Quantitative fiber tracking after perinatal hypoxic-ischemia and neurodevelopmental outcome at 2 years

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Introduction. Hypoxic-ischemic encephalopathy (HIE) is an important cause of mortality and morbidity in infants who are born at term. Previous studies correlate abnormal signal intensities (SI) on conventional MRI with neurodevelopmental outcome (1-3). SI changes in the posterior limb of the internal capsule (PLIC) on Diffusion-weighted Imaging are an accurate predictor of neuromotor outcome in term newborns with HIE (4). Quantitative fibertracking is a feasible tool in studying the asphyxiated neonatal brain (5). However, investigations to determine whether fibertract anomalies correlate with neonatal outcome are lacking. The aim of this study was to assess the relationship between the volume of the fibers traced through the PLIC and neurodevelopmental outcome at 2 years in term neonates with perinatal HIE.

Methods.

Patients. The study group comprised 17 term neonates (14 male, 3 female), mean gestational age 39.9 weeks ± 2.0 (sd), with neonatal encephalopathy due to perinatal hypoxic ischemia (HI). Perinatal HI was diagnosed when clinical symptoms of neonatal encephalopathy were present with 2 or more of the following risk factors: fetal heart rate abnormality, umbilical artery pH level < 7.10, meconium-stained fluid and Apgar score 5 minutes after birth < 7. Neonates with congenital abnormalities, neurometabolic disease, and/or perinatal infection were excluded.

MRI examinations. MRI was performed between day 1 and 17 after birth (mean 7.5 ± 3.4) (t=0). Follow-up MRI at 3.6 months ± 0.4 (t=1). Sedation with chloralhydrate in all patients. MRI protocol: Philips Gyroscan 1.0 Tesla, included T1, T2, IR-T1 and Diffusion-tensor images (DTI) in the axial plane. DTI with a single-shot EPI sequence and Pulsed Field Gradients in 6 directions; voxel size 1.2 x 1.2 x 4 mm; b-values 0, 400 and 800 s/mm^2. Fibertracking: using a line propagation technique with stopping criteria: $C_l < 0.10$ and angle > 10^0 (6). Quantification of fibers by calculation of volume (5). ROIs were drawn manually around the PLIC in left and right cerebral hemisphere (on the FA map). The first ROI was placed at the anatomic level of Monro's foramen, the second on the adjacent slice above this landmark. By using the AND criterium only all fibers passing through the two ROIs in PLIC were selected. Mean fiber volumes of both PLICs were calculated out of 5 measurements. The mean ADC and mean FA of all fibers from the left and right PLIC were calculated.

Neurodevelopmental assessment at 2 years with the Bayley Scales of Infant Development, version II-NL and with a pediatric-neurological examination. For neurodevelopmental outcome comparison, we used 3 groups: no disability (I), mild to moderate disability (II), severe disability and death (III).

Statistical analysis. For group comparison of fiber volumes, ADC and FA a one-way ANOVA and Bonferroni post-hoc comparison was used. For differences in fiber volume, ADC and FA over time a paired t-test was used. P-values ≤ 0.05 were considered significant.

Results.

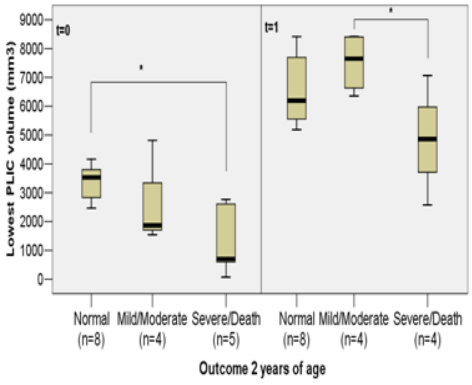

Figure 1.

	PLIC	Vol. (mm³) t=0 (n=17)	Vol. (mm³) t=1 (n=16)	Abs.diff. (mm³)**
Group I (n=8)	Left	3557 (497)*	7245 (1143)*§	3688
	Right	3472 (673)*	6908 (1172)§	3436
Group II (n=4)	Left	3379 (1735)	7711 (1039)†§	4332
	Right	2630 (1491)	7519 (1049)§	4889
Group III (n=4/5)	Left	1436 (1203)	5004 (1868)§	3717
	Right	1442 (1284)	5061 (2103)§	3408

Table. Data expressed as mean (sd). **Absolute difference in volume between t=0 and t=1, calculated on 4 patients in Group III, one patient died in perinatal period and was excluded.
§ Statistically significant difference compared to the corresponding PLIC at t=0. * P < 0.05 Group I compared to Group III. † P < 0.05 Group II compared to Group III.

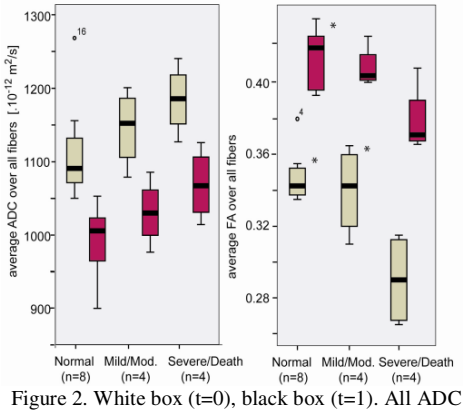

Figure 2. White box (t=0), black box (t=1). All ADC and FA values over time were significantly different within outcome groups, except ADC values over time in the severe/death group.

Two out of 17 patients died during follow-up (day 1; 11 months). The lowest and highest fiber volume from the left or right PLIC and the mean fiber volume from both left and right PLIC separately were analysed. A significant difference between groups in lowest PLIC volumes is depicted in figure 1. This significant difference was also seen when highest (data not shown) and mean (table) PLIC volumes were compared to outcome groups. The PLIC fiber volume increases over time in both left and right PLIC. This increase was similar within group I and III, despite of a lower PLIC volume in group III at t=0 (table). Figure 2 shows the results of mean ADC (10^{-12} m^2/s) and mean FA values. A higher ADC and significant lower FA are seen in the severe/death group compared to the normal group, at 0 and 3 months.

Discussion. Our study shows that volume measurements of PLIC fibers in the neonatal period and at 3 months correlate with neuromotor outcome at 2 years. However, the correlation at 3 months is less obvious than in the neonatal period. The significantly lower fiber volume in the severe/death group can be explained by tissue edema and membrane disruption in the neonatal period, leading to definite changes in structure integrity at 3 months. This is supported by the ADC and FA values of the fibers at 0 and 3 months and the differences between the outcome groups. Methodological problems (e.g. defined stopping criteria) might have influenced the calculations of ADC and FA. However, these ADC and FA changes are also seen in a comparable group in which we studied ADC and FA within a well defined ROI in the PLIC (unpublished data). The increase in PLIC fibers over time between the normal and severe/death group is in the same range, however the volume at 3 months is significant lower in the severe/death group (table). We speculate that the damage in this group is of such an extent that despite mechanisms of brain plasticity and regeneration, the increase is insufficient to reach a normal outcome level. Further research including detailed analysis of the anisotropy of tissue and fibers is needed to get more insight in the underlying pathophysiology.

References. 1. Barnett A et al. Neuropediatrics 2002;33:242-48. 2. Rutherford MA et al. Pediatrics 1998;102:323-28. 3. Coskun A et al. Am J Neuroradiol. 2001; 22:400-05. 4. Hunt et al. Pediatrics 2004;114:999-1003. 5. van Pul C et al. Radiology 2006;203-14. 6. Mori S et al. MRI atlas of human white matter. Elsevier, 2005.