 h than after one month (see Table 1. for details). No voxels appeared to be significant on the opposite contrasts (72h > 1 month for FA, one month > 72h for MD). The two time point comparison of control subjects revealed no statistical difference regarding MD or FA.

Cross-sectional analysis: imaging within 72h after injury:

Comparison between the mild TBI group's 72h imaging and the control group's first time point imaging showed FA to be significantly decreased (corrected $p < 0.05$) and MD to be significantly increased (corrected $p < 0.05$) in the traumatic group diffusely in several white matter tracts of both hemispheres (Table 1. for details). The contrast of control group MD minus mild TBI group MD, or mild TBI group FA minus control group FA yielded no significant voxels.

Cross-sectional analysis: imaging at one month:

The comparison of mild TBI group data at one month to control group data at the second time point also highlighted significantly (corrected $p < 0.05$) reduced FA in the mild TBI group, but only in the right hemispherium, in much smaller extent (see Table 1. for details). The opposite contrast did not reveal any significant results. MD values showed changes in the opposite direction as FA values, but without reaching statistical significance.

Table 1.

Details of significant (corrected $p < 0.05$) voxels yielded by TBSS

Contrast	Voxel no.	Average [a]		p [b]
		72h	1 month	
FA				
mTBI 72h < mTBI 1 month	3408	0.5653	0.5883	0,041
		mTBI	Control	
mTBI 72h < Control	40737	0.4994	0.548	0,01
mTBI 1 month < Control	1932	0.5541	0.612	0,045
MD [c]				
mTBI 72h > mTBI 1 month	7450	8.12	7.7	0,032
		mTBI	Control	
mTBI 72h > Control	39078	7.9	7.36	0,005
mTBI 1 month > Control	0	-	-	0,084

[a]Average values of subjects' white matter "skeleton" voxels that were yielded significantly different in given contrast. [b]P value for voxel with highest statistical difference [c]10^{-4} mm^2/sec.

Volumetric analysis, FreeSurfer volumetric segmentation:

Significant differences ($p < 0.05$) were detected between the 72h and one month volumes of the cortex, ventricles and extracerebral CSF in the mild TBI group (Table 2). Cortical grey matter volume at 72h was larger than at one month. Ventricular (more pronouncedly lateral ventricle) and extracerebral CSF volume was lower at 72h. No significant volume change over time was found in other investigated structures such as white matter, hippocampus, amygdala, pallidum, caudate nucleus, nucleus accumbens and thalamus. The average loss of cortical volume over one month was 1.02%. Gain of average ventricular volume over time was 3.4%. Volume changes in control group were not significant (Table 2). Cross-sectional comparison of any normalized (to ICV) brain structure volumes revealed no significant difference between control and traumatic group either at 72h or one month, see Table 3.

Table 2.

Longitudinal comparison of brain structure volumes (μl) in mTBI and control groups

Structure	mTBI 72h Mean (SD)	mTBI 1 month Mean (SD)	pª	Control Initial Mean (SD)	Control 1 month Mean (SD)	pª
Cortical GM	474917 (69264)	470068 (65550)	0,029	479175 (52835)	478777 (51015)	0,44
Ventricles	20198 (16545)	20882 (16830)	0,023	20860 (16443)	20920 (16151)	0,38
Lateral ventricles	16857 (14736)	17558 (15075)	0,007	17160 (14800)	17212 (14717)	0,34
E.C. CSF	1402 (572)	1466 (597)	0,013	1436 (315)	1444 (300)	0,3

E.C. CSF = Extra cerebral cerebrospinal fluid; GM = Grey matter; SD = Standard deviation ªPaired t-test

Table 3.

Comparison of brain structure volumes between mTBI and control subjects

Structure	mTBI 72h Mean (SD)	pª	mTBI 1 month Mean (SD)	pª	Control Mean (SD)
Cortical GM /ICV	0,3601(0,0424)	0,41	0,3569 (0,0409)	0,49	0,3568 (0,0352)
Ventricles/ICV	0,0148 (0,0111)	0,47	0,0153 (0,0114)	0,43	0,0145 (0,0104)
Lateral ventricles/ICV	0,0123 (0,0099)	0,45	0,0129 (0,0102)	0,40	0,01189 (0,0097)
E.C. CSF/ICV	0,00105 (0,00039)	0,47	0,00110 (0,00041)	0,32	0,00104 (0,00019)

E.C. CSF = Extra cerebral cerebrospinal fluid; GM = Grey matter; ICV = Intracranial volume; SD = Standard deviation ªUnpaired t-test

Functional MRI

Cortical patterns during hometown walking task:
Average activation map of the mild TBI group at <72h: Activation was detected bilaterally in the parahippocampal gyri, temporal fusiform cortex, precuneus cortex and lateral occipital cortex; details are listed in Table 4. No marked difference appeared by visual inspection when comparing the <72h average activation map to the activation map at 1 month, or to activation map of the control group at any time point.

Longitudinal analysis, i.e. contrast of <72h and 1 month images of the traumatic group revealed significantly ($Z > 2.3$, $p < 0.05$) higher BOLD signal at 1 month bilaterally in voxels of the parahippocampal gyri and temporal pole. Details are listed in table 4. BOLD signal was not significantly higher in any voxels at the <72h acquisition.

In the control group, apart from a subtle cluster (275 voxels) referring to significantly (Z > 2.3, p < 0.05) higher BOLD signal at the first acquisition compared to the second at the occipital lobe (table 4.), no significant differences were observed between the first and second measures.

The contrast of mild TBI and control data revealed no significant (Z > 2.3, p < 0.05) differences in BOLD signal.

Table 4.

			Local maxima related to hometown walking task				
Analysis	Cluster	Voxel#	Z max	x	y	z	Anatomical area
mTBI 72h	1	2212	9.29	-20	-40	-18	Parahippocampal gyrus p.d. (L)
			7.02	-28	-32	-26	Temporal fusiform cortex p.d. (L)
			5.64	-22	-16	-30	Parahippocampal gyrus a.d. (L)
	2	1591	6.54	20	-34	-18	Parahippocampal gyrus p.d. (R)
			5.37	30	-32	-20	Temporal fusiform cortex p.d. (R)
			4.6	22	-16	-30	Parahippocampal gyrus a.d. (R)
	3	648	6.06	0	-68	54	Precuneus cortex
	4	505	5.78	-34	-76	42	Lateral occipital cortex s.d. (L)
	5	451	4.37	50	-70	36	Lateral occipital cortex s.d. (R)
mTBI 72h > 1 month	-	-	-	-	-	-	-
mTBI 1 month > 72h	1	1415	4.22	54	10	-36	Temporal pole (R)
			2.9	16	-6	-28	Parahippocampal gyrus a.d. (R)
	2	1333	3.82	-54	6	-32	Temporal pole (L)
			3.36	-20	-18	-28	Parahippocampal gyrus a.d. (L)
			2.65	-18	-32	-20	Parahippocampal gyrus p.d. (L)
Control 1st > 2nd	1	275	3.6	16	-88	46	Occipital pole
Control 2nd > 1st	-	-	-	-	-	-	-

List of local maxima in group analyses related to hometown walking task cortical activations. The x-, y- and z-values correspond to the MNI coordinates of local maxima in mm. More local maxima are reported in each cluster when the cluster encompasses more than one anatomical location. L = left hemisphere, R = right hemisphere, a.d. = anterior division, p.d. = posterior division, s.d. = superior division.

Cortical patterns during covert word generation task:

Covert word generation task related average activation map of the mild TBI group at <72h: Activation was detected in the left inferior frontal gyrus triangular and opercular part (Broca area), frontal orbital cortex, supplementary motor area, right insula and cingulate gyrus, see table 5. Subcortical activations occurred in the caudate nucleus, thalamic nuclei, putamen and pallidum bilaterally. No marked difference appeared by visual inspection when comparing the <72h average activation map to the activation map at 1 month, or to activation map of the control group at any time point.

Contrast of the <72h and 1 month measurements of the traumatic group revealed significantly (Z > 2.3, p < 0.05) higher BOLD signal at <72h compared to 1 month mainly in the medial prefrontal cortex. Exact locations are presented in table 5. The opposite contrast, i.e. 1 month data minus <72h data showed no significant results. The contrasts of the two time point data in the control group: First time point minus second showed significant (Z > 2.3, p < 0.05) difference in BOLD signal in the right frontal opercular cortex and left subcortical areas. Second time point minus first showed significant difference in the left anterior hippocampus. Cluster details are included in Table 5. The contrast of mild TBI and control data has revealed no significant (Z > 2.3, p < 0.05) differences.

Table 5.

Local maxima related to covert word generation task

Analysis	Cluster	Voxel#	Z max	x	y	z	Anatomical area
mTBI 72h	1	3067	8.31	-52	-2	46	Precentral gyrus (L)
			8.1	-32	22	-10	Frontal orbital cortex (L)
			8.0	-40	34	4	Inf. Frontal gyrus triangular part (L)
			3.6	-54	16	14	Inf. Frontal gyrus opercular part (L)
	2	2901	9.14	-2	-4	60	Supplementary motor area (L)
			8.18	38	18	-8	Insula (R)
			7.63	8	18	34	Cingulate gyrus a.d. (R)
mTBI 72h > 1 month	1	1485	4.89	-16	58	14	Frontal pole (L)
			4.68	-10	50	-4	Medial prefrontal cortex (L)
	2	512	5.01	22	-46	6	Cingulate gyrus p.d. (R)
MTBI 1 month > 72h	-	-	-	-	-	-	-
Control 1st > 2nd	1	353	3.78	36	22	10	Frontal opercular cortex (R)
Control 2nd > 1st	1	318	3.98	-20	-10	-16	Hippocampus (L)
			3.2	-22	0	-28	Parahippocampal gyrus a.d. (L)

List of local maxima in group analyses related to covert word generation task cortical activations. The x-, y- and z-values correspond to the MNI coordinates of local maxima in mm. More local maxima are reported in each cluster when the cluster encompasses more than one anatomical location. L = left hemisphere, R = right hemispheres, a.d. = anterior division, p.d. = posterior division, inf. = inferior

IV. QUANTITATIVE CT IN SEVERE TRAUMATIC BRAIN INJURY

4.1 Subjects and methods

Subjects

This retrospective analysis was performed on data from 84 adults with blunt severe TBI (Glasgow Coma Scale ≤ 8) requiring a ventriculostomy presenting to a Level I Trauma Center (University of Florida Trauma System, Shands Hospital in Gainesville, Florida) from 2007 to 2010. For image analyses, 76 patients were included for whom both admission and follow-up CT scans were available (eight patients without follow-up imaging were excluded from the analyses). This group of patients included 57 males and 19 females, with an average age of 40 years (SD = 15.1, min = 18, max = 75).

To test normal lateral ventricle volume asymmetry, a control group including 74 random patients from University of Florida Shands Hospital (26 patients) and the Department of Neurosurgery, University of Pécs (48 patients) without a history of moderate or severe TBI nor any pathological CT alteration were added to the study (40 males, average age: 57.27 years, SD = 18.68, min = 18, max = 93).

Approval from the Institutional Review Board (IRB) of the University of Florida, and University of Pécs to conduct this study was received. Written informed consent was obtained from all participants (or legally authorized representative) in the study.

Imaging

Admission CT scans were performed within three hours in average after injury (average = 2.44, min = 1, max = 7, SD = 1.56, hours). An average of three follow-up scans within the first 10 days of severe TBI were available. Routine head trauma imaging protocol was performed on Toshiba Aquilion One helical CT scanner. Scans of same parameters were acquired in the control group.

Image analysis

Lateral Ventricle Volume measurement

Computer assisted manual volumetric measurement was conducted using Osirix™ 5.8.5 [open source] Imaging Software (http://www.osirix-viewer.com/). Left and right lateral ventricles were manually outlined in each slice using "Pencil" (freehand region of interest) tool. Based on the outlined areas and slice thickness information a three dimensional (3-D) reconstruction and volume estimation of the lateral ventricle was performed. Choroid plexus and intraventricular hemorrhage were included in ventricle outlines, if present.

Lateral ventricle volume ratio (LVR) calculation

Lateral ventricular asymmetry was quantified by dividing the larger lateral ventricle volume by the smaller which we term the LVR. For each severe TBI patient's admission scan, the LVR was calculated. Evaluators were blinded to later patient CT scans, clinical information and outcomes.

LVR was also calculated in each control patient, to assess normal lateral ventricular asymmetry.

Inter- and intra-rater reliability of LVR measurement

Inter- and intra-rater reliability of LVR measurement was determined using Intraclass Correlation Coefficient. I measured LVRs on 10 random traumatic CTs twice for intra-rater analysis, and a second rater measured them for inter-rater analysis. Two-way model, absolute agreement type was applied, both single and average measurement reliability was calculated. Analysis was run in MedCalc statistical software.

Midline shift assessment

Midline shift was measured as the distance between skull midline (line between anterior and posterior attachment of the falx to the skull) and the septum pellucidum at the level of the foramina of Monro. A midline shift greater than 5 mm was considered significant. Midline shift was evaluated on all (admission and follow-up) scans of the severe TBI patients.

Statistics

ROC analysis of LVR and midline shift development

To determine the best admission scan LVR threshold that may be associated with the development of midline shift, a Receiver Operating Characteristic (ROC) curve analysis was performed using LVR as variable and midline shift development as the classification variable as follows:

Negative group: patients with no significant midline shift on admission or follow-up scans. Positive group: patients with no significant midline shift on admission scan, but with significant midline shift present on any follow-up scans. Thus, patients with significant midline shift on admission scan were excluded from this test.

Odds ratio and relative risk test for "high LVR" and midline shift development

The LVR threshold of best sensitivity and specificity yielded by ROC analysis was then used to define "high admission LVR" and "low admission LVR" patient groups. Odds (OR) and relative risk (RR) ratios were calculated taking "high admission LVR" group as exposed group; "low admission LVR" group as control group; patients with no midline shift on admission or follow-up scans as good outcome cases, patients with

no significant midline shift on admission scan, but with significant midline shift on any follow-up scans as poor outcome cases using MedCalc statistical software.

4.2 Results

The average LVR for all evaluated severe TBI patients (n = 76) on admission scans was 2.03 (SD = 1.401), median was 1.51 (min. LVR = 1.01, max. LVR = 9.67). Sixteen patients had significant midline shift on admission scans while 60 did not. Of these 60 patients, 15 (25%) patients developed significant (>5mm) midline shift on follow-up scans.

In the control group (n = 74), average LVR was 1.14 (SD = 0.11), median was 1.11 (min. LVR = 1.00, max. LVR = 1.44).

Inter- and intra-rater reliability of LVV ratio measurement

Intra-rater intraclass correlation was 0.9445 for single measures (95% confidence interval = 0.8018 - 0.9858) and 0.9715 for average measures (95% confidence interval = 0.8900 - 0.9928). Inter-rater intraclass correlation was 0.9061 for single measures (95% confidence interval = 0.6840 - 0.9755) and 0.9508 for average measures (95% confidence interval = 0.8124 - 0.9876).

ROC analysis of LVR and midline shift development

Admission LVR of >1.67 was shown to have a sensitivity of 73.3% and a specificity of 73.3% for subsequent midline shift development (AUC = 0.782, standard error = 0.0659, 95% confidence interval = 0.657 to 0.878, z statistic = 4.28, Significance level p (area = 0.5) <0.0001). ROC curve is shown in Fig 1.
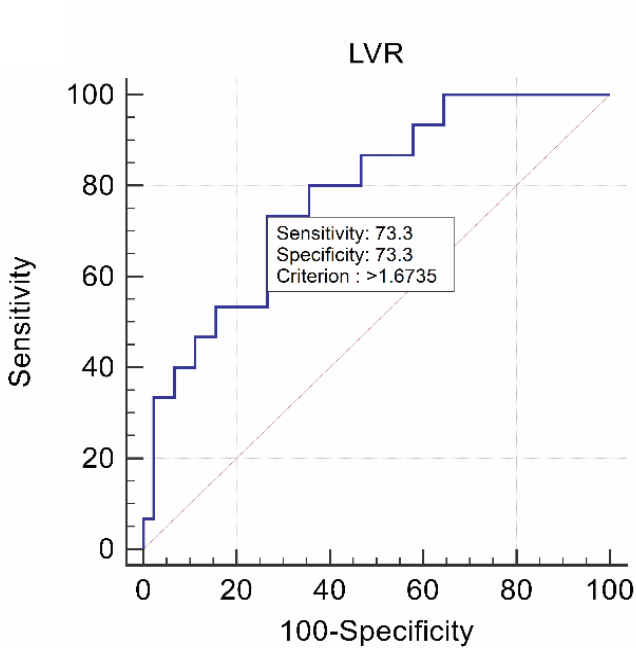
Figure 1. ROC curve analysis of Lateral Ventricle Volume Ratio (LVR) on predicting subsequent midline shift development.

Odds ratio and relative risk test

When using LVR of >1.67 as criterion for "high admission LVR", 23 patients out of 60 were included in the "high admission LVR" group without significant midline shift on admission scans. Eleven of these patients (47.8%) developed midline shift on follow-up scans. In the "low admission LVR" group (n = 37), 4 patients developed midline shift on follow-up scans (10.8%). This yielded an OR of 7.56 (95% CI = 2.0173 - 28.3502, p = 0.0027), and a RR of 4.42 (95 % CI = 1.5965 to 12.2586, p = 0.0042).

V. NOVEL FINDINGS AND CONCLUSION

Ad. Aim 1.:

Even in uncomplicated mild TBI, in which by definition, conventional imaging (CT, T1w-, T2w-, FLAIR MRI) is negative, both structural and functional alterations can be detected by advanced MRI acutely after the injury:

a. High resolution volumetric analysis revealed significant brain volume changes indicative of the presence of edema in the hyperacute phase, or accelerated degenerative process in the subacute phase.

b. DTI showed a widespread diffusivity alteration in the white matter suggesting axonal disintegration acutely, which did not fully recover in a month.

c. Functional MRI has shown that both activation and deactivation rate might be reduced in the acute phase that is indicative of an overall reduced flexibility in the brain blood flow redistribution.

d. SWI allows the dichotomization of DAI into hemorrhagic and non-hemorrhagic forms based on the presence of microbleeds. Uncomplicated mild TBI was associated with non-hemorrhagic DAI in our studies.

Though the majority of these alterations appeared to recover over time, a portion of them still exists over a month, in the sub-acute phase. These findings suggest that organic pathology might be just as important as the psychogenic factors in the development of the persistent post-traumatic disorders. These and similar findings by other groups should induce a paradigm shift in the understanding of mild TBI. The possible long-term consequences of the mild head injuries including sports concussions should not be overlooked, a referral to these cases as "mild" appears to be an understatement. Legal regulations regarding mild TBI and concussion should be re-stated since mild TBI, or a significant portion of the mild TBI cases do not seem to be a disease that recovers within 8 days.
MRI may become a unique tool to recognize mild TBI patients with significant underlying microstructural pathologies. These patients should be selected for a timely neurorehabilitation, which is known to lead to better outcome. Advanced MRI might also help specifying the safe return-to-activities time point after injury.

Ad aim 2.:

The three dimensional volumetric analysis allowed an objective assessment of the ventricle deformation and asymmetry that may follow severe TBI due to space occupying pathologies as bleedings and edema. We have shown that lateral ventricle asymmetry is not just linked to, but generally precedes midline shift, which is known to be a prognostic factor of poor outcome and might indicate a need of surgical intervention. The recognition of ventricular asymmetry might therefore have a similar clinical significance as midline shift has, however it indicates pathologies having a mass effect earlier than midline shift itself.

VI. LIST OF PUBLICATIONS

6.1 Publications related to the thesis

1. Multi-modal magnetic resonance imaging in the acute and sub-acute phase of mild traumatic brain injury: Can we see the difference? ***Toth A,*** *Kovacs N, Perlaki G, Orsi G, Aradi M, Komaromy H, Ezer E, Bukovics P, Farkas O, Janszky J, Doczi T, Buki A, Schwarcz A.*
JOURNAL OF NEUROTRAUMA 2013 Jan 1;30(1):2-10. doi: 10.1089/neu.2012.2486
IF: 3.968

2. Lateral Ventricle Volume Asymmetry Predicts Midline Shift in Severe Traumatic Brain Injury ***Tóth A****, Schmalfuss I, Heaton SC, Gabrielli A, Hannay H, Papa L, Brophy GM, Wang KK, Büki A, Schwarcz A, Hayes RL, Robertson CS, Robicsek SA.* JOURNAL OF NEUROTRAUMA 2015 Sep 1;32(17):1307-11. doi: 10.1089/neu.2014.3696. IF: 4.377

3. Magnetic Resonance Imaging Application in the Area of Mild and Acute Traumatic Brain Injury: Implications for Diagnostic Markers? ***Tóth A.*** FRONTIERS IN NEUROENGINEERING. Chapter 24 in: Brain Neurotrauma: Molecular, Neuropsychological, and Rehabilitation Aspects. Boca Raton (FL): CRC Press/Taylor & Francis; 2015.

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6.2 Abstracts that can be cited related to the thesis

1. Advanced magnetic resonance imaging in the acute and sub-acute phase of mild traumatic brain injury: Can we see the difference? ***Toth A**, Kovacs N, Perlaki G, Orsi G, Aradi M, Komaromy H, Bukovics P, Farkas O, Doczi T, Janszky J, Schwarcz A, Buki A.* JOURNAL OF NEUROTRAUMA 29:(10) pp. A41-A42. (2012) (Neurotrauma Symposium 2012, 2012.07.22-25. Phoenix, USA) IF: 4.295

2. Lateral Ventricle Volume Asymmetry is Related to Spectrin Breakdown Product (SBDP145) Levels in Severe Traumatic Brain Injury. ***Tóth A**, Schmalfuss I, Heaton SC, Gabrielli A, Hannay H, Papa L, Brophy GM, Wang KK, Büki A, Schwarcz A, Hayes RL, Robertson CS, Robicsek SA.* JOURNAL OF NEUROTRAUMA 31:A-1–A-73 (March 1, 2014) pp. A67-68. (The 11th Symposium of the International Neurotrauma Society March 19–23, 2014 Budapest, Hungary) IF: 3.714

3. Conventional vs. quantitative approach in assessing post-traumatic ventriculomegaly and its relation to 6-month outcomes in severe traumatic brain injury. ***Tóth A**, Schmalfuss I, Heaton SC, Gabrielli A, Hannay H, Papa L, Brophy GM, Wang KK, Büki A, Schwarcz A, Hayes RL, Robertson CS, Robicsek SA.* JOURNAL OF NEUROTRAUMA 31:A-1–A-73 (March 1, 2014) pp. A66-67. (The 11th Symposium of the International Neurotrauma Society March 19–23, 2014 Budapest, Hungary) IF: 3.714

4. Lateral Ventricle Volume Asymmetry Predicts Midline Shift and 6-month Outcome in Severe Traumatic Brain Injury ***Tóth A**, Schmalfuss I, Heaton SC, Gabrielli A, Hannay H, Papa L, Brophy GM, Wang KK, Büki A, Schwarcz A, Hayes RL, Robertson CS, Robicsek SA.* JOURNAL OF NEUROTRAUMA 31:A-1–A-73 (March 1, 2014) pp. A66. (The 11th Symposium of the International Neurotrauma Society March 19–23, 2014 Budapest, Hungary) IF: 3.714

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6.3 Other publications

1. Cortical involvement during myotonia in myotonic dystrophy: an fMRI study. **_Toth A_**, _Lovadi E, Komoly S, Schwarcz A, Orsi G, Perlaki G, Bogner P, Sebok A, Kovacs N, Pal E, Janszky J._ ACTA NEUROL SCAND. 2015 Jul;132(1):65-72. doi: 10.1111/ane.12360. Epub 2015 Jan 28. IF: 2.559

2. Microbleeds may expand acutely after traumatic brain injury. **_Toth A_**, _Kovacs N, Tamas V, Kornyei B, Nagy M, Horvath A, Rostas T, Bogner P, Janszky J, Doczi T, Buki A, Schwarcz A._ NEUROSCI LETT. 2016 Mar 23;617:207-12. doi: 10.1016/j.neulet.2016.02.028. Epub 2016 Feb 18. IF: 2.03

3. In vivo detection of hyperacute neuronal compaction and recovery by MRI following electric trauma in rats. **_Tóth A,_** _Kátai E, Kálmán E, Bogner P, Schwarcz A, Dóczi T, Sík A, Pál J._ J MAGN RESON IMAGING. 2016 Mar 10. doi: 10.1002/jmri.25216. IF: 3.25

4. Both hemorrhagic and non-hemorrhagic traumatic MRI lesions are associated with the microstructural damage of the normal appearing white matter. **_Tóth A,_** _Kornyei B, Kovacs N, Rostas T, Buki A, Doczi T, Bogner P, Schwarcz A._ BEHAV BRAIN RES. 2017 Feb 27. pii: S0166-4328(17)30324-8. doi: 10.1016/j.bbr.2017.02.039. [Epub ahead of print]
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6. Increased diffusion in the normal appearing white matter of brain tumor patients: is this just tumor infiltration? _Horváth A, Perlaki G,_ **_Tóth A_**_, Orsi G, Nagy S, Dóczi T, Horváth Z, Bogner P._ J NEUROONCOL. 2016 Mar;127(1):83-90. doi: 10.1007/s11060-015-2011-y. Epub 2015 Nov 27. IF: 2.754

7. Biexponential diffusion alterations in the normal-appearing white matter of glioma patients might indicate the presence of global vasogenic edema. *Horváth A, Perlaki G, **Tóth A**, Orsi G, Nagy S, Dóczi T, Horváth Z, Bogner P.* J MAGN RESON IMAGING. 2016 Feb 23. doi: 10.1002/jmri.25202. IF: 3.21

6.4 Other abstracts and presentations

1. Functional Magnetic Resonance Imaging Reveals Impaired Recruitment of Neural Resources in the Acute Phase after Mild Traumatic Brain Injury. ***Tóth Arnold**, Kovács Noémi, Perlaki Gábor, Orsi Gergely, Aradi Mihály, Komáromy Hedvig, Bukovics Péter, Farkas Orsolya, Dóczi Tamás, Janszky József, Büki András, Schwarcz Attila*; EANS 2012, 2012.10.24-27. Bratislava, Slovakia.

2. Imaging the minimally damaged brain ***Tóth Arnold**, Kovács Noémi, Perlaki Gábor, Orsi Gergely, Aradi Mihály, Komáromy Hedvig, Bukovics Péter, Farkas Orsolya, Dóczi Tamás, Janszky József, Büki András, Schwarcz Attila*; 6th Pannonian Symposium on Central Nervous System Injury, 2013.04.5-6., Pécs, Hungary

3. Az enyhe koponyasérülés okozta strukturális és funkcionális eltérések vizsgálata speciális mágneses rezonancia képalkotási (MRI) módszerekkel. ***Tóth Arnold**, Kovács Noémi, Perlaki Gábor, Orsi Gergely, Aradi Mihály, Komáromy Hedvig, Bukovics Péter, Farkas Orsolya, Dóczi Tamás, Janszky József, Büki András, Schwarcz Attila* Magyar Neuroradiológiai Társaság XX. Kongresszusa, 2012.11.8-10. Eger. (2012)

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5. Degeneratív porckorong betegségek vizsgálata kvantitatív T2 MR mérésekkel. *Juhász Ivett, Aradi Mihály, Nagy Szilvia, Papp Marianna, Perlaki Gábor, Orsi Gergely,* ***Tóth Arnold**, Nagy Gyöngyi, Bogner Péter* Magyar Neuroradiológiai Társaság 20. kongresszusa. 20th Annual Meeting of the Hungarian Society of Neuroradiology. Eger, Magyarország, 2012.11.08-2012.11.10. p. 19-20.

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Schwarcz Attila, Pál József Neuroimaging Workshop Pécs, Magyarország, 2013.04.19-2013.04.20. Pécs: p. 17.

7. Nemek közti különbség a hippokampusz térfogatában? *Perlaki G, Orsi G, Nagy Sz A, Plózer E, Altbäcker A, Darnai G, **Tóth A**, Dóczi T, Komoly S, Bogner P, Schwarcz A, Janszky J* Neuroimaging Workshop Pécs, Magyarország, 2013.04.19-2013.04.20. Pécs: p. 16.

8. Megváltozott szöveti diffúzió gliómás betegek épnek tűnő fehérállományában. *A Horváth, Sz A Nagy, G Perlaki, G Orsi, **A Tóth**, T Dóczi, Zs Horváth, P Bogner.* Magyar Neuroradiológiai Társaság 22. Kongresszusa Hajdúszoboszló, Magyarország, 2014.11.06-2014.11.08. Debrecen: p. 33.

9. Microbleeds may progress acutely after traumatic brain injury ***Tóth Arnold*** 11th Hungarian-Croatian-Slovenian Radiological Symposium 2015. november 13-14 Hévíz. (2014)

10. Követéses SWI vizsgálatok koponyasérülésben: a léziók dinamikájának feltárása. ***Tóth Arnold,*** *Kovács Noémi, Környei Bálint, Perlaki Gábor, Orsi Gergely, Bogner Péter, Büki András, Schwarcz Attila* Magyar Neuroradiológiai Társaság XXII. Kongresszusa Hajdúszoboszló, 2014. november 6-8. (2014)

11. Diffusion alterations in the normal appearing white matter of glioma and meningioma patients. *Andrea Horváth, Gábor Perlaki, **Arnold Tóth**, Gergely Orsi, Szilvia Nagy, Tamás Dóczi, Zsolt Horváth, Péter Bogner* Neuroimaging Workshop 2015. Szeged, Magyarország, 2015.04.17-2015.04.18.p. E-kiadvány

Cumulative impact factor of publications related to the thesis: 10.375
Cumulative impact factor of all publications: 28.554
Number of independent citations (MTMT): 75
H-index: 4