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Neonatal Hydrocortisone Treatment Related to ^{1}H-MRS of the Hippocampus and Short-Term Memory at School Age in Preterm Born Children

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ABSTRACT: Animal studies have shown that corticosteroids (dexamethasone) cause neuronal loss in the hippocampus and deficits in short term memory. Proton magnetic resonance spectroscopy can measure brain metabolites *in vivo* and give an indication of neuronal integrity. We investigated whether prolonged administration of hydrocortisone during the neonatal period for bronchopulmonary dysplasia (BPD) in preterm born children changes the metabolism in the hippocampus, measured at school age. Secondly, we investigated whether hippocampal metabolism and short-term memory and neurodevelopmental outcome are related. In this observational study 37 preterm born children (≤ 32 wk (range 25.0-33.0) and/or a birth weight ≤ 1500 g) underwent proton spectroscopy of the hippocampus at school age. Eighteen children were treated with hydrocortisone for BPD (starting dose 5 mg/kg/d tapered over a minimum period of 22 d, median duration 28 d) and 19 never received corticosteroids during the perinatal period. N-acetyl aspartate/ Choline + Creatine/ phosphocreatine (NAA/(Cho+Cr)) ratios were determined. A 15-word recall memory test and an IQ measurement were obtained on the same day. Hydrocortisone treated children were younger, lighter and sicker than their nonsteroid treated counterparts. Mean NAA/(Cho+Cr) ratios in the hippocampus were not significantly different in the hydrocortisone group compared with the non-steroid group. Performance on the 15-word memory test and IQ were similar in the two groups. There was no relation between NAA/(Cho+Cr) ratios and memory nor between NAA/(Cho+Cr) ratios and IQ. We conclude that hydrocortisone in the mentioned dose, administered in the neonatal period for BPD, does not appear to have any long-term effects on memory and/or hippocampal metabolism. (***Pediatr Res* 59: 309–313, 2006**)

The hippocampus plays a critical role in memory functioning and is a principal neural target for glucocorticoids, the adrenal steroids secreted during stress (1). Previous studies have demonstrated reduced volumes of many parts of the brain, including the hippocampus, in preterm children in comparison with their term-born peers (2–6). Rodent as well as non-human primate studies suggest that prolonged exposure to glucocorticoids or to stress can accelerate hippocampal neuronal loss during aging, as well as increase the severity of neurologic insults to the hippocampus (7,8) In addition, neonatal dexamethasone treatment has been shown to affect social behavior such as social memory in adult rats (9). Preterm born infants are often treated with corticosteroids sometime during their perinatal period, either antenatally to stimulate fetal lung maturation, or post-natally to treat bronchopulmonary dysplasia (BPD), or both. Negative effects on brain development in preterm infants, who were treated with dexamethasone during their Neonatal Intensive Care Unit (NICU) period, are increasingly recognized. Corticosteroids affect long-term neurofunction and several reports on the adverse effects of dexamethasone have emerged over the last years (10–13).

Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) is a technique to assess brain metabolism *in vivo*. Metabolites most easily identified are N-acetyl aspartate (NAA), choline (Cho), (phospho)creatine (Cr), and lactate. NAA is a free amino acid, localized almost uniquely in neuronal tissue, neurons and axons of the adult brain. During development it is also found in oligodendrocyte-type-2 astrocyte progenitor cells and in immature oligodendrocytes (14,15). Bhakoo and Pearce demonstrated in cell culture that mature oligodendrocytes can also express NAA *in vitro* (16). Lowered NAA/(Cho+Cr) ratios would imply a decreased neuronal integrity of the tissue.

The steroid prescribed in our NICU is hydrocortisone, a much less potent glucocorticoid than dexamethasone, which is generally used for the treatment of BPD.

The aim of the present study was to investigate the impact of neonatal hydrocortisone treatment in preterm infants on hippocampal metabolism as estimated with ^{1}H-MRS, and short-term memory and IQ measured at school age.

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Abbreviations: BPD, bronchopulmonary dysplasia; **BW,** birth weight; **Cho,** choline; **Cr,** (phospho)creatine; **GA,** gestational age; **^{1}H-MRS**, proton magnetic resonance spectroscopy; **IVH,** intraventricular hemorrhage; **MRI,** magnetic resonance imaging; **NAA,** N-acetyl aspartate; **NICU,** Neonatal Intensive Care Unit; **PVL,** periventricular leukomalacia; **US,** ultrasound; **VOI,** volume of interest

PATIENTS AND METHODS

The children described in this paper are part of a cohort of consecutively admitted patients soon after birth over a period of two years to the NICU of the Wilhelmina Children's Hospital, a tertiary referral hospital. All children, born between March 1, 1991, and March 1, 1993, with a gestational age (GA) $\leq$ 32 wk (range 25.0–33.0) and/or a birth weight (BW) $\leq$ 1500 g were subsequently enrolled in a long-term follow-up study. The original group consisted of 375 children. Sixty-four children (17%) died and 28 (7.5%) were excluded from the study because of (multiple) congenital abnormalities and/or chromosomal disorders. At the age of seven or eight (rarely nine and ten) the children were invited to the hospital for one day to have several tests. Of the remaining 283, 22 children (7.8%) could not be traced due to moving and the parents of 25 children (8.8%) refused to participate in the study. Finally 236 children (83.4%) participated. They were seen by a child psychologist to have their IQ estimated and to perform a 15-word memory test. On the same day Magnetic Resonance Imaging (MRI) of their brain was obtained. During the last 6 mo of the study period, quantitative volumetric 3D MRI and ^{1}H-MRS of both hippocampi was added to the MR protocol in 59 children. However, in nine children spectroscopy failed due to movement artifacts. For the present study we looked at the preterm children, who had never received any steroids during the neonatal period (n = 19) and preterm children who received prolonged corticosteroid therapy for BPD (n = 18). Preterm children with antenatal administration of betamethasone only (n = 11) and children receiving dexamethasone before extubation (n = 2) were excluded from this study.

The Medical Ethics Committee of the University Medical Centre Utrecht approved of the study and parental informed consent was obtained.

Cranial ultrasound. Cranial ultrasound (US) in the neonatal period was performed within six hours after admission, at least three times during the first week of life and subsequently once a week until discharge. Intraventricular hemorrhages (IVH) were classified according to Papile (17) and periventricular leukomalacia (PVL) according to De Vries (18). Cranial US findings were classified into three groups: normal when no or minor abnormalities like germinal layer or plexus cysts, subependymal pseudocysts or calcifications (lenticulostriate vasculopathy) as exclusive findings were present (group one), mildly abnormal when an IVH grade I or II, PVL grade I or germinal layer necrosis or a combination of these features were present (group two), severely abnormal when one or more of the following features were present: IVH grade III or IV, cystic-PVL grade II or III, thalamic lesion, focal infarction or hemorrhage at the convexity of the brain (group three).

^{1}H-MRS and MRI. MRI was performed without the use of sedation. Using a mirror placed above their head, the children had eye contact with one of their parents who was present in the MRI unit. Hearing protection was provided using headphones through which they could listen to their favorite music throughout the examination. Median age at follow-up was 8.5 y for the non-treated group (range 8.2–10.5 y) and 8.4 y for the treated group (range 8.2–9.9 y).

The children were all imaged on a 1.5 Tesla Philips Gyroscan ACS-NT system (Philips Medical Systems, Best, The Netherlands). Details of MRI acquisition were described extensively previously (19). Additionally, coronal IR sequences of the hippocampus (TR/TE/TI 2933/13/400 ms, slice thickness 2 mm, no gap) were obtained.

MRI findings were also classified into three groups: normal when no abnormalities were present or when a solitary finding like an arachnoid cyst or a pineal cyst was found (group one), mildly abnormal when mild gliosis, mild ventricular dilatation, an irregular shape of the ventricles, thinning of the corpus callosum or a combination of these features were present (group two), severely abnormal when extensive gliosis or gliosis in combination with marked ventricular dilatation was present (group three).

MRS: The hippocampus was identified on coronal, sagittal and transverse planes and for proton spectroscopy a volume of interest (VOI) of 25 $\times$ 15 $\times$ 10 mm^3 was placed in the hippocampus, avoiding contact with cerebrospinal fluid and white matter (Fig. 1). An echo time of 144 ms was used and after water suppression spectra were obtained with three separate peaks that could be identified as N-acetyl-aspartate (NAA), (phospho)creatine (Cr) and choline (Cho) (Fig. 2). MRUI (Magnetic Resonance User Interface) software (Matlab for Windows, version 4.2c.1′94, The MathWorks inc) was used for curve fitting (20). From the areas under the curve the NAA/(Cho+Cr) ratios were calculated (21).

One investigator (MR), who was blinded to the neonatal data and the outcome of the child, performed all the curve fitting. To estimate the inter-observer variability a random sample of 28 left-sided and 25 right-sided spectra were processed by a second investigator. The mean difference between the two investigators was 1.2%. To estimate the intra-observer variability a random sample of 12 left-sided and 3 right-sided spectra were processed for a second time. The mean difference was 1.1%.

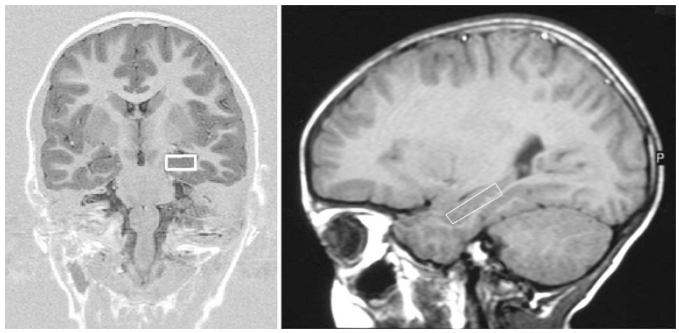

Figure 1. Image of the Volume of Interest (VOI) placed in the hippocampus.

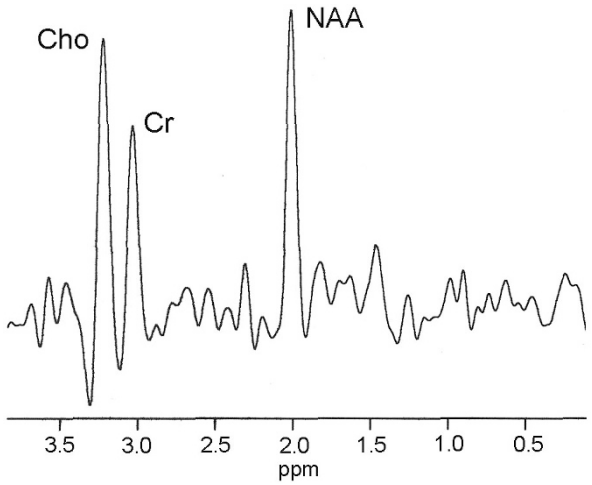

Figure 2. Proton spectroscopy of the hippocampus, echo time 144 ms. NAA: N-acetyl-aspartate, Cr: (phospho)Creatine, Cho: Choline.

15-word Test. The "15-word Test" is a Dutch adaptation of Rey's Auditory Verbal Learning Test (22). It consists of a list of 15 unrelated, concrete nouns. These nouns are presented over five learning trials, with immediate recall after each trial. After a delay interval of 20 min and without further presentation, delayed recall is assessed. The 15-word are: curtain, bird, pencil, glasses, shop, sponge, river, color, flute, plant, coffee, chair, drum, shoe, and air. The number of correctly recalled words after each trial and after the delayed recall provides the scores for the test. For this paper only the delayed recall results after 20 min are used as this correlates with short-term memory.

IQ. All children performed five subtests of the Wechsler Intelligence Scale for Children-Revised (Dutch version): similarities, vocabulary, block design, picture arrangement and digit span. They were supervised by a child psychologist (AFL), who was unaware of the neonatal status of the child. Using the procedures and tables published by Kaufman (23) scaled scores were converted to an estimated IQ score which is within a 95% confidence interval of the full scale IQ score, with a SE of estimate of 6.3. A psychologist experienced in conducting standardized assessments with children performed all neuropsychological examinations

Data analysis. Patient characteristics were tabulated by steroid use as means (SD) or as absolute numbers. Differences in mean patient characteristics were tested using student t-tests or Mann Witney U-tests when appropriate. Treatment group differences in proportional data were tested using χ^2 tests or Fisher's exact test when appropriate. Univariate general linear regression models were used to calculate both unadjusted and adjusted mean values of NAA/(Cho+Cr), 15-word recall score and IQ, respectively to test for treatment group differences. Findings were considered statistically significant at $p < 0.05$. SPSS for Windows, release 11.0.1 was used for all analyses.

RESULTS

Patient characteristics. As expected, mean GA of the steroid treated children was less and mean BW was lower compared with the children who never received steroids (Table 1). The children treated with steroids were also sicker as shown by a significantly higher incidence of mechanical ven-

Table 1. *Patient characteristics*

	No Steroids ($n = 19$)	Steroids ($n = 18$)	p
GA (mean, SD) (weeks)	30.6 (1.7)	27.9 (1.7)	< 0.0001*
BW (mean, SD) (grams)	1379 (392)	1091 (303)	0.017*
Boys/girls	10/9	11/7	0.60
Mechanical ventilation (n)	13	18	0.02*
Surfactant (n)	7	11	0.14
PDA requiring treatment (n)	4	9	0.065**
Inotropes (n)	3	8	0.057**
Cerebral US group 1/2/3 (n)	8/8/3	5/11/1/1m	0.37
MRI group 1/2/3 (n)	11/6/2	8/8/2	0.69
Cerebral Palsy (n)	1	2	0.60
Handedness l/r (n)	4/15	1/17	0.34

GA, gestational age; BW, birth weight; PDA, patent ductus arteriosus; US, ultrasound; MRI, magnetic resonance imaging; 1m, one ultrasound missing; handedness l, left-handed; handedness r, right-handed.

Group one, normal findings; group two, minor lesions; group three, major lesions (see methods section).

* significant $p < 0.05$, ** almost significant.

tilation. The difference in need for inotropes and presence of a significant patent ductus arteriosus almost reached significance. Importantly, there were no differences in neonatal cranial US and school age MRI lesions, nor in incidence of cerebral palsy between the two groups.

The mothers of six of the 18 steroid children were treated with a complete course of betamethasone (2×5.7 mg i.m., repeated 24 h later) to accelerate fetal lung maturation. All 18 steroid children received hydrocortisone for treatment of BPD. Generally, hydrocortisone was started when the postnatal age was at least >1 wk and the child was ventilatory dependent with increasing oxygen requirements, which could not be explained by infection or a haemodynamic significant patent ductus arteriosus. Hydrocortisone was started at a median age of 18 d with an inter quartile range of 13.5 d. Neonatal hydrocortisone treatment consisted of a starting dose of 5 mg/kg/d, divided into four doses for one week, followed by a tapering course of three, two and one dose(s) each for 5 d (total of 3.75, 2.5 and 1.25 mg/kg/d, respectively). In the absence of respiratory improvement or when respiratory deterioration occurred after reduction of the dose, steroid treatment was either prolonged or repeated. Median length of administration of hydrocortisone was 28 d with an inter quartile range of 11 d. In 17 of the 18 steroid treated patients we were able to calculate the cumulative dose/kg mean body weight, (*i.e.*, weight at the start of treatment plus weight at the end of treatment divided by 2). The median cumulative hydrocortisone dose was 72.2 mg/kg.

^{1}H-MRS. In 13 of the 37 children unilateral spectroscopy measurement (four left-sided and nine right-sided) was obtained and in 24 children bilateral spectroscopy measurements. There were no significant differences between left-sided and right-sided ratios, so a decision was made to take the mean of the left and right NAA/(Cho+Cr) in children with bilateral measurements.

Mean NAA/(Cho+Cr) ratio was not significantly different in the hydrocortisone group compared with the non-treated group (0.67 vs. 0.63), as shown in Table 2. Adjustment for gender did not influence the difference in the ratio. There was

Table 2. *Mean NAA/(Cho+Cr) ratio related to steroids during perinatal period*

	No steroids ($n = 19$)	Steroids ($n = 18$)	p-value
NAA/(Cho+Cr) ratio(SEM)	0.63 (0.02)	0.67 (0.02)	0.20
NAA/(Cho+Cr) ratioadj (SEM)	0.63 (0.02)	0.67 (0.02)	0.19

SEM, standard error of mean; adj, adjusted for gender.

no relation between hydrocortisone dose and MRS findings (linear regression coefficient $-4.88*10^{-4}$ mg/kg, $p = 0.481$). In a linear regression model with NAA/(Cho+Cr) as dependent and an interaction term, multiplying variables gender and treatment, together with the main effects as independent variables, there was no interaction between gender and treatment (regression coefficient $-4.1*10^{-4}$, $p = 0.995$). Obviously, children received hydrocortisone on the basis of a clinical indication as reflected in differences in GA and BW (Table 1). In a further attempt to distinguish effects of hydrocortisone from effects of these differences in clinical parameters we did an analysis with adjustment for GA. This analysis showed still no significant differences in NAA/(Cho+Cr) between the hydrocortisone and nonsteroid groups ($-6.55*10^{-2}$, $p = 0.09$).

15-word recall. The hydrocortisone group scored in the same range on the 15-word memory test (delayed recall after 20 min) in comparison with the nonsteroid group (Table 3). Adjustment for gender, NAA/(Cho+Cr) ratio and IQ did not change the outcome. Using linear regression no association between NAA/(Cho+Cr) ratio and 15-word recall was found for the whole group ($p = 0.11$), nor for the treated group ($p = 0.51$) nor for the non-treated group ($p = 0.13$). There was no relation between dose and memory recall findings (linear regression coefficient $-1.83*10^{-3}$ mg/kg, $p = 0.884$). In a linear regression model with memory recall findings as dependent and an interaction term, multiplying variables gender and treatment, together with the main effects as independent variables, there was no interaction between gender and treatment (regression coefficient 0.63, $p = 0.654$). In a further attempt to distinguish effects of hydrocortisone from effects of these differences we did an analysis with adjustment for GA. This analysis showed no significant group differences in memory recall (-1.131, $p = 0.22$).

IQ. Mean IQ was almost the same in the non-treated group and in the treated group (Table 3). Again using linear regression, there was no association between NAA/(Cho+Cr) ratio

Table 3. *Mean 15-word Recall and IQ in preterm infants at school age with and without prolonged use of steroids*

	No steroids ($n = 19$)	Steroids ($n = 18$)	p-value
Recall (SEM)	6.21 (0.52)	6.61 (0.47)	0.57
$\text{Recall}_{\text{adj I}}$ (SEM)	6.16 (0.47)	6.66 (0.49)	0.47
$\text{Recall}_{\text{adj II}}$ (SEM)	6.32 (0.48)	6.49 (0.50)	0.81
$\text{Recall}_{\text{adj III}}$ (SEM)	6.25 (0.48)	6.57 (0.49)	0.64
IQ (SEM)	95 (2)	97 (3)	0.67

SEM, standard error of mean; adj $_{\text{I}}$, adjusted for gender; adj $_{\text{II}}$, adjusted for NAA/(Cho+Cr) ratio; adj $_{\text{III}}$, adjusted for IQ.

and IQ ($p = 0.29$). When analyzed with adjustment for GA, we found no significant group differences in IQ (−4.281, $p = 0.38$).

DISCUSSION

In this study, no differences were found in ^{1}H-MRS of the hippocampus, short-term memory and IQ in preterm born children with or without prolonged administration of hydrocortisone for BPD during the neonatal period. Previously, we reported no difference in total intracranial volume, cerebral gray matter, white matter, cerebrospinal fluid volume and hippocampal volume between the treated and the non-treated group (4).

Before interpreting the current data, some matters need to be taken into account. In measuring NAA levels it is important to have a homogenous age group as NAA levels are dependent on age (24,25). Median age at follow-up was comparable for both groups (8.4 in the treated and 8.5 y in the non-treated group) and all children were tested before puberty had started. It is equally important to have a VOI which is definitely located in the hippocampus. In the present study every effort was made to avoid cerebral white matter and cerebral spinal fluid, as these structures will influence the NAA/(Cho+Cr) ratio. The location of the VOI was established in three MRI planes: coronal, transverse and sagittal. Moreover, the size of the volume (25x15x10 mm = 3.75 mL) was chosen to really fit into the hippocampus. Inter and intra observer differences were very low, indicating accurate processing of the raw spectroscopy data.

We cannot exclude the possibility that there are effects of hydrocortisone that, given our relatively small group sizes, could just not be statistically detected. We did an observational study on the effects of hydrocortisone which does not rule out the influence of confounding variables. One group apparently had a clinical indication for hydrocortisone therapy whereas the other had not and therefore we have taken into account important group differences. Children receiving hydrocortisone had a lower GA and were smaller. We cannot be certain about whether the apparent absence of effects of hydrocortisone is due to real absence of effects or due to group differences in GA or BW. Our analysis adjusted for GA showed larger, but not significant effects of hydrocortisone for both NAA/(Cho+Cr) ratio, recall and IQ.

The hippocampus is particularly susceptible to injury in preterm infants. Many studies have demonstrated loss of hippocampal volume in preterm born children (5,6). Animal studies, mainly in rodents and primates, suggest that prolonged exposure to glucocorticoids or to stress can accelerate hippocampal neuronal loss during aging, as well as increase the severity of neurologic insults to the hippocampus (7,8,26). Abnormalities of the hippocampus were found in two-thirds of autopsies in preterm infants (27).

To our best knowledge, there are no other studies addressing the effect of neonatal corticosteroid treatment on later hippocampal metabolism in humans. Although we found no difference in hippocampal volume between hydrocortisone and untreated children (4), this would not necessarily imply that the NAA/(Cho+Cr) ratios would be the same in the two groups. In the absence of volume changes, anatomical structure (and thus metabolic rates) of the hippocampus can still be different between the two groups.

NAA is a free amino acid, localized almost uniquely in neuronal tissue, neurons and axons of the adult brain. During development it is also found in oligodendrocyte-type-2 astrocyte progenitor cells and in immature oligodendrocytes (14,15), Bhakoo and Pearce demonstrated in cell culture that mature oligodendrocytes can also express NAA *in vitro* (16).

From the loss of hippocampal volume due to accelerated neuronal loss found in animal studies after exposure to glucocorticoids, one might expect lower NAA/(Cho+Cr) ratios in the children treated with corticosteroids. The glucocorticoid used in animal studies was always dexamethasone. Dexamethasone is a synthetic glucocorticoid, which has a 25 times higher anti-inflammatory power than hydrocortisone. The biologic half-life time of hydrocortisone is 8–12 h in contrast to the 36–72 h of dexamethasone. Our starting dose of 5 mg/kg/d of hydrocortisone is equivalent to about one-third of the glucocorticoid activity of a dexamethasone dose of 0.5 mg/kg/d given in most published studies. From the fact that we found no difference in NAA/(Cho+Cr) ratio between the treated and non-treated group we conclude that hydrocortisone in the doses used did not affect hippocampal metabolism as measured with ^{1}H-MRS. This is in line with the lack of volumetric differences we found between the treated and untreated group.

Adult patients receiving chronic corticosteroid therapy for asthma or rheumatic diseases (prednisone $\geq$ 10 mg per day for $\geq$ 6 mo) were found to have smaller hippocampal volumes, lower NAA/ Cho and NAA/(Cho+Cr) ratios and lower scores on the Rey Auditory Verbal Learning Test compared with controls (28). Although less potent than dexamethasone, prednisone is still four times stronger than hydrocortisone and these patients received the medication for a much longer period than our BPD neonates.

Many reports on the adverse effects on neurodevelopmental outcome of neonatal dexamethasone treatment have emerged over the last years and there is an ongoing debate about optimal dose, timing, duration and type of glucocorticoid (11,13). Children with BPD, who were treated with dexamethasone, performed less well on developmental outcome tests at the age of eight years than their nonsteroid BPD counterparts, although no information about dose and duration of the steroids was provided (29). A recent study with early dexamethasone treatment for BPD confirmed these observations (12). However, Gross *et al.* (30) reported this year 22 survivors of a very high risk population in which a 42-d course of dexamethasone beginning at 2 wk of age was associated with improved long-term neurodevelopmental outcome at fifteen years compared with the 18-d dexamethasone and the placebo group (mean IQ 85, 69 and 73 respectively.). These children were younger and smaller than the children in our study. In a retrospective study, Van der Heide *et al.* (31) compared hydrocortisone or dexamethasone treated preterm children with non-treated children. Improvement in respiratory status was comparable after dexamethasone or hydrocortisone ad-

ministration. However, significant differences in short- and long-term effects between hydrocortisone vs. dexamethasone treated children were found. Neonatal dexamethasone treated children needed special school education significantly more often than controls, whereas hydrocortisone treated children had the same neurodevelopmental outcome as controls. In our unit, historically only hydrocortisone is used for treatment of BPD, so no conclusions can be drawn as to whether hydrocortisone does influence the metabolism of the hippocampus less than dexamethasone. Still, in our opinion, it is an important finding that we were not able to show differences in NAA/(Cho+Cr) ratios of the hippocampus between the hydrocortisone and the non-treated group.

Isaacs *et al.* were the first to draw attention to the relation of reduced hippocampal volumes and deficits in everyday memory in a small group of children of very low birth weight (2). Abernethy *et al.* (32) showed in a larger group of 105 preterm born children that hippocampal volume was the best predictor of performance in tests of everyday memory in a comparable cohort as in this study. No correlation between IQ and hippocampal size was found. Studies in adult rats indicate decreased spatial learning and working memory when treated with dexamethasone in the neonatal period (33). Memory is an extremely complicated cognitive domain with many facets and the use of only one test has its limits in drawing conclusions. Still, in our study, the hydrocortisone treated children performed the same on the memory test and had the same IQ as the non-treated group. This is another indication that hydrocortisone might be an alternative for dexamethasone in the treatment of neonatal chronic lung disease, especially as it seems to be just as powerful in reducing oxygen dependency (31).

We could not show that preterm children treated with hydrocortisone for BPD in the described dose have different hippocampal NAA/(Cho+Cr) ratios at school age than preterm born children who never had any steroids during the neonatal period. Moreover, no difference between the treated and non-treated group was found for IQ and 15-word memory test. Our study suggests that hydrocortisone might be used in neonates with BPD without major negative side effects on hippocampal development and memory as tested with the Rey's Auditory Verbal Learning Test. These findings have potentially important implications for clinical practice of treating neonates with chronic lung disease.

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