# Apparent Diffusion Coefficients and R2 Relaxation Rates in Term Infants with Hypoxic Ischemic Encephalopathy: Relation to Postnatal Age

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## Introduction:

In neonates with hypoxic ischemic encephalopathy (HIE) the apparent diffusion coefficient (ADC) in tissue is reduced shortly after birth, but then increases with postnatal age at scan (PNAS).[1,2] The normalization time for ADC, defined as the PNAS at which ADC reaches a "normal" value, was previously reported to occur at 7 days[3], however, this estimate was based on a case report of only two infants. T2-weighted image contrast is also affected by HIE, but there are relatively few reports quantifying the change in the R2 (1/T2) relaxation rate following HIE. The goal of our study is to estimate (i) the rate of change of ADC with PNAS in brain regions of term infants with HIE (ii) the ADC normalization time for each region and (iii) changes in R2 values for each region.

## Methods:

A retrospective analysis was performed on cerebral images obtained from (N = 34) term infants, 37-42 weeks gestational age (GA), who had received 1.5 T MRI scan (Siemens Vision System) at our center between 2001 and 2004. An analysis of the ADC for several brain regions was performed for nine patients with HIE and thirteen others with various diagnoses including: transient/mild HIE (3), known CNS anomalies (4), neonatal seizures (1), intracranial hemorrhages (1), hypotonia (3), and other undefined neurological conditions (1). Four HIE patients were scanned twice and one patient three times. An analysis of R2 values of several brain regions was performed from ten infants with HIE and twenty-three others with various diagnoses including: transient/mild HIE (4), known CNS anomalies (7), neonatal seizures (2), intracranial hemorrhages (2), hypotonia (6), and other undefined neurological conditions (2). R2 values in five infants with HIE were collected at two time points. Infants had been scanned at different times after birth (2 days -19 days for infants with HIE and 0 days to 35 days for others).

Maps of the ADC were retrospectively generated from diffusion-weighted images that had been acquired with a single shot spin-echo echo planar imaging sequence (15 slices, TE =103ms, TR = 4s, b = 0, 1000 s/mm$^2$). Trace ADC maps were obtained by averaging ADC maps for each of the three orthogonal directions. Quantitative maps of R2 were generated from images that had been acquired using a multi-echo fast spin echo sequence (20 slices, TE = 15, 75, 135ms, TR = 3.3s). A log-linear least squares regression was applied to the signal intensity data obtained at each of the three echo times.

Region of interest R2 and ADC measurements were performed bilaterally from eight brain regions: parietal white matter (PWM), frontal white matter (FWM), occipital white matter (OWM), lentiform nucleus (LN), posterior limb of the internal capsule (PLIC), thalamus (TH), basil pons (BP) and cerebellum (CERE). ADC and R2 values were averaged between left and right.

For each region, the relationship between ADC PNAS was investigated using a linear regression. A Bonferroni adjustment for alpha (p value for determining significance) was conducted by dividing the critical per comparison value of 0.05 by the number of brain regions investigated. This new alpha was then used to determine whether or not the regression equations were significant. A separate analysis was applied to determine if the slopes and intercepts were significantly different between infants with definitive HIE and others.[3] The normalization time was estimated for each region by calculating the value of PNAS at the intersection of the definitive HIE regression line and the other patients regression line. R2 data was analyzed in SPSS (ver. 10.0) with a two-way mixed ANOVA with REGION as the within-subjects factor and DIAGNOSIS as the between-subjects factor. Postmenstrual age (PMA) was considered as a covariate.

## Results:

For infants with definitive HIE, a significant association was observed between ADC and PNAS in the OWM, LN, PLIC, and TH after Bonferroni correction for multiple tests (Table 1). For these regions, slopes and intercepts were significantly different between infants with definitive HIE and those without definitive HIE. The strongest association between ADC and PNAS was observed for the OWM (Fig. 1). The rate of ADC change with respect to PNAS, and the normalization point for the four significant regions are shown in table 1. A significant correlation ($p < 0.05$, Bonferroni corrected) of ADC and PMA was only observed in the LN of control patients.

No significant correlations between R2 values and PNAS were found. For R2 values, a significant region by pma interaction, [$F(7,29)=2.66$, $p<0.05$], was observed. Also, a significant main effect for region [$F(1,35) = 2.82$, $p<0.05$], PMA [$F(1,35) = 28.45$, $p<0.001$] and diagnosis [$F(1,35)=6.14$,$p<0.05$] was observed. A univariate ANCOVA with PMA covariate was used to investigate each region separately. R2 was significantly reduced in the PAR [$F(1,36) = 4.65$, $p<0.05$, $\varepsilon^2 = 0.115$, power = 0.55] and PLIC [$F(1,35) = 5.33$, $p<0.05$, $\varepsilon^2 = 0.088$, power = 0.61]. The covariate PMA was significant for FWM, PLIC, BP and CERE. A Kruskal-Wallis non-parametric analysis was also performed because of the presence of outlier data points (>3 STD) in the HIE group (one outlier in each of 3 regions). This test showed a significant reduction in R2 values observed for PWM, LN, PLIC, and TH.

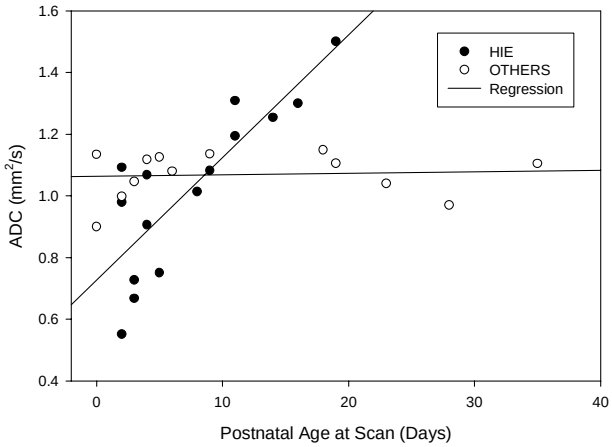


**Figure 1**. ADC values for HIE and Others vs. PNAS in the OWM. Regression lines are shown for both HIE and OTHERS

| Region | Slope (mm$^2$/s/day) | R | p value (corrected) | Normalization Point (days) |
|---|---|---|---|---|
| OWM | 0.09± 0.02 | 0.83 | <0.001 | 9±3 |
| LN | 0.05± 0.01 | 0.75 | <0.01 | 9±3 |
| PLIC | 0.031± 0.008 | 0.70 | <0.05 | 9±4 |
| TH | 0.04± 0.007 | 0.83 | <0.005 | 9±3 |

**Table 1.** Rate of change of ADC values vs. PNAS (slope) for HIE patients for regions with significant regressions. p values reported are Bonferroni corrected (×8) for multiple comparisons.

## Discussion:

For infants with definitive HIE, the rate of change of ADC with PNAS between 2-19 days was found to vary considerably between the four brain regions for which ADC was significantly correlated to PNAS. However, the normalization time, the PNAS at which HIE patients and others cannot be differentiated, was found to be similar between these four brain regions. R2 was reduced in HIE compared to controls but changes were not dependent on the PNAS. The quantification of time-variation for ADC values is essential for accurate diagnosis of HIE.

## References:

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