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Prognostic Value of the Apparent Diffusion Coefficient in Newborns with Hypoxic-Ischaemic Encephalopathy Treated with Therapeutic Hypothermia

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Abstract
Background: Apparent diffusion coefficient (ADC) quantification has been proven to be of prognostic value in term newborns with hypoxic-ischaemic encephalopathy (HIE) who were treated under normothermia. ***Objectives:*** To evaluate the prognostic value of ADC in standardized brain regions in neonates with HIE who were treated with therapeutic hypothermia (TH). ***Methods:*** This prospective cohort study included 54 term newborns who were admitted with HIE and treated with TH. All magnetic resonance imaging examinations were performed between days 4 and 6 of life, and ADC values were measured in 13 standardized regions of the brain. At 2 years of age we explored whether ADC values were related to composite outcomes (death or survival with abnormal neurodevelopment). ***Results:*** The severity of HIE is inversely related to ADC values in different brain regions. We found that lower ADC values in the posterior limb of the internal capsule (PLIC), the thalami, the semioval centre, and frontal and parietal white matter were related to adverse outcomes. ADC values in the PLIC and thalami are good predictors of adverse outcomes (AUC 0.86 and 0.76). ***Conclusions:*** Low ADC values in the PLIC, thalamus, semioval centre, and frontal and parietal white matter in full-term infants with HIE treated with TH were associated with a poor outcome.

Introduction

Neonatal hypoxic-ischaemic encephalopathy (HIE) occurs in 1–8 per 1,000 term infants [1]. Even with therapeutic hypothermia (TH), 30–70% of infants with moderate to severe HIE will die or will survive with neurological impairments. Magnetic resonance imaging (MRI) in the second week of life has proven to be the most reliable and useful technique as an outcome predictive assessment in term infants with HIE [2–4].

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Conventional T1- and T2-weighted images are the main sequences that are used in MRI, but interpretation is subject to subjectivity and low interobserver agreement has been reported [5]. Diffusion-weighted imaging (DWI) and quantitative assessment via apparent diffusion coefficient (ADC) might be more objective sequences that can allow an earlier evaluation after ischaemic injury.

The detection of lower ADC values in different regions of the brain is associated with neurological impairment after HIE [2, 6, 7]. In these studies, ADC quantification was performed at different moments and all newborns were treated under normothermia.

ADC values in patients with HIE decrease during the first 7–10 days of life with a later pseudonormalization of values. Therefore, the sensitivity of MRI diffusion methods is dependent on the timing of the study relative to the time of the hypoxic-ischaemic insult.

Only a few studies have reported the utility of ADC as a prognostic marker in infants with HIE who were treated with TH [8], and none of them measured ADC values in different brain regions.

In the present study, we investigated the value of ADC quantification on the fifth day of life in 13 standardized regions of the brain on the prediction of outcomes in neonates with HIE who were treated with TH.

Table 1. Perinatal characteristics, HIE classification, MRI pattern, and outcomes of our studied population

Variables	Patients (n = 54)
Gestational age, weeks	39.4±1.64
Birth weight, g	3,323.1±527
Male	30 (55.56)
Umbilical cord pH	6.93±0.13
1-min Apgar score	2 (0–6)
5-min Apgar score	4.5 (0–8)
Caesarean section	15 (27.7)
Clinical HIE grade	
Mild	10 (18.52)
Moderate	29 (53.7)
Severe	15 (27.78)
Outcome	
Normal	36 (66.7)
Abnormal	14 (25.9)
Death	4 (7.4)
MRI pattern in moderate and severe HIE patients	
Normal	30 (55)
BG/thalamus	13 (24)
Watershed	8 (14.8)
Near total injury	3 (5.5)

Values represent the mean ± SD, n (%), or median (range). HIE, hypoxic-ischaemic encephalopathy; MRI, magnetic resonance imaging; BG, basal ganglia.

Material and Methods

Subjects

We conducted a prospective cohort study of term newborns with HIE who were admitted to the neonatal intensive care unit at Puerta Del Mar University Hospital (Cádiz, Spain) from May 2009 to November 2013. All of the included patients met the criteria for TH established by the Spanish Neonatal Society [9], which includes an Apgar score of ≤5 at 5 min or a continued need for resuscitation 10 min after birth, a pH of <7.00 or a base excess of ≥16 mEq/L within 60 min of birth, an abnormal background activity of at least a 30-min duration or seizures on amplitude-integrated electroencephalography, and moderate to severe encephalopathy consisting of lethargy, stupor, or coma, and at least one of the following: hypotonia, abnormal reflexes, absent or weak suck, or seizures. The eligible patients received whole-body cooling to a rectal temperature of 33.5°C, which was initiated before 6 h of life and continued for 72 h. Exclusion criteria were intrauterine infection or trauma, central nervous system malformation, chromosomal abnormality, imminent death, and/or inborn metabolic error.

The research protocol was approved by the Institutional Review Board and informed parental consent was obtained in all cases.

All infants were included in a neurological follow-up programme that lasted up to 24 months. At 2 years of age, a neurodevelopmental assessment was performed using the Bayley Scales of Infant and Toddler Development (BSID), Third Edition [10]. Outcome was graded at 2 years of age as follows: (1) normal; (2) abnormal, i.e., children with a score of <70 in any of the 3 developmental domains on the BSID or cerebral palsy [11], and a level II-V of the Gross Motor Function Classification System (GMFCS) [12]; and (3) death. Outcome was dichotomized as "favourable" or "adverse." Death or survival with abnormal neurodevelopment was used as the adverse composite outcome.

MRI

All MRI examinations were performed between days 4 and 6 after birth. We followed a previously reported protocol [13] to ensure the stability of our patients. No sedation was used and disposable earplugs were applied.

All studies were performed with a 1.5-T machine (Symphony; Siemens Medical Systems, Erlangen, Germany). Routine imaging consisted of transverse T2-weighted turbo spin-echo imaging (4,180.00/98.00), and DWI. Single-shot spin-echo echo-planar sequences were implemented for DWI (2,200.00/90.00) by varying the diffusion gradient strength along each of the 3 orthogonal directions. The corresponding b values that were generated were 0 and 1,000 s/mm^2. Images were corrected for eddy current distortions and an ADC map was constructed.

ADC measurements were independently performed in 13 standardized regions of the brain. Trace maps were used to calculate ADC values in all regions of interest (ROI). ROI were identified on the original T2-weighted images and were visually matched and

Table 2. ADC values and clinical HIE grades

HIE	Mild (n = 10)	Moderate (n = 29)	Severe (n = 15)
PLIC*, **, ***	106.25 (100.8–109.15)	100 (94.6–103)	88 (80.25–94.1)
Thalamus**, ***	96.18 (92.1–99.7)	91.3 (87.05–96.1)	83.5 (72–92.5)
SOC **, ***	147.65 (132.5–154.7)	138.7 (127.9–156.7)	121.5 (89.6–135)
Frontal WM***	170.35 (158.7–177.7)	169.4 (143.1–176.2)	146 (119.6–164.4)
Parietal WM***	158.7 (141.3–174.1)	157.6 (142.2–168.4)	142.1 (121.8–159)

ADC values and clinical HIE grades. Values represent the median (range). ADC, apparent diffusion coefficient; PLIC, posterior limb of internal capsule; SOC, semioval centre; WM, white matter. * $p < 0.05$ among mild-moderate HIE; ** $p < 0.05$ moderate-severe HIE; *** $p < 0.05$ mild-severe HIE.

positioned on the b0 image of the DWI acquisition, which can be considered a fast T2-weighted echo-planar MRI. From there, the ROI was copied into the corresponding ADC map. Circular ROIs were drawn manually over the following loci for the calculation of ADC: cerebellar white matter, ventrolateral thalami, posterior limb of the internal capsules (PLIC), semioval centre, frontal white matter, parietal white matter, and in the centre of the pons, in a transverse cross section through the middle cerebellar peduncles. The area of each ROI was 30 mm^2 in the pons, cerebellum, frontal white matter, parietal white matter, semioval centre, and ventrolateral thalami, and a smaller irregular ROI (10 $mm^{2)}$ was used in the PLIC. At least 2 measurements were collected for each ROI, and the average was used in the results. We used the mean ADC values among the right and left ADC values in every locus. ADC values are expressed in units of $10^{-5}/mm^2/s$.

Statistical Analysis

All variables were tested for normal distribution and were reported as the mean and standard deviation (SD) if distributed normally, or as the median and range if a significant non-normality distribution was detected. For bivariate analysis, an unpaired 2-tailed Student *t* test, Mann-Whitney U-test, simple linear regression, or logistic regression were used depending on the variables that were studied.

Once the prognosis was dichotomized as "favourable" or "adverse," we performed binary logistic regression to study the relationship among ADC values and prognosis.

To analyze the predictive value of ADC values in the different ROIs, we performed a postestimation analysis of the logistic regression models that were generated for each locus, with the estimation of the optimal cut-point ADC value as a diagnostic test.

Results

Fifty-four newborns with HIE who were treated with hypothermia were included in the present study. Ten patients (18.5%) were graded as mild HIE, 29 (53.7%) as moderate HIE, and 15 (27.7%) as severe HIE. A total of 33.3% of the included patients (18/54) died or survived with an abnormal neurological outcome (adverse outcome), and 66.7% (36/54) of the patients survived with normal neurodevelopment (favourable outcome). Those with moderate to severe HIE had the following MRI patterns: in 37% (20/44) of patients no injury was found in DWI, 25.9% (14/44) developed basal ganglia injury, 13% (7/44) developed watershed injury, and 5.6% (3/44) developed near total injury (Table 1).

All ADC values in the 13 loci studied, except for the cerebellum and the brain stem, were found to be inversely related to the HIE grade, which indicates that the more severe the HIE, the lower the ADC values (Table 2).

When we analyzed ADC values in relation to outcome, we found that lower ADC values in the PLIC, thalamus, semioval centre, and frontal and parietal white matter were related to adverse outcomes ($p < 0.05$), but ADC values in the cerebellum and brain stem were not related to outcome (Table 3).

We estimated the optimal ADC value cut-point at which the PLIC and thalamus showed the best AUC, while other ROIs demonstrated lower predictive values (Table 4).

Discussion

In newborns with HIE who were treated without hypothermia, several authors [6, 7] have demonstrated that low ADC values that were measured during the first 12 days after birth in different brain regions (perirolandic cortex, PLIC, hippocampus, thalamus, putamen, and white matter) were significant for outcome prediction. Our findings are similar to the results of these studies, and we could demonstrate that low ADC values in the PLIC, thalamus, semioval centre, and frontal and parietal white matter were associated with an adverse outcome. However, other investigators did not find this relationship in newborns with

Table 3. ADC values related to outcome

	Outcome		*p*
	normal (*n* = 36)	adverse (*n* = 18)	
PLIC	100.75 (79.7–118.7)	87 (51.6–119.75)	0.0001
Thalamus	93.6 (77.9–103.1)	78.75 (50–105.4)	0.0016
SOC	143.4 (102.5–173.3)	122.2 (60–173)	0.0015
Frontal WM	170.65 (83.5–194.4)	141.75 (57.8–190.6)	0.0056
Parietal WM	159.35 (85.4–179.1)	144.55 (53.6–163.1)	0.0143
Cerebellum	118.9 (107.3–136.9)	116 (89.3–145.3)	0.5170
Brain stem	109.6 (94.8–131.4)	111 (95–911)	0.4741

ADC values related to outcome. Values represent the median (range). Adverse outcome accounts for the combined outcomes of death or neurological abnormal development. ADC, apparent diffusion coefficient; PLIC, posterior limb of internal capsule; SOC, semioval centre; WM, white matter.

Table 4. ADC optimal cut-point values in measured locations

	Cut-point	Sensitivity	Specificity	PPV	NPV	AUC (95% CI)
PLIC	94.43	86.11	83.33	91.18	75	0.86 (0.74–0.99)
Thalamus	86.25	91.43	66.67	84.21	80	0.79 (0.67–0.91)
CSO	131.25	77.78	72.22	84.85	61.9	0.75 (0.62–0.88)
Frontal WM	165.45	66.67	83.33	88.89	55.56	0.75 (0.63–0.87)
Parietal WM	163.35	100	0	51.35	–	0.50 (0.50–0.50)

ADC optimal cut-point values in measured locations. The different loci studied and its predictive values for adverse neurological outcome. ADC, apparent diffusion coefficient; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve of the receiver operating curve; CI, confidence interval; PLIC, posterior limb of internal capsule; SOC, semioval centre; WM, white matter [8].

HIE who were treated without hypothermia [5, 14]. These conflicting findings may be attributable to the limited sample size of the studies (*n* = 10–30) and variable timing of MRI in the patient cohorts (ranging from 1 to 18 days). Our study has a larger sample size than the reported studies and all infants were scanned 4–6 days before the pseudonormalization of ADC values is known to occur.

Few studies have studied the association between low ADC values and outcomes in neonates with HIE who were treated with TH and were examined within 7 days of birth. Two studies [8, 15] found that low ADC values in the corpus callosum were associated with an adverse outcome. These studies lacked other predefined study regions. In our study, we found an association among adverse outcomes and lower ADC values in the PLIC, thalamus, semioval centre, and frontal and parietal white matter, but not in the cerebellum or brain stem.

Only a few published studies have addressed the predictive value of ADC measurements in neonates with HIE, and most of these were performed in normothermia-treated infants [16, 17]. In a meta-analysis [3], ADC was reported to have a sensitivity of 66% (95% CI: 52–79) and a specificity of 64% (95% CI: 35–87). This relatively poor prognostic ability of ADC values may be partly related to the pseudonormalization of ADC since some of the included studies included MRIs that were performed later in life and the comparison was performed with relative heterogeneity in the differential anatomic positioning of the ROIs in which ADC was assessed.

Only 3 previous studies have addressed the prognostic value of ADC quantification after having TH as the standard treatment. Alderliesten et al. [8] demonstrated that the ADC value in the corpus callosum is a good predictor (AUC = 0.87) of death or survival with adverse neurode-

velopment at 18 months of age. Charon et al. [18] studied 32 patients treated with TH, 5 of them with an adverse outcome (death or disability at 2 years), and found, in a similar manner to our results, that ADC values on MRI that was performed on days 3–6 of life were good predictors of outcome. In this study the best predictors of neurological outcome with the highest AUCs were ADC values within the posterior white matter, semioval centres, and PLIC. In contrast to our study, the study by Charon et al. was retrospective, with a wide follow-up range (18–41 months), and in 4 patients MRI was performed during hypothermia, which could be responsible for the lower ADC values [19]. There was also a small number of neonates who experienced adverse outcomes (21%), which is lower than in our study (32%) and in other previous studies (30–46%) with larger sample sizes [20, 21]. Alderliesten et al. [22] measured ADC values in 88 newborns with HIE who were treated with TH. MRI was performed on a 1.5-T (n = 38) or 3.0-T (n = 50) MR system from 2.5 to 6 days of life. In accordance with our results, they found that ADC values in the basal ganglia and the thalamus were significantly lower in infants with later adverse outcomes than in those with normal outcomes, with a reported AUC for ADC values in the basal ganglia and thalamus of 0.89 and 0.88, respectively. We should consider the 2 different magnetic fields (1.5 or 3.0 T) that were used in this study as well as the timing of MRI performance since patients with an adverse outcome underwent MR examination within 72 h after birth, during TH, which can lead to lower ADC values. Our group demonstrated that ADC values , measured at 4-6 days of life, in the PLIC (AUC = 0.86), the thalamus (AUC = 0.76), the semioval centre (AUC = 0.75) and frontal white matter (AUC = 0.75) were good predictors of death or survival with abnormal neurodevelopment at 2 years of age in newborns with HIE treated with TH.

The timing of MRI is critical in the evaluation of hypoxic-ischaemic injury. ADCs are maximally reduced 3 days after perinatal injury, whereas after 7 days they pseudonormalize [23]. TH may "slow down" the evolution of the mean diffusivity changes, with a delay in "pseudonormalization" [19]. Most authors performed MRI in a wide postnatal age range (1–18 days). In our study, all neonates were scanned 4–6 days after birth. We therefore avoided pseudonormalization as a confounding factor that may have affected the results of other studies. Moreover, our patients were examined at the same field strengths, with the same scanning protocols including the same DWI b values and in normothermia (after rewarming from TH).

Although our sample size was larger than most of the published studies, some of our sample characteristics and size can be considered as limitations. Ten patients (18.5%) were graded as having mild HIE. We found this proportion of patients with mild HIE in a similar manner as reported in previous studies [8, 22].

Although the follow-up at 2 years of age is longer than in most of the published studies, the duration of follow-up in our study is still limited. A neuropsychological examination at later times may highlight alterations in complex cognitive functions that cannot be fully appreciated at 2 years of age.

The predictive ability of ADC quantification at 4–6 days of life in terms of neurodevelopmental outcome in neonates treated with TH could be of help in those cases where the redirection of therapy must be considered since this issue is mostly relevant in the first days of life [24]. Moreover, ADC quantification should add predictive value to other prognostic markers in infants with HIE who were treated with TH [2].

In future studies, we will establish the value of ADC quantification in defined brain regions as prognostic for specific neurodevelopmental outcomes in infants with HIE who were treated with TH.

In conclusion, low ADC values that were quantified at 4–6 days of life in the PLIC, thalamus, semioval centre, and frontal and parietal white matter in full-term infants with HIE who were treated with TH were associated with a poor outcome at 24 months of age.

Disclosure Statement

We declare that we have no conflict of interest.

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