Brain imaging and neurodevelopmental outcome at school age in preterm-born infants: Effects of neonatal hydrocortisone treatment

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Beeldvorming van de hersenen en neurologische uitkomst
op de schoolleeftijd bij te vroeg geboren kinderen:
Effecten van neonatale hydrocortison behandeling
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. W.H. Gispen, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op vrijdag 10 november 2006 des middags te 12.45 uur

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Karssina Jantina Rademaker
geboren op 6 februari 1957 te Veendam

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	Prof.dr. D.E. Grobbee
Co-promotoren:	Dr. C.S.P.M. Uiterwaal
	Dr. F. Groenendaal

"Life can only be understood backwards,
but it must be lived forwards"
Søren Kierkegaard (1813-1855)

"Parents hold their children's hands a while,
and their hearts forever"
(proverb)

Aan mijn ouders

Voor Ab, Lennart, Jur en Sander

Contents

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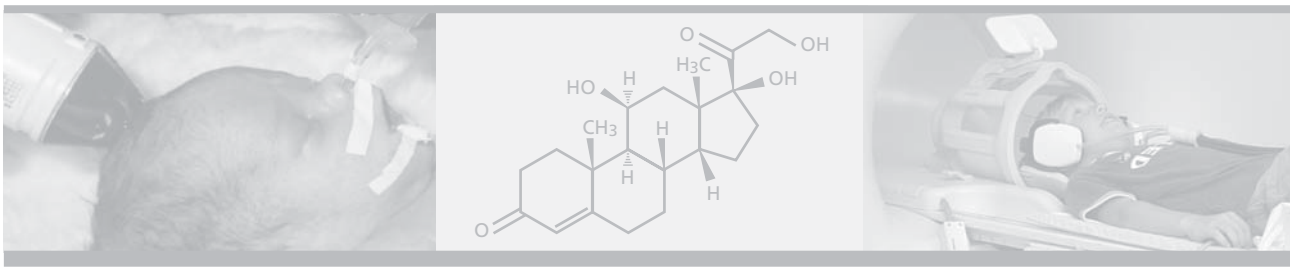
Introduction and outline of the thesis



Introduction

Preterm delivery, defined as delivery before 37 completed weeks of gestation, occurs in 7 to10% of all pregnancies in western countries and is the most important cause of infant morbidity and mortality. In the nineteen seventies, the mortality of children with respiratory distress syndrome with a mean gestational age of 32 weeks was as high as 29%.[1] The introduction of prenatal steroids, postnatal surfactant treatment, new ventilatory strategies, aggressive management of patent ductus arteriosus, improved total parental nutrition, intravenous central lines, designed specially for extremely low birth weight infants, new surgical techniques, and other treatment modalities have resulted in major improvements in the clinical course and outcome of preterm-born infants over the past four decades.[2-6]

Although the increased survival of extremely low birth weight infants is a major achievement of contemporary neonatal care, just keeping these children alive should not be the only or ultimate goal in neonatal medicine. Long-term neurodevelopmental outcome of vulnerable high-risk preterm infants, and their quality of life is a matter of serious concern. Several publications have shown that the impact of preterm birth can extend far into childhood and real progress only occurs when morbidity and disabilities of NICU graduates also decrease.

Preterm-born infants need special education more often than their term-born peers (reflecting cognitive deficits), have an increased incidence of motor problems (cerebral palsy but also clumsiness) and behavioral disturbances are well recognized.[7-11]

Neonatologists become more and more aware of these facts, and great effort is made to predict long-term sequelae already during the neonatal intensive care period. The earlier outcome is predicted, the sooner appropriate developmental intervention like physical therapy or learning aids can be offered. In some cases, early prognosis of a disastrous outcome may even lead to withdrawal of intensive care treatment.

Severe motor problems like cerebral palsy (CP) can be predicted in the majority of the cases. In most NICUs, preterm-born infants are subjected to cranial ultrasound (US) examinations as part of routine care. Although there is some debate about the predictive value and accuracy of cranial ultrasonography,[12-15] we have recently shown that seventy-nine percent of our CP cases had major US abnormalities.[16] Cystic periventricular leukomalacia was the most predictive US marker for CP, but sequential scans with a 7.5-MHz transducer are required.

Magnetic resonance imaging (MRI) is a more sophisticated technique to detect brain lesions. However, in contrast to cranial US examination, which is performed at the

bedside, transport to an MRI unit and sedation is necessary. We wondered whether an MRI, obtained at an age when myelination is more or less completed (2 years) would be better in predicting neurocognitive outcome and motor performance at school age than neonatal cranial US. Performing MRI routinely in all very low birth weight infants would be expensive and more of a burden to the child who might even need general anesthesia, as motion artifacts can be a problem at this age. In this follow-up study, preterm-born children had an MRI of their brain at the age of 7 to10, because at that age, with support from their parents who were present in the MRI unit, and while listening to their own favorite music, we could avoid sedation. We speculated, that the aspect of the brain (ventricular dimensions, gliosis, parenchymal lesions, pattern of myelination) would not have changed between the age of 2 and 10 years, except when rare incidents like trauma, meningitis/encephalitis or brain tumors had occurred.

Cognitive deficits are often more difficult to predict than motor problems. It is well recognized that preterm infants with intrauterine growth retardation are more at risk to develop learning disabilities. The first studies, using volumetric analysis of the different brain structures in preterm-born infants at term age, are now becoming available. Infants with significantly reduced cortical gray matter and deep nuclear gray matter volumes and increased cerebrospinal fluid volumes exhibited moderate to severe neurodevelopmental disability at 1 year of age. The major predictors of altered cerebral volumes were gestational age at birth and the presence of cerebral white matter injury.[17;18] However, preterm-born infants appropriate for gestational age and without brain injury, showed no decreased cortical gray matter volumes at term compared with term-born infants.[18]

The second part of the thesis focuses on long-term neurodevelopmental outcome following neonatal hydrocortisone treatment for chronic lung disease (bronchopulmonary dysplasia). In contrast to most NICUs all over the world, the Wilhelmina Children's Hospital has always used the steroid hydrocortisone instead of the much stronger dexamethasone, to facilitate extubation of ventilator-dependent preterm infants. In the context of reported adverse long-term outcome after dexamethasone administration,[19-22] an alternative steroid with less negative long-term effects would be welcomed.
Because of this hydrocortisone prescription policy of the neonatologists of the Wilhelmina Children's Hospital, and because none of the infants described in this part of the thesis were also treated with dexamethasone, the studied cohort of 62 hydrocortisone-treated and 164 non-treated preterm infants with a gestational age ≤ 32 weeks and/or a birth weight ≤ 1500 grams provided a unique opportunity to assess the impact of hydrocortisone treatment on structural and functional brain development.

Outcome measures

Standardized tests were used to evaluate long-term outcome at school age in the children described in this thesis. For assessment of *neurocognitive performance*, five subtests of the Wechsler Intelligence Scales for Children-Revised (Dutch version) were obtained: similarities, vocabulary, block design, picture arrangement and digit span. Using the procedures and tables published by Kaufman,[23] scaled scores were converted to an estimated IQ score, based on the subtests scores for vocabulary and block design, which is within a 95% confidence interval of the full scale IQ score, with a standard error of estimate of 6.3.

The children were also examined with the VMI Developmental Test of Visual-Motor Integration.[24] VMI raw scores were converted to VMI standard scores with a mean of 100, based on the 4th revised edition norms.

Memory was tested with the 15-word Test: a Dutch adaptation of Rey's Auditory Verbal Learning Test.[25] It consists of a list of 15 unrelated, concrete nouns, which are presented over five learning trials, with immediate recall after each trial. After a delay interval of 20 minutes and without further presentation, delayed recall is assessed. The number of correctly recalled words after each trial and after the delayed recall provides the scores for the test.

Each child was examined for the presence of cerebral palsy. If present, CP was classified according to the criteria of Hagberg.[26] The Movement Assessment Battery for Children (Movement ABC) derived from Sugden and Henderson, age band 2 for 7 and 8 years and rarely age band 3 for 9 and 10 years, was used to further assess *motor performance*.[27] The test contains three domains: manual dexterity (placing pegs, threading a lace, drawing a flower trail), ball skills (one-hand bounce and catch, throwing a beanbag into a box) and static and dynamic balance (stork balance, jumping in squares and heel-to-toe walking). Each item is scored from 0 (best score) to 5 (poorest score) so the subscore for manual dexterity varies between 0 and 15, for ball skills between 0 and 10 and for balance between 0 and 15. The total impairment score (TIS) is the sum of the three subscores and varies therefore between 0 (best score) and 40 (poorest score). The raw subscale scores are converted to percentile scores and classified as follows: < p5: definitely abnormal, between p5 and p15: borderline, and > p15: normal motor performance.

Brain imaging was obtained with MRI without sedation on a 1.5-Tesla Philips Gyroscan ACS-NT system (Philips Medical Systems, Best, The Netherlands). 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. Images were

acquired with a 256 x 256 matrix, a field of view of 230 mm and included a sagittal T_1 survey (TR/TE 512/15 ms, slice thickness 4.0 mm, interslice gap 0.6 mm), transverse dual turbo spin echo (TSE) images (first echo TR/TE 4000/17 ms; second echo TR/TE 4000/110 ms; slice thickness 5.0 mm, interslice gap 1.0 mm), transverse T_1 inversion recovery (IR) TSE images (TR/TE/TI 2346/10/300 ms; slice thickness 5.0 mm, interslice gap 1.0 mm) and coronal T_2 fluid attenuated inversion recovery (FLAIR) images (TR/TE/TI 7262/100/2000 ms; slice thickness 5.0 mm, interslice gap 1.0 mm). In a subset of the children, quantitative volumetric three-dimensional MRI with advanced image-processing and proton spectroscopy (^{1}H-MRS) of both hippocampi was added to the MR protocol.

Aims of the thesis

1. To investigate the relation between neonatal cranial ultrasound and later (school age) conventional brain magnetic resonance imaging (MRI).
2. To determine which imaging technique (cranial ultrasound versus conventional MRI after completion of myelination) best predicts neurodevelopmental outcome at school age.
3. To study the impact of postnatal hydrocortisone treatment for bronchopulmonary dysplasia in preterm-born infants on structural and functional brain development at school age.

Outline of the thesis

Chapter 1 presents the aims and outline of the thesis. In *Chapter 2* the correlation between neonatal cranial ultrasound and school age MRI and neurodevelopmental outcome is investigated. *Chapter 3* determines the relation between the size of the corpus callosum (measured as frontal, middle, posterior and total area on midsagittal MRI) and motor performance at school age.

The next four chapters deal with the impact of postnatal hydrocortisone treatment on brain development and neurodevelopmental outcome. In *Chapter 4* the effects of hydrocortisone treatment on neurocognitive and motor performance as well as on brain MRI is evaluated at school age in a cohort of 226 preterm-born infants. *Chapter 5* describes in a subset of this group the long-term effects of prematurity itself and of neonatal hydrocortisone treatment on structural and functional brain development using three-dimensional MRI with advanced image-processing and neurocognitive assessment.

In *Chapter 6* the impact of neonatal hydrocortisone treatment on the metabolism of the hippocampus, as measured with proton magnetic resonance spectroscopy (^{1}H-MRS), is presented. The relation between hippocampal metabolism and short-term memory and neurodevelopmental outcome is investigated. *Chapter 7* gives an overview of the literature on the two main clinical indications for postnatal hydrocortisone administration in preterm-born infants and the available long-term neurodevelopmental outcome data following this treatment.

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2

Neonatal cranial ultrasound versus MRI and neurodevelopmental outcome at school age in children born preterm

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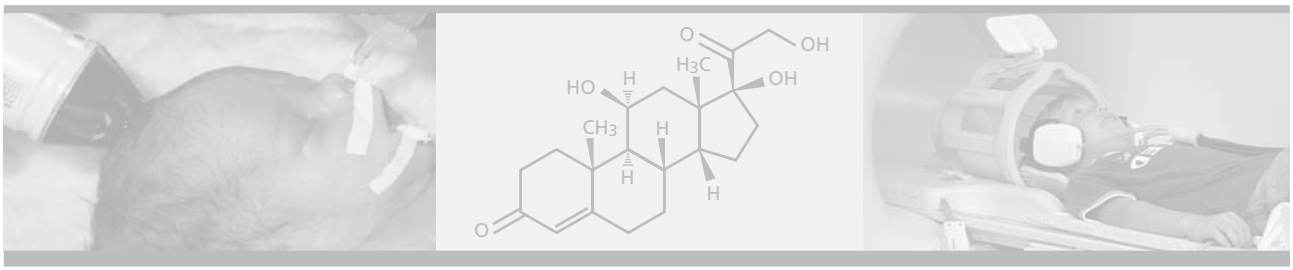

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Abstract

Aim: To examine the correlation between neonatal cranial ultrasound and school age magnetic resonance imaging (MRI) and neurodevelopmental outcome.

Methods: In a prospective two-year cohort study, 221 children (gestational age ≤ 32 weeks and/or birth weight ≤ 1500 g) participated at a median age of 8.1 years (inclusion percentage 78%). Conventional MRI, IQ (subtests of the WISC-R) and motor performance (Movement Assessment Battery for Children) at school age were primary outcome measurements.

Results: Overall, there was poor correspondence between ultrasound group classifications and MRI group classifications, except for the severe group (over 70% agreement). There was only a 1% chance of the children with a normal cranial ultrasound having a major lesion on MRI. Mean IQ (standard deviation) was significantly lower in children with major ultrasound or MRI lesions, but was also lower in children with minor lesions on MRI compared to children with a normal MRI (91 ± 16, 100 ± 13, 104 ± 13 for major lesions, minor lesions, and normal MRI, respectively). Median total impairment score (TIS) was significantly higher in children with major lesions on ultrasound or MRI as well as in children with minor lesions on MRI (TIS 4.0 and 6.25 for normal and minor lesions on MRI, respectively; $p < 0.0001$).

Conclusions: A normal neonatal cranial ultrasound excluded a severe lesion on MRI in 99% of cases. MRI correlated more strongly with mean IQ and median TIS than ultrasound. Subtle white matter lesions are better detected with MRI which could explain the stronger correlation of MRI with IQ and motor performance.

Introduction

Neonatal cranial ultrasound (US) remains the method of choice to detect brain injury in high-risk preterm infants on Neonatal Intensive Care Units (NICU). It is a non-invasive, inexpensive bedside tool and examinations can be repeated as often as necessary without major disturbance of vulnerable infants. The anterior and posterior fontanelles form excellent acoustic windows to examine the deep midline and periventricular regions of the brain.[1] We recently demonstrated that cerebral palsy (CP) can be accurately predicted with US.[2] However, cranial US is not very suitable for investigating cortical regions or structures in the posterior fossa.[3]

Over the last decades, magnetic resonance imaging (MRI) has increasingly become available. It provides high resolution, non-invasive imaging of the brain and all areas can be easily visualized.[4] However, it requires transportation of sometimes critically ill children to an MRI unit, is time consuming, and is not available on a routine basis.

Good correlation between US and neonatal MRI was found for hemorrhages and ventriculomegaly.[5] Agreement between US and MRI was also good for cystic periventricular leukomalacia (PVL), but for more subtle white matter injury MRI proved to be far more sensitive.[6-10]

The aim of the present study was to compare neonatal cranial US with school age MRI and to investigate whether a normal US excludes major lesions on future MRI. We also investigated which imaging technique correlated best with two parameters of neurodevelopmental outcome.

Patients and methods

The children described in this paper are part of a cohort of patients consecutively admitted soon after birth to the NICU of the Wilhelmina Children's Hospital, a tertiary referral hospital. All 375 children, born between March 1, 1991, and March 1, 1993, with a gestational age (GA) of ≤ 32 weeks (range 25.0-33.0) and/or a birth weight (BW) of ≤ 1500 g were enrolled in a long-term follow-up study. Sixty-four children (17%) died and 28 (7.5%) were excluded because of (multiple) congenital abnormalities and/or chromosomal disorders. At the age of 7 or 8, the children were invited to the hospital to undergo several tests (WISC-R,[11] Movement Assessment Battery for Children (ABC),[12] and brain MRI). Of the remaining 283 children, 22 (7.8%) could not be traced and the parents of 25 (8.8%) refused participation. As a result, 236 children (83.4%) took part in the study.

Neonatal cranial US results were available in 234 of the 236 children. MRI could not be

completed because of anxiety in 10 children. Children with a congenital abnormality (n=2) on US were excluded as well as one child who developed an unknown neuromuscular disorder. This resulted in a total study population of 221 children (78% of the original cohort). Mean GA of the children was 29.4 weeks (standard deviation (SD) 2.0) and mean BW 1197 g (SD 315). In this group 54.8% were male and 45.2% female.
The Medical Ethics Committee of the University Medical Center Utrecht approved the study and parental informed consent was obtained.

Cranial US

Cranial US was performed within six hours after admission, at least three times during the first week, subsequently once a week until discharge, and again at term age. A standardized protocol of acquiring images (coronal, midsagittal and parasagittal planes) was used. Infants were examined with an ATL UM-4 mechanical sector scanner (Philips Medical Systems, Best, The Netherlands) using the 7.5 MHz transducer to ensure the best possible resolution.
All US scans were analyzed by one neonatologist (LDV), who at that time could not be aware of later MRI findings and outcome. US scans were classified according to the most severe lesions seen at any time.
Intraventricular hemorrhages (IVH) were graded according to Papile [13] and PVL according to De Vries.[14] Neonatal US scans were also analyzed for the presence of ventricular dilatation (VD; post hemorrhagic or ex vacuo), calcifications, germinal layer necrosis, germinal layer/choroid plexus cysts, or subependymal pseudocysts.
Cranial US findings were classified into three groups: normal when no or minor abnormalities, such as germinal layer/plexus cysts, subependymal pseudocysts or calcifications as exclusive findings were present (group 1); mildly abnormal when an IVH grade I/II, PVL I, or germinal layer necrosis, or a combination of these features, was present (group 2); and severely abnormal when one or more of the following features were present: IVH grade III/IV, cystic-PVL II/III, thalamic lesion, focal infarction, or convexity hemorrhage (group 3).
VD as a single feature was assigned to the mildly abnormal group. VD following a hemorrhage (PHVD) with need for therapeutic intervention was listed in the severely abnormal group.

MRI

MRI was performed without sedation on a 1.5 Tesla Philips Gyroscan ACS-NT system (Philips Medical Systems, Best, The Netherlands). Images were acquired with a 256 x 256 matrix and a field of view of 230 mm and included a sagittal T_1 survey (TR/TE 512/15 ms;

slice thickness 4.0 mm, interslice gap 0.6 mm), transverse dual turbo spin echo (TSE) images (first echo TR/TE 4000/17 ms; second echo TR/TE 4000/110 ms; slice thickness 5.0 mm, interslice gap 1.0 mm), transverse T_1 inversion recovery (IR) TSE images (TR/TE/TI 2346/10/300 ms; slice thickness 5.0 mm, interslice gap 1.0 mm) and coronal T_2 fluid attenuated inversion recovery (FLAIR) images (TR/TE/TI 7262/100/2000 ms; slice thickness 5.0 mm, interslice gap 1.0 mm).

All MRI scans were assessed by one radiologist (FJAB), blinded to neonatal US findings and outcome. MRI images were scored for the presence of periventricular gliosis on coronal FLAIR images, VD, corpus callosum thinning, abnormalities in the retrochiasmatic region of the visual system, thalamic abnormalities, and cerebellar and cortical atrophy. Gliosis was divided into two groups: mild gliosis when no more than five scattered distinct, small (2mm) areas of hyperintensity were present and extensive gliosis when larger or more than five areas of hyperintensity were present.

MRI findings were also classified into three groups: normal when no abnormalities were present or when a solitary finding such as an arachnoid cyst was found (group1); mildly abnormal when mild gliosis, mild VD, irregularly shaped ventricles, corpus callosum thinning or a combination of these was present (group 2); and severely abnormal when extensive gliosis or gliosis combined with marked VD was present (group 3). Thalamic lesions, an abnormal retrochiasmatic region of the visual system, and cerebellar and cortical atrophy were also classified as major abnormalities.

IQ

All children performed the following five subtests of the WISC-R (Dutch version): similarities, vocabulary, block design, picture arrangement, and digit span. They were supervised by a psychologist (AFL), unaware of their neonatal status. Using the procedures and tables published by Kaufman,[11] scaled scores were converted to an estimated IQ score which is within a 95% confidence interval of the full-scale IQ score, with a standard error of estimate of 6.3.

Motor function

Motor performance was assessed by a physiotherapist (ICVH), blinded to MRI outcome. The Movement ABC contains three domains: manual dexterity (three items), ball skills (two items) and balance (three items). Each item is scored from 0 (best score) to 5 (poorest score). The total impairment score (TIS) is the sum of the subscores. Raw scores are converted to percentile scores and classified as follows: < p5 (definitely abnormal), between p5 and p15 (borderline), and > p15 (normal).

The presence of cerebral palsy (CP) was classified according to the Hagberg criteria.[15]

Table 1: Neonatal cranial US findings in a cohort of 221 preterm infants

Normal	n (%)	92 (41.6%)
IVH	n (%)	79 (35.7%) IVH grade I: 11 (13.9%) IVH grade II: 48 (60.8%) IVH grade III: 9 (11.4%) IVH grade IV: 11 (13.9%) PHVD: 18
PVL	n (%)	41 (18.6%) PVL grade I: 32 (78.0%) PVL grade II: 4 (9.8%) PVL grade III: 5 (12.2%)
Other	n (%)	26 (11.8%) convexity hemorrhage: 2 infarction: 2 thalamus lesion: 2 calcifications: 3 pseudocysts: 3 ventricular dilatation: 9 GL cyst: 1 GL necrosis: 1 plexus cyst: 3

Legend: IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; PHVD, post hemorrhagic ventricular dilatation; GL, germinal layer. It should be noted that 92 infants had a completely normal US; the other numbers do not add up to 129 due to multiple findings in some of the children

Data Analysis

Descriptives of specific findings on cranial US and MRI were calculated. For each US group, predictive values and corresponding 95% confidence intervals were calculated for inclusion in each of the three MRI groups. Mean IQ and median Movement ABC TIS were tested between US and MRI groups 1 and 2 and between groups 1 and 3 using *t*-tests and Mann Whitney *U*-tests, respectively. Similar group comparisons were made for proportions with low versus normal IQ and for proportions in percentiles of Movement ABC using chi-square tests. SPSS (version 10.1; SPSS, Chicago, Il, USA) was used for all analyses.

Results

US findings

Neonatal cranial US findings are listed in Table 1. Ninety-six infants were assigned to group 1 (normal US), 89 to group 2 (mildly abnormal US), and 36 to group 3 (severely abnormal US).

MRI findings

MRI findings at a median age of 8.1 years are listed in Table 2. Eighty-seven children were assigned to group 1 (normal MRI), 104 to group 2 (mildly abnormal MRI), and 30 to group 3 (severely abnormal MRI).

Table 2: MRI findings at school age in a cohort of 221 preterm infants

Normal	n (%)	83	(37.6%)
Gliosis	n (%)	64	(29.0%)
			mild gliosis: 38 (59.4%)
			extensive gliosis: 26 (40.6%)
Ventricular dilatation	n (%)	81	(37.7%)
			global: 65 (80.2%)
			focal: 16 (19.8%)
Abnormal shape corpus callosum	n (%)	56	(25.3%)
			generalized thinning: 19 (33.9%)
			focal thinning: 37 (66.1%)
Abnormal retrochiasmatic region of the visual system	n (%)	8	(3.6%)
Thalamus abnormalities	n (%)	6	(2.7%)
Cerebellar atrophy	n (%)	3	(1.4%)
Cortical atrophy	n (%)	1	(0.5%)
Other	n (%)	9	(4.1%)
			pineal cyst: 2
			arachnoidal cyst: 3
			small pituitary gland: 1
			extra cerebral CSF cyst: 1
			lesion mesencephalon: 1

Legend: CSF, cerebrospinal fluid. It should be noted that 83 children had a completely normal MRI; the other numbers do not add up to 138 due to multiple findings in some of the children

Table 3: Predictive values (95% CI) of ultrasound results for findings on MRI

US / MRI	MRI group 1 (n=87)	MRI group 2 (n=104)	MRI group 3 (n=30)
US group 1 (n=96)	45 (46.9; 36.6-57.3)	50 (52.1; 41.6-62.4)	1 (1.0; 0.0-5.7)
US group 2 (n=89)	40 (44.9; 34.4-55.9)	46 (51.7; 40.8-62.4)	3 (3,4; 0.7-9.5)
US group 3 (n=36)	2 (5.6; 0.7-18.7)	8 (22.2; 10.1-39.2)	26 (72.2; 54.8-85.8)

Association between US and MRI

Table 3 shows the predictive values of US group classifications for MRI group classifications. Overall, there was poor correspondence between US and MRI. Those in US groups 1 and 2 had an approximately 50% chance of being in the corresponding MRI groups. Despite poor overall correspondence, over 70% of those with major lesions on US had major lesions on MRI. There was only a 1% chance among those with a normal US of having a major lesion on MRI.

IQ

Mean IQ overall was 100 (Table 4). Mean IQ in US group 1 was marginally higher than in group 2 but substantially and significantly higher than in group 3. Mean IQ in MRI group 1 was marginally but significantly higher than in group 2, however substantially and significantly higher compared to group 3.

Table 4: IQ at school age related to US and MRI groups

US	group 1 (n=96)	group 2 (n=89)	P for difference 1 - 2	group 3 (n=36)	P for difference 1 - 3	all (n=221)
IQ mean (sd)	102 (13)	101 (13)		94 (18)		100 (14)
min-max	74 -135	65 -129	0.39	56 -138	0.005	56 -138
IQ > 85 (n)	85	77		23		185
IQ ≤ 85 (n)	11	12	0.68	13	0.001	36
MRI	**group 1 (n=87)**	**group 2 (n=104)**	**P for difference 1 - 2**	**group 3 (n=30)**	**P for difference 1 - 3**	**all (n=221)**
IQ mean (sd)	104 (13)	100 (13)		91 (16)		100 (14)
min-max	77 -138	65 -135	0.026	56 -126	< 0.0001	56 -138
IQ > 85 (n)	80	88		17		185
IQ ≤ 85 (n)	7	16	0.12	13	< 0.0001	36

Table 5: Movement ABC at school age related to US and MRI groups

US	group 1 (n=96)	group 2 (n=89)	P for difference 1 - 2	group 3 (n=36)	P for difference 1 - 3	all (n=221)
TIS median	5.25	5.0		15.75		5.5
min-max	0-36.5	0-40	0.67	0.5-40	< 0.0001	0-40
Mov ABC < p5 (n)	6	12		19		37
Mov ABC p5-p15 (n)	10	6	0.19	5	< 0.0001	21
Mov ABC > p15 (n)	80	71		12		163
MRI	**group 1 (n=87)**	**group 2 (n=104)**	**P for difference 1 - 2**	**group 3 (n=30)**	**P for difference 1 - 3**	**all (n=221)**
TIS median	4.0	6.25		19.25		5.5
min-max	0-21	0-40	< 0.0001	2.5-40	< 0.0001	0-40
Mov ABC < p5 (n)	4	14		19		37
Mov ABC p5-p15 (n)	7	10	0.095	4	< 0.0001	21
Mov ABC > p15 (n)	76	80		7		163

Legend: Mov, Movement; TIS, total impairment score

The proportion of children with an IQ ≤ 85 was not different between US groups 1 and 2 but was significantly higher in US group 3. For MRI groups the same pattern was seen.

Motor function

Movement ABC tests resulted in a median overall TIS of 5.5 (Table 5). Median TIS in US group 1 was not significantly different from group 2, but it was substantially and significantly different between US groups 1 and 3. In the MRI groups, median TIS between groups 1 and 2 and between groups 1 and 3 were both significantly different.

The proportions of children with definite motor problems (TIS < p5), borderline problems (TIS p5-p15) and normal motor performance (TIS > p15) were not significantly different between US and MRI groups 1 and 2. However, a significant difference between groups 1 and 3 for both US and MRI was found.

CP was present in 20 children: hemi/di/quadriplegia in six each and cerebellar ataxia in two. Only one child, with cerebellar ataxia, had a normal neonatal cranial US, but a severely abnormal MRI. Of the remaining 19 children with CP, four had a mildly abnormal US (two VD, one IVH II, one IVH II with PVL I) and 15 had a severely abnormal US. Not one of the CP children had a normal MRI, three had a mildly abnormal MRI and 17 a severely abnormal MRI.

Discussion

Neonatal cranial US and school age MRI were compared in 221 preterm infants. Almost half of the children with a normal US had a normal MRI, while the abnormalities seen in the other half were usually very mild. In only one case was a major lesion (cerebellar atrophy and VD) diagnosed on MRI. Of the children with minor abnormalities on US, again almost half had a normal MRI and only 3.4% had major lesions. However, over seventy percent of the children with major abnormalities on US had severe abnormalities on MRI. Two children with a severely abnormal cranial US (IVH III) had a completely normal school age MRI. Our data show that if cranial US is performed according to strict criteria, a normal US excludes severe lesions on later MRI in 99% of cases.

When considering these results, some matters should be taken into account. We performed a prospective, population-based study in which all neonates with GA ≤ 32 weeks and/or BW ≤ 1500 g had serial cranial US examinations according to a strict protocol. The inclusion percentage was high (78%). We assessed the US according to the most severe lesions seen at any time in contrast to previous investigators who usually examined only one single US at a fixed moment.[16]

We have recently shown that performing sequential US scans is important as localized cysts (PVL II) may take a long time to develop and may have resolved by term age.[17] If only one US is done at term age, cystic lesions may be missed. However, slight VD, irregular ventricular walls and long T_2 suggestive of gliosis might be noticed on later MRI. In our 221 children, we found no abnormalities on MRI in 37.6 % of the cases. Skranes et al [18] investigated 20 very low birth weight infants when aged 6 and a normal MRI was seen in only two children. Gliotic changes and VD were both seen in 60% in contrast to 29% with gliosis and 37.7% with VD in our group. These differences might be explained by the large variations in the sizes of the study groups and the fact that Skranes et al excluded children who had a normal MRI at the age of 1 year.

Our data are more in agreement with two other studies.[19;20] In the first study, 42.5% of 87 children showed abnormalities on MRI at 15-17 years of age. In the second study (n=72), 40 children had definitely abnormal and 15 had equivocal MRI scans at 14-15 years of age. Similar to the first study, abnormalities in the white matter, the size of the lateral ventricles, and the corpus callosum were especially common. Of the 59 children with a normal or mildly abnormal neonatal US scan, 13 had equivocal and 30 definite abnormalities on MRI. Our better correlation between major US abnormalities and severe lesions on later MRI can probably be explained by the use of a mechanical sector scanner with a 7.5 MHz transducer instead of a linear array machine with a 5-7 MHz transducer, which is less well suited for the detection of lesions in the periventricular white matter.

Although a normal US almost excluded severe lesions on later MRI and a severely abnormal US correlated well with severe lesions on later MRI, there was little correspondence between normal and mildly abnormal US and MRI groups. This is most likely due to poor detection of subtle white matter lesions with cranial US.[7-9] In a recent editorial, Volpe[21] highlighted the importance of diffuse white matter injury with subsequently impaired white matter development. Infants with a normal cranial US could subsequently develop subtle gliotic changes and infants with PVL I could either normalize or show persistent changes in the white matter, seen as gliotic changes or mild VD on later MRI. Counsell et al [22] carried out a diffusion-weighted MRI study in preterm infants at term equivalent and showed that diffuse excessive high signal intensity (DEHSI) represents diffuse white matter anomalies. It is possible that the US equivalent of DEHSI is prolonged flaring, like in PVL I. A large proportion of our mildly abnormal US group consisted of infants with an IVH I or II. In the absence of associated PVL I, a normal MRI is to be expected. Kuban et al[23] suggested from their US data in 1605 infants that IVH and VD were powerful predictors of white matter damage, both localized as well as diffuse. However, no MRI study was performed to confirm this.

Recently, more sophisticated techniques such as volume measurements,[24-26] diffusion tensor imaging,[27] and fMRI[28] have become available. Our study is limited in the sense that only conventional MRI techniques were used. However, our aim was to evaluate the effect of neonatal US lesions on subsequent brain development.

One of the main clinical reasons for examining the neonatal brain is to predict neuromotor development. Two parameters for outcome (IQ and motor performance) were measured in this study. Whether a child was in the normal or in the mildly abnormal US group did not have an effect on mean IQ. Mean IQ was only significantly decreased with major abnormalities on US, but the range of IQ in US group 3 was considerable. MRI at school age appeared to be more accurate in the prediction of learning abilities. However, the clinical relevance of a statistically significant difference of 4 IQ points between MRI groups 1 and 2 can be questioned. There were no significant differences in the number of children with a low IQ ($\leq$ 85) between either US or MRI groups 1 and 2. Both the US and MRI groups 3 had a significantly higher number of children with an IQ $\leq$ 85.

The same pattern was seen for motor function: US group 1 did not differ in median TIS from group 2 but was significantly better than US group 3. MRI group 1 scored significantly better in median TIS compared with MRI groups 2 and 3. Although very significant as regards p value, a median TIS of 4 in MRI group 1 is similar in daily practice to a TIS of 6.25 in MRI group 2. The number of children with serious motor problems was not significantly different between US and MRI groups 1 and 2.

We conclude that a normal neonatal cranial US, if obtained in a systematic way within regular time intervals, excludes a severely abnormal MRI at school age in 99% of cases. However, half of the children with normal US do have minor abnormalities on MRI. MRI findings correlated better than US with mean IQ and median TIS at school age. Although significant, these differences appear not to be clinically relevant for normal and mildly abnormal MRI groups. Subtle white matter lesions are better detected with MRI, which could explain the stronger correlation of MRI with neurodevelopmental outcome.
More sophisticated MRI techniques or MRI in selected patients may show even better differentiation but further research will be needed to support this assumption.

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3

Larger corpus callosum size with better motor performance in prematurely born children

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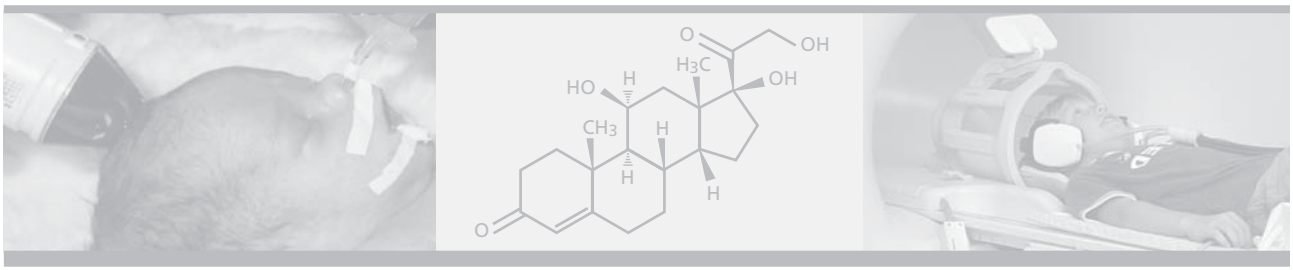

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Abstract

Objective: To determine the relation between the size of the corpus callosum (CC) and motor performance in a population-based cohort of preterm children.

Patients and Methods: Preterm-born children (n=221) with a gestational age (GA) ≤ 32 weeks and/or a birth weight (BW) ≤ 1500 g were eligible for this study. At the age of 7 or 8 years, frontal, middle, posterior, and total areas (mm^2) of the corpus callosum were measured on true midsagittal MRI. Due to anxiety of 10 children and motion artifacts in 7 other children, 204 MRIs could be assessed in the preterm group (mean GA 29.4 weeks, standard deviation (SD) 2.0; mean BW 1200 g, SD 323). The preterm group consisted of 15 children with cerebral palsy (CP) and 189 children without CP. Motor function was established using the Movement Assessment Battery for Children (ABC) and the Developmental Test of Visual-Motor Integration (VMI) was obtained. The same examinations were performed in 21 term-born children.

Results: The mean total cross-sectional CC area was significantly smaller in preterm-born infants compared with their term-born controls (338 mm^2 versus 422 mm^2, $p < 0.0001$).The preterm children with CP had significantly smaller mean CC areas compared to the preterms who did not develop CP ($p < 0.0001$ - $p < 0.002$). However, the preterms born without CP also had significantly smaller body, posterior and total CC areas compared with term-born controls ($p < 0.0001$ - $p < 0.002$). Only the difference in frontal area measurements did not reach significance between the preterm group without CP and the term-born controls ($p = 0.096$).

There was a significant inverse association between the total impairment score (TIS) and its subdomains of the Movement ABC and the areas of the CC in the group of preterm children. Higher TIS (indicating poorer motor function) was strongly related to smaller total CC area: linear regression coefficient (lrc) -3.3 mm^2/score point (95% CI -4.5, -2.1). The association existed in all parts of the CC but increased in the direction of the posterior part: frontal: lrc -0.8 mm^2/score point (-1.2, -0.4), middle: lrc -1.1 mm^2/score point (-1.7, -0.5) and posterior: lrc -1.4 mm^2/score point (-1.8, -0.9).

An association between CC area and its subareas and the standard scores of the VMI was also found. A larger CC was strongly related to better scores on the VMI test : total area CC: lrc 0.05 score/mm^2 (95% CI 0.03, 0.07), frontal: lrc 0.12 score/mm^2 (0.05, 0.19), middle: lrc 0.10 score/mm^2 (0.05, 0.15) and posterior: lrc 0.12 score/mm^2 (0.06, 0.18). After adjustment for GA, BW and total cerebral area, these associations were still significant.

Conclusions: There is a strong association between the size of the corpus callosum (total midsagittal cross area as well as frontal, middle, and posterior area) and motor function in preterm children, investigated at school age. A poorer score on the Movement ABC was related to a smaller CC. A larger CC was strongly associated with better VMI standard scores.

Introduction

Long-term outcome of high-risk, very low birth weight infants remains a matter of serious concern. Only a relatively small number of preterm infants goes on to develop cerebral palsy, but many will later show a developmental coordination disorder often referred to as clumsiness. Learning disabilities are also a common problem at long-term follow-up.[1-6]
The corpus callosum forms the main white matter gateway between the two hemispheres. There has been considerable interest in the normal development of the corpus callosum with increasing age and in the effect of acquired morphological changes on subsequent motor functioning. The corpus callosum consists of the anterior rostrum and the genu, which are first to develop at about 8 weeks of gestation, the body, and the splenium, which is the last part to develop. The gross morphology of the corpus callosum is formed by 18 to 20 weeks at midgestation. It continues to increase in size throughout infancy and childhood due to ongoing myelination, which starts at about 4 months of postnatal age.[7]
Initial imaging studies, showing an association between abnormal morphology of the corpus callosum and developmental difficulties, mainly dealt with congenital malformations or acquired lesions due to callostomy, tumors, or trauma.[8-11] However, Iai et al[12] showed a reduction of the ratio of the thickness of the body and the splenium to the length of the corpus callosum on magnetic resonance imaging (MRI) in 43 prematurely born children who developed spastic diplegia following periventricular leukomalacia (PVL). The more severe the diplegia, the more reduced the ratio of the thickness of the splenium to the length. Mercuri et al[13] studied 21 prematurely born infants, who were selected on the basis of a poor motor performance. Morphological abnormalities of the corpus callosum were significantly associated with functional abnormalities, but no association was found between the area of the corpus callosum and functional abnormalities.
The aim of the present study was to assess whether there is an association between the size of the corpus callosum and the occurrence of motor problems in a group of preterm-born children at school age.

Patients and methods

The children described in this paper are part of a 2-year cohort admitted soon after birth to the Neonatal Intensive Care Unit of the Wilhelmina Children's Hospital, a tertiary referral hospital. Children, born between March 1, 1991, and March 1, 1993, with a gestational age (GA) ≤ 32 weeks and/or a birth weight (BW) ≤ 1500 g were subsequently enrolled in a long-term follow-up study. The original cohort 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 7 or 8 (rarely 9 and 10), the children were invited to the hospital to have several tests. Of the remaining 283 children, 22 (7.8%) could not be traced anymore due to moving, and the parents of 25 (8.8%) refused to participate. As a result, 236 of the 283 children (83.4%) took part in the study. For the present analyses, all of the children who were at the age of 7 or 8 (78.1%, n=221) were included. At that time, they were seen by a child psychologist to have their IQ estimated (based on two subtests of the WISC-R),[14] and a Developmental Test of Visual-Motor Integration (VMI)[15] was obtained. Their motor performance was assessed using the Movement Assessment Battery for Children (Movement ABC),[16,17] and they had an MRI of their brain.

In 10 children, MRI failed because of anxiety of the child, and in a further 7 children, detailed MRI measurements could not be performed due to motion artifacts. This lead to a total study group of 204 prematurely born children.

The reference group consisted of 21 term-born children, born between July 1, 1993, and June 1, 1994, who had no medical problems during their neonatal period and at the time of evaluation were 7 or 8 years old.

The study was approved by the Medical Ethics Committee of the University Medical Center Utrecht.

Motor function

All children were seen by a pediatric physiotherapist (ICVH) and a neonatologist (KJR), who were blinded to the outcome of the MRI. The Movement ABC age band 2 for 7 and 8 years was used.[16] The test contains three domains: manual dexterity (placing pegs, threading a lace, drawing a flower trail), ball skills (one-hand bounce and catch, throwing

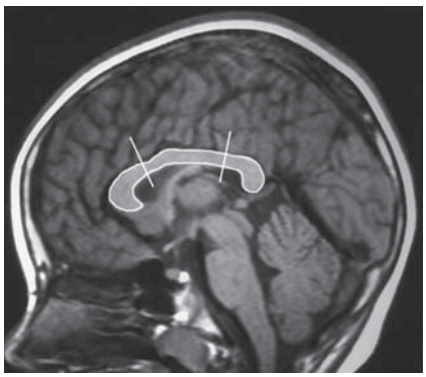

Figure 1: midsagittal T1 weighted image. Manually drawn contour of the corpus callosum.Two lines drawn at a 90-degree angle 1 cm from the incurvation near the genu and the splenium

a beanbag into a box), and static and dynamic balance (stork balance, jumping in squares, and heel-to-toe walking). Each item is scored from 0 (best score) to 5 (poorest score), so the subscore for manual dexterity varies between 0 and 15, for ball skills between 0 and 10, and for balance between 0 and 15. The total impairment score (TIS) is the sum of the three subscores and varies therefore between 0 (best score) and 40 (poorest score). The raw subscale scores are converted to percentile scores and classified as follows: 1 = < p5 (definitely abnormal), 2 = between p5 and p15 (borderline), and 3 = > p15 (normal).

VMI

All children performed the Developmental Test of Visual-Motor Integration, supervised by a child psychologist (AFL), who was unaware of the neonatal status of the child. VMI raw scores were converted to VMI standard scores with a mean of 100, based on the 4th revised edition norms.[15]

Brain imaging

MRI, without sedation, was performed on the same day as the clinical assessment. The children had eye contact with their mother or father, who was present in the MRI unit, using a mirror placed above their head and they could listen to their favorite music during the examination.

The children were imaged on a 1.5 Tesla Philips Gyroscan ACS-NT (Philips Medical Systems, Best, The Netherlands). T_1 and T_2 weighted images were made in the sagittal, coronal and transverse plane. For the present study, only the sagittal T_1 SE images (TR 512 ms, TE 15 ms, slice thickness: 4 mm, interslice gap: 0.6 mm) were used. The midsagittal image that most clearly delineated both the rostral and caudal end of the corpus callosum was selected for measurement. The shape of the corpus callosum was assessed visually with regard to focal (genu, body, splenium) and generalized thinning. MR data were transferred in digital format to an Easy Vision Workstation, where all images were analyzed by one examiner (JNGPL), who was blind to the outcome of the Movement ABC. The images were first enlarged from 256x256 to a magnification at which the contour of the corpus callosum could be easily manually traced with a mouse-controlled cursor. A natural incurvation is present near the level of the splenium and the genu. One centimeter from this incurvation a line was drawn at a 90-degree angle to the contour of the corpus callosum. The different parts of the corpus callosum (frontal, middle and posterior) were identified and the area (mm^2) was measured separately (Fig. 1). The total area of the corpus callosum was the sum of these three different parts. The total midsagittal brain area was also measured in order to make adjustment possible for a smaller or larger brain as a confounding factor.

A random sample of 27 cases was measured twice to assess intra-observer variability of the measurements. An average difference of 0.5% was found for the area of the whole corpus callosum. A difference between 5.7% and 7.8% was found for the difference in measurements of the subregions, which is similar to data reported by Rauch.[18]

Data analysis

For descriptive purposes, group specific means (SD) and proportions were calculated. Associations between corpus callosum area measurements and Movement ABC were analyzed by using linear regression models. These models were also used to adjust the associations for possible confounding factors. Results were expressed as linear regression coefficients and 95% confidence intervals. Statistical significance was considered if 95% confidence intervals did not include the value of 0, indicating no association. SPSS (version 10.1; SPSS, Chicago, Il, USA) was used for all analyses.

Results

Clinical findings

The prematurely born children were divided into two groups. Group I consisted of 15 children who developed cerebral palsy. Their mean GA was 29.1 weeks (SD 2.2) and their mean BW was 1085 g (SD 343). Three children developed a hemiplegia following an intraventricular hemorrhage (IVH) associated with a unilateral parenchymal hemorrhage, diagnosed on their neonatal cerebral ultrasound, 3 developed a spastic diplegia, following localized cystic periventricular leukomalacia (c-PVL grade II), 3 developed a quadriplegia after extensive cystic-PVL (grade III) and 2 children had milder spastic diplegia following prolonged periventricular echogenicity (PVL grade I). One child with cerebral palsy showed bilateral thalamic lesions on neonatal cerebral ultrasound, 1 other had ventricular dilatation, 1 had a focal arterial infarction and 1 child had a completely normal ultrasound in the neonatal period. This latter child was born at 27 weeks and was extremely small for gestational age with a birth weight of 485 g.

Group II consisted of 189 children who did not develop cerebral palsy. Their mean GA was 29.4 weeks (SD 2.0) and their mean BW was 1208 g (SD 321).

Mean GA of the reference group was 40.2 weeks (SD 1.1) and mean BW was 3501 g (SD 614) (Table 1).

Movement ABC

The median scores for the Movement ABC test are shown in Table 2. In group I, 13 children (87%) had a TIS below the 5th centile, none scored between the 5th and

Table 1: Clinical data

	Preterm all (n=204)	Preterm + CP group I (n=15)	Preterm – CP group II (n=189)	Controls (n=21)
GA (wks) mean (sd)	29.4 (2.0)	29.1 (2.2)	29.4 (2.0)	40.2 (1.1)
BW (g) mean (sd)	1200 (323)	1085 (343)	1208 (321)	3501 (614)
males / females	116/88	9/6	107/82	13/8

Legend: GA, gestational age; wks, weeks; sd, standard deviation; BW, birth weight; CP, cerebral palsy

15th centile, and 2 (13%) had a normal score. In group II, 21 children (11%) scored below the 5th centile, 20 (11%) between the 5th and 15th centile, and 148 (78%) had a normal score. None of the controls scored below the 5th centile and only 2 (9.5%) between the 5th and 15th centile.

Corpus callosum

On visual analysis, the shape of the corpus callosum was abnormal in 10 (67%) of the prematurely born children with cerebral palsy (group I) and in 40 (21%) of the children without cerebral palsy (group II) ($p < 0.0001$, Fisher's Exact Test). The abnormal shape consisted of generalized thinning in 4 and 11 children for group I and II respectively (Fig. 2). Focal thinning was found in 6 and 29 children for group I and II respectively (Fig. 3). Focal thinning most commonly involved the body of the corpus callosum. The shape of the corpus callosum was found to be normal in all controls (Table 3).

Table 2: Movement ABC scores

	Preterm all (n=204)	Preterm + CP group I (n=15)	Preterm – CP group II (n=189)	Controls (n=21)
Mov. ABC total median (range)	5.5 (0-40)	34.5 (8-40)	5.5 (0-36.5)	2.0 (0-10)
Hand skills median (range)	1.5 (0-15)	10.0 (2.5-15)	1.0 (0-15)	0.0 (0-4.0)
Ball skills median (range)	2.5 (0-10)	9.0 (1-10)	2.5 (0-10)	1.5 (0-8)
Balance median (range)	0.75 (0-15)	15.0 (1-15)	0.5 (0-15)	0.0 (0-4.5)
Mov.ABC class 1/2/3	34/20/150	13/0/2	21/20/148	0/2/19

Legend: CP, cerebral palsy; Mov, movement; Mov. ABC class 1/2/3: 1 = < p5, 2 = between p5 and p15, 3 = > p15

The measured areas of the different parts of the corpus callosum are also shown in Table 3. All measured areas of the corpus callosum were significantly smaller for the entire group of preterm children compared with term controls. When we again split up the preterm group in those with and those without CP, we found that all measured areas of the children with CP (group I) were significantly smaller compared with the preterms without CP (group II). However, most measurements in the preterm children without CP were also significantly smaller than those in term-born controls. Only the difference in areas measured in the frontal part of the corpus callosum did not reach significance in children without CP compared to the term controls ($p = 0.096$). The most significant difference was found for the posterior area ($p < 0.0001$).

Association between the Movement ABC and the area of the corpus callosum

Table 4 shows data regarding the total impairment score and the scores for the different subdomains in relation to area of the different regions of the corpus callosum in all preterm-born children. Statistically significant inverse associations were found between the TIS and its subdomains and the area of the corpus callosum. The higher the TIS, the smaller the area of the corpus callosum. This association was found in all parts of the corpus callosum but clearly increased in the direction of the posterior part. Strongest associations were seen for ball skills and corpus callosum area, particularly the posterior part. However one should realize that ball skills are scored on a 10-point scale whereas manual dexterity and balance are scored on a 15-point scale. Adjustment for GA, BW, and total cerebral area did not change the findings.

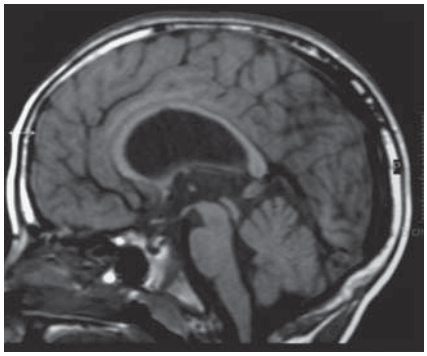

Figure 2: corpus callosum with generalized thinning

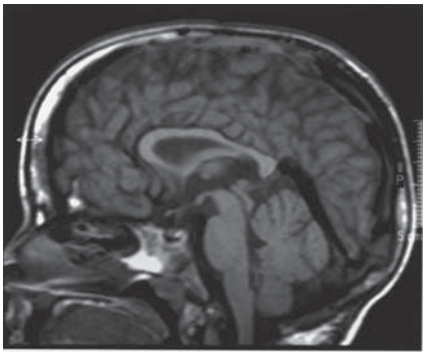

Figure 3: corpus callosum with focal thinning

Table 3: Shape and area of the corpus callosum

	Preterm all (n=204)	Preterm + CP group I (n=15)	Preterm – CP group II (n=189)	Controls (n=21)
Abnormal shape cc n (%)	50 (25%)	10 (67%)	40 (21%)	0 (0%)
Generalized thinning n	15	4	11	
Focal thinning n	35	6	29	
Frontal n	7	2	5	
Body n	28	2	26	
Posterior n	7	3	4	
Mean (sd) area cc (mm^2)				
Total	338 (82)	249 (87)	345 (78)	422 (76)
Frontal	103 (27)	79 (25)	105 (26)	118 (27)
Body	143 (37)	112 (42)	146 (36)	177 (34)
Posterior	91 (31)	59 (29)	94 (29)	127 (25)

Legend: cc, corpus callosum; CP, cerebral palsy; sd, standard deviation

Association between the VMI test and the area of the corpus callosum

Table 5 shows the association between the area of total and different regions of the corpus callosum and the standard score of the VMI. There is a positive linear association for all measured areas of the corpus callosum and the VMI, also after adjustment for the same factors as in Table 4. This implies that a larger area of the corpus callosum was associated with a better outcome on the VMI.

Discussion

The results of this prospective 2-year cohort study in 204 prematurely born children show that there is a clear relation between size of the corpus callosum and motor performance. To appreciate these results, some issues need to be addressed. We investigated the relation between motor function and corpus callosum without a preselection of the children on motor outcome. Moreover, the children were all within a small age range at the time of follow-up (7 or 8 years old), and our study population was much larger than previous ones.[12,13,19,20] By using the total brain area, we were also able to adjust for the possible confounding effect of a small or large total brain as determining factor for the size of the corpus callosum. The stronger association of the posterior part of the corpus

callosum with the performance on the Movement ABC in our cohort fits in well with the occurrence of mild and cystic-PVL, which are more common in preterm infants and mainly affect the parietal and occipital periventricular white matter. As structural changes of the corpus callosum have been shown to progress throughout childhood and adolescence,[21] our children were all examined at 7 or 8 years of age in order to limit the effect of age. Giedd et al[22] also showed an enormous variability in corpus callosum size. We therefore decided to study a larger cohort of preterm infants than reported so far. The data were adjusted for GA, BW, as well as total cerebral area as it is well known that the corpus callosum and especially the splenium are larger in boys than in girls. This difference, however, is no longer seen when the callosal index (ratio corpus callosum area/total brain area) is taken into account.

Our data show significant inverse associations between the total Movement ABC score and its subdomains and all measured areas of the corpus callosum. The association was especially marked for the posterior part of the corpus callosum. In our cohort, all measured areas of the corpus callosum, in the entire preterm group, were significantly smaller compared with those in the term controls. The 15 children with CP showed the most severe volume loss (either generalized or focal) compared with the preterm-born children without CP and the term controls. Interestingly, the preterm children without CP also had significantly smaller areas (except for the frontal area) compared with the term controls. This is in accordance with volumetric studies in preterm-born children, where the volume of the white matter was found to be smaller in preterm

Table 4. Inverse association between (domains of) Movement ABC and corpus callosum area in preterm-born children

	Frontal		Middle		Posterior		Total	
	unadjusted	adjusted	unadjusted	adjusted	unadjusted	adjusted	unadjusted	adjusted
Total impairment score	-0.8 (-1.2,-0.4)	-0.7 (-1.1,-0.3)	-1.1 (-1.7,-0.5)	-0.7 (-1.3,-0.2)	-1.4 (-1.8,-0.9)	-1.3 (-1.7,-0.8)	-3.3 (-4.5, -2.1)	-2.7 (-3.8, -1.5)
Manual skills (score)	-1.9 (-2.9,-0.8)	-1.5 (-2.5,-0.5)	-2.2 (-3.6,-0.7)	-1.3 (-2.7,0.05)	-2.9 (-4.1,-1.8)	-2.5 (-3.6,-1.4)	-7.0 (-10.1, -3.8)	-5.3 (-8.2, -2.3)
Ball skills (score)	-2.1 (-3.4,-0.7)	-1.8 (-3.0,-0.5)	-2.9 (-4.7,-1.1)	-2.0 (-3.7,-0.4)	-3.6 (-5.1,-2.2)	-3.4 (-4.7,-2.0)	-8.6 (-12.5, -4.7)	-7.2 (-10.8, -3.6)
Balance (score)	-1.7 (-2.5,-0.8)	-1.3 (-2.2,-0.5)	-2.3 (-3.5,-1.1)	-1.5 (-2.6,-0.4)	-2.7 (-3.7,-1.7)	-2.5 (-3.4,-1.6)	-6.6 (-9.3, -4.0)	-5.3 (-7.8, -2.9)

Values are linear regression coefficients (mm^2/score point) with 95% confidence intervals in brackets. Adjusted = association adjusted for gestational age, birth weight, and total cerebral area. Manual skills and balance were scored on a 15-point scale, ball skills on a 10-point scale

children as compared with term-borns.[23] A regional reduction in the size of the corpus callosum was found by Moses et al,[24] who studied 10 children with unilateral focal brain injury that had occurred prenatally or within the first 6 weeks of life. The most common etiology was hemorrhagic or ischemic focal infarction. Fujii et al[25] found the same degree of thickening of the body of the corpus callosum in 21 low-risk preterm infants (30-36 weeks) compared to 17 term infants at the same postconceptional age. However, they studied a limited number of patients and did not include children born before 30 weeks of gestation.

Our data are also in agreement with previous studies by Iai et al,[12] Hayakawa et al,[19] Davatzikos et al,[20] and Mercuri et al.[13] Iai et al[12] focused on 43 prematurely born infants who had developed spastic diplegia and showed a pattern compatible with PVL on an MRI performed during infancy and childhood. They showed a reduction of the ratio of the thickness of the body and the splenium to the length of the corpus callosum. The more severe the diplegia, the more reduced the ratio of the thickness of the splenium to the length. Hamayaka et al[19] investigated 43 preterm and 20 term infants with spastic diplegia and found a good correlation between the severity of CP and the extent of corpus callosum involvement. The best correlation was found between severity and corpus callosum area. Davatzikos et al[20] also studied children with varying degrees of CP due to PVL and found a thicker corpus callosum body in diplegics compared with quadriplegics. Mercuri et al[13] excluded children who had developed CP and focused on 21 prematurely born infants, who were selected on the basis of a poor motor performance, as assessed using the Movement ABC. Morphological abnormalities of the corpus callosum were found to be significantly associated with functional abnormalities such as diadochokinesis and finger tapping. They were, however, unable to show an association between the area of the corpus callosum and functional abnormalities. This can possibly

Table 5: Association between corpus callosum area and VMI_ss in preterm-born children

		VMI_ss unadjusted	VMI_ss adjusted
Corpus callosum			
Total area	(mm^2)	0.05 (0.03, 0.07)	0.04 (0.01, 0.06)
Frontal	(mm^2)	0.12 (0.05, 0.19)	0.09 (0.01, 0.16)
Middle	(mm^2)	0.10 (0.05, 0.15)	0.06 (0.04, 0.11)
Posterior	(mm^2)	0.12 (0.06, 0.18)	0.10 (0.04, 0.17)

VMI: Visual-Motor Integration, ss: standard scores

Values are linear regression coefficients (score/mm^2) with 95% confidence intervals in brackets

Adjusted = association adjusted for gestational age, birth weight, and total cerebral area

be explained by the a priori selection of the patients with poor scores on the Movement ABC and by the wide age range (6-10 years) at the time of the MRI examination. In the studies by Iai and Hayakawa, the ages of the investigated patients at the time of the MRI varied also from 7 months to 16 years and from 6 months to 13 years, respectively.

As the splenium is composed of axons from the occipital cortex, including axons from the primary and secondary visual cortex, we expected to find an association between a reduction of the splenium and the VMI. However, there was an association between all separate areas of the corpus callosum as well as the total area and the VMI. After adjustment for GA, BW, and total cerebral area, the relation was indeed strongest for the posterior region. This is different from the data of Peterson, who found a significant correlation of the regional volume of the body of the corpus callosum with the VMI test, but not of the genu, isthmus or splenium.[23]

Peterson et al[23] compared 26 eight-year-old prematurely born children with 39 term controls and were able to measure regional brain volumes. The preterm infants differed significantly from term controls with regard to regional brain volumes. The basal ganglia, hippocampus and corpus callosum were found to be significantly reduced in volume and the reduction in volume of these structures was disproportionately greater than predicted by the smaller brains of preterm children. The findings persisted when those children who suffered from an IVH in the neonatal period were excluded. They also noted that area measurements of the posterior corpus callosum (including the midbody, isthmus and splenium) were significantly associated with the respective projection areas of the interhemispheric axons contained in those corpus callosum subregions.

At the time that our cohort was examined, volume measurements were not yet performed on a routine basis. Whalley and Wardlaw[26] showed that, for brain structures like the corpus callosum, simple methods of measuring are as reproducible and reliable as more complex volume measurements. Measurement reliability, however, decreases as the size of the structure being measured decreases. The mean difference between the measurements of two raters as a percentage of the corpus callosum area was 0.8%. The intra-observer variation was 0.5% which was the same as found in our cohort.

A recent longitudinal, representative, population-based MRI study in preterm-born infants by Inder et al[27] reported marked thinning of the corpus callosum in 69% of the cases already present at term age. However, myelination has not yet started at this very young age and the meaning of this finding for future motor function remains to be established at follow-up. On functional MRI in young adults, Santhouse et al[28] found significantly different activation patterns in very preterm-born children with damaged corpora callosa compared with preterms without structural damage and full-term controls.

In our study, at the age of 7 or 8, we found thinning of the corpus callosum in 25% of the preterm-born children. Although there is a considerable increase in volume of the corpus callosum during childhood, we know from our children who develop CP, who are usually examined around two years of age when myelination is more or less completed, that changes of the corpus callosum are already present at this earlier age. As more and more preterm-born infants will undergo an MRI at this age, it might be useful to pay special attention to the shape and size of the corpus callosum on midsagittal images, as it appears to be a good predictor of later motor performance and visual-motor integration. Children who at this early age already show abnormalities of their corpus callosum might benefit from early intervention.

In conclusion, our findings in a large cohort of prematurely born children followed until 7 or 8 years of age, provide strong support for a critical role of corpus callosum size in predicting motor performance. The larger the size of the corpus callosum, in particular the posterior region, the better motor performance is preserved.

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4

Neonatal hydrocortisone treatment: neurodevelopmental outcome and MRI at school age in preterm-born children

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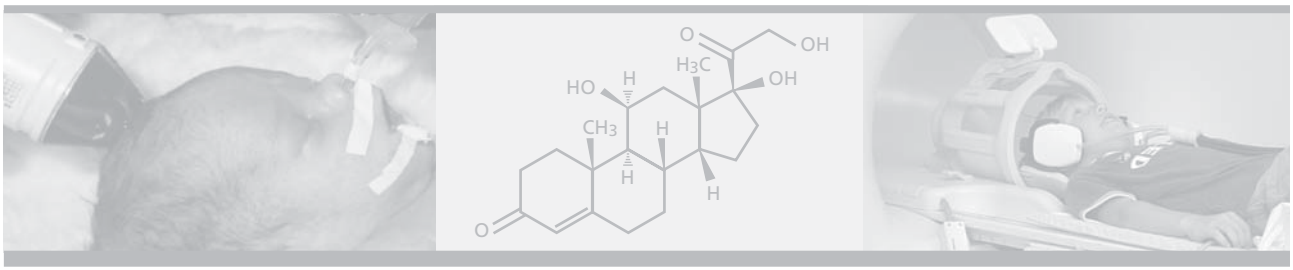

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Abstract

Background: Dexamethasone for bronchopulmonary dysplasia (BPD) has a negative impact on neurodevelopment.

Aim of the study: To investigate neurodevelopment at school age in preterm infants, treated with *hydrocortisone* in the neonatal period.

Patients and Methods: 226 Preterms (GA ≤ 32 weeks and/or BW ≤ 1500) performed subtests of the WISC-R, the Visual-Motor Integration test (VMI), a 15-word memory test and the Movement Assessment Battery for Children (ABC) at school age. Conventional MRI of the brain was obtained. Sixty-two children, who received hydrocortisone for BPD (starting dose 5 mg/kg/d, median duration 27.5 d) were compared with 164 non-treated neonates.

Results: Hydrocortisone-treated infants were younger, lighter and sicker than their non-steroid-treated counterparts. Adjustment for GA, BW, gender, mechanical ventilation and small for gestational age was made.

Adjusted mean IQ, VMI and memory test results were the same in the hydrocortisone and the non-steroid group (99 vs. 101, $p = 0.62$; 97 vs. 99, $p = 0.49$, 7.9 vs. 7.5, $p = 0.42$ respectively). Motor function and incidence of cerebral palsy (CP) in both groups was not different (11% vs. 7%, $p = 0.97$). Occurrence of brain lesions on MRI was identical for the two groups.

Conclusion: Neonatal hydrocortisone treatment for BPD has no long-term effects on neurodevelopment.

Introduction

Despite improved mechanical ventilatory strategies and administration of exogenous surfactant, bronchopulmonary dysplasia (BPD) remains a problem in neonatal intensive care. The prevalence of BPD is high, and the condition is a significant cause of mortality, morbidity and prolonged hospitalization.[1] The almost exclusively administered drug to prevent chronic lung disease and to treat BPD is dexamethasone (DXM), which has been used now for over twenty years. Corticosteroids improve short-term respiratory function, leading to a reduction in supplemental oxygen requirements and earlier extubation. The choice of DXM appears to have been arbitrarily based upon it having the greatest anti-inflammatory power, however, many short-term as well as long-term negative side effects of DXM therapy in preterm infants have been reported. Short-term adverse effects include impaired glucose tolerance, hypertension, increased risk of nosocomial infections, gastrointestinal hemorrhage and impaired weight gain and head growth.[2] These effects are generally transient and reversible after withdrawal of the DXM treatment. Because of these relatively mild reversible effects in relation to the improved respiratory function, the use of DXM increased spectacularly in the *early* 1990s.

In the *late* 1990s concerns on the long-term neurodevelopmental consequences arose, when follow-up of randomized controlled trials indicated an increased risk of cerebral palsy (CP) after early postnatal DXM exposure.[3] Since then, more reports on negative effects concerning long-term follow-up after neonatal DXM prescription have been published,[4;5] and recently reviewed by Baud.[6] An alternative corticosteroid, with fewer side effects would therefore be welcomed. In our unit, hydrocortisone, a much less potent glucocorticoid than DXM, has always been the steroid of choice to treat ventilator-dependent preterm infants with BPD.

The aim of the present study was to investigate the impact of neonatal hydrocortisone administration in preterm infants on long-term neurodevelopment, measured at school age.

A small subset of this cohort has been reported earlier in a different context;[7;8] the present paper describes the entire group of children with more extensive outcome measures.

Patients and methods

The children presented 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 center. All children, born between March 1, 1991, and March 1, 1993, with a gestational age (GA) ≤ 32 weeks (range 25.0-33.0) and/or a birth weight (BW) ≤ 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 present study because of (multiple) congenital anomalies and/or chromosomal disorders. At the age of 7 or 8 (occasionally 9 and 10), the children were invited to the hospital for one day to undergo several tests. Of the remaining 283 children, 22 (7.8%) could not be traced due to moving and the parents of 25 (8.8%) refused to participate in the follow-up. Eventually, 236 children (83.4%) participated. For the present study, seven children who had received DXM (six prior to extubation, one during part of his treatment in an other hospital) were excluded, as well as two children with a congenital abnormality on neonatal cranial ultrasound (US) (cavum septum pellucidum agenesis) and one child who developed an unknown neuromuscular disorder. This resulted in a study population of 226 children: 62 had been treated postnatally with hydrocortisone and 164 had not been treated with steroids. Median age at follow-up was 8.1 y for both groups.
The Medical Ethics Committee of the University Medical Center Utrecht approved the study and parental informed consent was obtained.

Hydrocortisone treatment

In all 62 children hydrocortisone treatment was given for BPD and generally 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 at the discretion of the attending neonatologist.

Cranial US

Cranial 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. Hemorrhages (IVH) were classified according to Papile [9] and periventricular leukomalacia (PVL) according to De Vries.[10] Cranial US findings were classified into three groups: normal when no or minor abnormalities like germinal layer or plexus cysts, subependymal

pseudocysts or lenticulostriate vasculopathy as exclusive findings were present (group 1); 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 2); 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 3).

MRI

MRI at school age was performed on the same day as the developmental tests, without sedation. Using a mirror placed above their head, the children had eye contact with one of their parents; hearing protection was provided by headphones. 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 in detail previously.[11]

MRI findings were also classified into 3 groups: normal (group1); 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 was present (group 2); severely abnormal when extensive gliosis or gliosis in combination with marked ventricular dilatation was present (group 3).

For calculation of the area of the corpus callosum the midsagittal T_1 SE image (TR 512 ms, TE 15 ms, slice thickness 4 mm, interslice gap 0.6 mm) that most clearly delineated both the rostral and caudal end of the corpus callosum was selected for measurement. MR data were transferred in digital format to an Easy Vision Workstation, where all images were first enlarged from 256x256 to a magnification at which the contour of the corpus callosum could be easily manually traced with a mouse-controlled cursor.

IQ, 15-word Test and VMI

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, unaware of the neonatal status of the child. Using the procedures and tables published by Kaufman,[12] scaled scores were converted to an estimated IQ score based on two subtests which is within a 95% confidence interval of the full-scale IQ score, with a standard error of estimate of 6.3.

The "15-word Test" is a Dutch adaptation of Rey's Auditory Verbal Learning Test.[13] It consists of a list of 15 unrelated, concrete nouns, which are presented over five learning trials, with immediate recall after each trial. After a delay interval of 20 minutes and without further presentation, delayed recall is assessed. The number of correctly recalled words after each trial and after the delayed recall provides the scores for the test. For this paper the delayed recall results after 20 minutes were used.

For the Developmental Test of Visual-Motor Integration (VMI) only the children without cerebral palsy (CP) were considered. Raw scores were converted to VMI standard scores with a mean of 100, based on the 4th revised edition norms.[14]

Motor function

All children were seen by a pediatric physiotherapist, blinded to the MRI findings. Children were examined for presence of CP. To further evaluate motor function, those with CP were not considered as the Movement ABC is not the most optimal test for these children.

Movement ABC age band 2 for 7 and 8 years was used.[15] The test contains three domains: manual dexterity (placing pegs, threading a lace, drawing a flower trail), ball skills (one-hand bounce and catch, throwing a bean bag into a box) and static and dynamic balance (stork balance, jumping in squares and heel-to-toe walking). Each item is scored from 0 (best score) to 5 (poorest score). The total impairment score (TIS) is the sum of the three subscores and varies therefore between 0 (best score) and 40 (poorest score). Raw subscale scores are converted to percentile scores and classified as follows: < p5 (definitely abnormal), p5-p15 (borderline) and > p15 (normal).

Data analysis

Treatment group differences in continuous baseline characteristics were tested using *t*-tests or using Mann Whitney *U*-tests and group differences in proportional values were tested using Chi-squared tests or Fisher's exact tests when appropriate.

Univariate general linear models were used for associating hydrocortisone use and continuous outcome variables, yielding group differences and associated significance tests. We used (multinomial) logistic regression models for associating hydrocortisone use with binary or categorical outcome variables.

As we used non-randomized clinical data, we had to account for treatment group differences in prognosis, because prescribing hydrocortisone is itself expected to be an indicator of worse developmental outcome, irrespective of treatment effects (confounding by indication). Therefore, we used logistic regression to calculate for each child a propensity score,[16] indicating the likelihood of hydrocortisone treatment as predicted by GA, BW, gender, mechanical ventilation, and small for gestational age (SGA). This propensity score, reflecting baseline prognostic differences, was used for adjusting associations between treatment and outcome.

Results are expressed as regression coefficients or as odds ratios with 95% confidence intervals and p-values (α = 0.05). All analyses were performed using SPSS version 12.0.2 for Windows (SPSS, Chicago, Il, USA).

Table 1: Baseline characteristics of hydrocortisone-treated versus non-treated preterm neonates

		Hydrocortisone (n=62)		No Hydrocortisone (n=164)		P value
GA wks mean	(sd, sem)	27.8	(1.7, 0.2)	30.0	(1.8, 0.1)	< 0.0001
BW g mean	(sd, sem)	1016	(256, 33)	1266	(321, 25)	< 0.0001
Age wks start HC	(sd, sem)	30.5	(2.0, 0.3)			
Gender boys/girls	n	37/25		84/80		0.30
SGA (< p2.3)	n	3	(5%)	14	(9%)	0.41
Singleton/twins/triplets	n	40/18/4		126/32/6		0.17
Antenatal steroids	n	24	(38.7%)	67	(43.8%)	0.50
Mechanical ventilation	n	60	(97%)	104	(63%)	< 0.0001
Duration of ventilation days, median	(min-max)	19	(7-72)	7	(1-53)	< 0.0001
Surfactant	n	33	(53%)	36	(22%)	< 0.0001
Inotropes	n	22	(36%)	21	(13%)	< 0.0001
PDA	n	25	(41%)	20	(12%)	< 0.0001
PDA ligation	n	7	(11%)	4	(2%)	< 0.0001
Sepsis	n	17	(27%)	34	(21%)	0.28
NEC	n	4	(7%)	6	(4%)	0.47
NEC surgery	n	2	(3%)	4	(2%)	0.77
Apgar 1 min median	(min-max)	5.0	(0-10)	6.0	(0-10)	0.01
Apgar 5 min median	(min-max)	8.0	(3-10)	9.0	(1-10)	< 0.0001
Cerebral US group						
1	n	19	(31.1%)	78	(47.9%)	0.01
2	n	34	(55.7%)	55	(33.7%)	
3	n	8	(13.1%)	30	(18.4%)	

Legend: GA, gestational age; wks, weeks; sd, standard deviation; sem, standard error of the mean; g, grams; HC, hydrocortisone; n, number; PDA, patent ductus arteriosus; NEC, necrotising enterocolitis; SGA, small for gestational age

Results

Patient characteristics

Mean GA of steroid-treated children was less and mean BW was lower compared with children who never received steroids (Table 1). Treated children were also sicker as shown by a significantly higher incidence of mechanical ventilation, need for surfactant and inotropes, and an increased incidence of patent ductus arteriosus (PDA). There was no difference in the proportion of mothers of steroid and non-steroid children, that had received a complete course of antenatal betamethasone (2 x 5.7 mg i.m., repeated 24 h later) for fetal lung maturation.

Generally, hydrocortisone was started when the postnatal age was at least >1 week and the child was ventilator-dependent with increasing oxygen requirements or needed re-intubation, not explained by infection or a hemodynamic significant PDA. Hydrocortisone was initiated at a median age of 19 d with an inter quartile range (IQR) of 14 d. The mean age of the steroid group had advanced until 30.5 postmenstrual weeks at start of treatment, which was not significantly different from the GA at birth of the non-treated group (p = 0.09). In two children hydrocortisone was prescribed without having been ventilated in order to avoid mechanical ventilation. Median duration of hydrocortisone treatment was 27.5 d (IQR: 12 d). In 58 of the 62 hydrocortisone-treated patients we could calculate the cumulative dose/ kg mean weight (mean weight: weight at the end of the treatment plus weight at the start of the treatment divided by 2). Median cumulative hydrocortisone dose was 70 mg/kg mean weight (IQR: 21 mg/kg).

Table 2: Relative risk for MRI lesions at school age in hydrocortisone-treated versus non-treated infants

	Hydrocortisone (n=58)	No Hydrocortisone (n=158)	OR (95% CI)	P value	OR adjusted (95% CI)	P value
MRI group 1 n	21 (36.2%)	63 (39.9%)	reference	reference	reference	reference
MRI group 2 n	29 (50%)	74 (46.8%)	1.2 (0.6, 2.3)	0.63	0.95 (0.4, 2.1)	0.89
MRI group 3 n	8 (13.8%)	21 (13.3%)	1.1 (0.4, 3.0)	0.78	0.57 (0.2, 1.9)	0.35

Legend: MRI, magnetic resonance imaging; group 1, normal MRI; group 2, minor lesions; group 3, major lesions; n, number; OR, odds ratio; CI, confidence interval; OR adjusted, odds ratio adjusted for gestational age, birth weight, gender, need for mechanical ventilation and small for gestational age

Table 3: Cognitive outcome at school age in hydrocortisone-treated versus non-treated infants

	Hydrocortisone (n=62)	No Hydrocortisone (n=164)	P value	Hydrocortisone adjusted	No Hydrocortisone adjusted	P value
IQ mean (sd, sem)	98 (13, 1.7)	101 (14, 1.1)	0.08	99 (2.0)	101 (1.1)	0.62
Recall mean (sd, sem)	7.8 (3.0, 0.4)	7.6 (2.6, 0.2)	0.53	7.9 (0.4)	7.5 (0.2)	0.42
VMI * ss mean (sd, sem)	97 (12, 1.7)	99 (11, 0.9)	0.34	97 (1.8)	99 (1.0)	0.49

Legend: sd, standard deviation; sem, standard error of the mean; VMI*: visual-motor integration, performed by non-cerebral palsy children only: 55 hydrocortisone and 152 non-treated children; ss, standard score. Adjusted (sem): adjusted for gestational age, birth weight, gender, need for mechanical ventilation and small for gestational age

MRI

MRI failed due to anxiety in ten children (four hydrocortisone and six non-treated children). There were no differences in brain lesions on MRI between the steroid and non-steroid group (Table 2). Also after adjustment for the propensity score, odds ratios for the risk on MRI lesions were not significantly different between the two groups.

Mean midsagittal corpus callosum area was significantly smaller in the hydrocortisone-treated group compared with the non-treated group (313 mm^2 versus 348 mm^2, p = 0.005) but this difference disappeared after adjustment (335 mm^2 versus 340 mm^2, p = 0.72).

Cognitive outcome

The unadjusted mean IQ at school age in the hydrocortisone group was 98 compared with 101 in the non-treated group (Table 3), which was close to statistical significance. However, this difference disappeared after adjustment. In line with the analysis of mean IQs, of the 62 children who received hydrocortisone, 14 (22.6%) had an IQ ≤ 85 compared with 23 (14.0%) of the 164 children who did not receive hydrocortisone. Thus, the hydrocortisone-treated children were at a slightly increased risk of a future lower IQ (OR = 1.8, 95% CI 0.9, 3.8; p = 0.12). Again, this was completely explained by differences in other prognostic factors ($OR_{\text{adjusted for propensity score}}$ = 1.2, 95% CI 0.5, 2.9; p = 0.76). Maternal level of education was not different between the hydrocortisone-treated and the non-treated group (p = 0.28).

Table 4: Motor outcome at school age in hydrocortisone-treated versus non-treated infants without CP

	Hydrocortisone (n=55)	No Hydrocortisone (n=152)	OR (95% CI)	P value	OR adjusted (95% CI)	P value
Total Mov ABC > median (n)	24 (43.6%)	72 (47.4%)	0.9 (0.5, 1.6)	0.63	0.9 (0.5, 2.0)	0.89
Manual dexterity > median (n)	30 (54.5%)	63 (41.4%)	1.7 (0.9, 3.2)	0.10	1.3 (0.6, 2.7)	0.51
Ball skills > median (n)	25 (45.5%)	69 (45.4%)	1.0 (0.5, 1.9)	0.99	1.1 (0.5, 2.2)	0.87
Balance > median (n)	23 (41.8%)	62 (40.8%)	1.0 (0.6, 2.0)	0.89	1.2 (0.6, 2.6)	0.61
TIS < p5 (n)	9 (16.4%)	13 (8.6%)	1.9 (0.8, 4.9)	0.16	1.3 (0.4, 4.0)	0.66
TIS p5-p15 (n)	3 (5.5%)	18 (11.8%)	0.5 (0.1, 1.7)	0.24	0.4 (0.1, 1.7)	0.20
TIS > p15 (n)	43 (78.2%)	121 (79.6%)	reference	reference	reference	reference

Legend: CP, cerebral palsy; n, number; Mov ABC, Movement Assessment Battery for Children; TIS, total impairment score; OR, odds ratio; CI, confidence interval; OR adjusted, odds ratio adjusted for gestational age, birth weight, gender, need for mechanical ventilation and small for gestational age

Memory test results were the same for both groups. For the VMI test the children with CP were left out, no difference was found between the hydrocortisone and non-treated group. Adjustment did not change the results.

Motor outcome

There was no significant difference in incidence of CP between the hydrocortisone and the non-hydrocortisone group (11.3% versus 7.3% respectively, OR 1.6, $OR_{\text{adjusted for propensity score}}$ 1.0, p = 0.97). In the hydrocortisone-treated group the median (minimum-maximum) values for the TIS, the total manual dexterity score, the total ball skills score, and the total balance score were 5.5 (0-34), 2.0 (0-15), 2.5 (0-10), and 0.5 (0-15), respectively. In the non-hydrocortisone group these values were 5.5 (0-36.5), 1.0 (0-15), 2.3 (0-10), and 1.0 (0-12.5), respectively. Table 4 shows, that for none of the scores there was an association between hydrocortisone treatment and the risk of a score above the overall median value.

There was also no difference in number of motor impaired children between the treated and non-treated children. Adjustment did not change the outcome.

Discussion

The findings of this cohort study among 226 preterm-born children followed up for 8 years do not demonstrate any unfavorable structural or functional effects of neonatal treatment with hydrocortisone on brain development at school age.

When considering these results, some issues need to be addressed. We estimated the effects of treatment using data obtained in routine care rather than conducting a randomized trial. Consequently, those children that had been treated were likely to have had a more pertinent indication than those who remained untreated. Indeed, treated children were generally more diseased and therefore had a priori a more problematic prognosis than untreated ones. To prevent confounding by indication from invalidating the results, we took major precautions, notably by thorough adjustments using propensity score methods. While some remaining confounding can not be excluded, this is unlikely to affect the conclusions. If anything, given the virtual identical prognosis in the two groups, the true outcomes may even have been more positive in the treated group should confounding due to their a priori more severe prognosis have remained. In the absence of a randomized comparison, this is probably the closest we can come to a true estimate of risk. In addition the study has a number of other advantages. This is a follow-up study of a 2-year cohort, treated in one and the same tertiary care level hospital, where hydrocortisone was the treatment of choice in preterm children who needed corticosteroids to prevent irreversible pulmonary damage. Age at follow-up was within close limits and the current investigators were blinded to the hydrocortisone status of the children when collecting the outcome data.

This is the largest report until now on long-term neurodevelopmental outcome in children following neonatal hydrocortisone treatment. We found no differences in neurocognitive and motor performance between hydrocortisone-treated and non-treated children. The incidence of brain lesions on conventional MRI was also similar. Midsagittal corpus callosum areas were the same after adjustment. Previously, we reported no differences in total intracranial, cerebral gray or white matter, cerebrospinal fluid and hippocampal volumes between the hydrocortisone-treated and the non-treated group in a subset of this cohort.[7] ^{1}H-Magnetic Resonance Spectroscopy findings of the hippocampus were also comparable.[8]

Interestingly, the first controlled trial of postnatal corticosteroid treatment investigated the ability of *hydrocortisone* to alter the outcome in infants with respiratory distress syndrome.[17] It already appeared in 1972, long before the widespread use of DXM. The aim of the study was to prevent mechanical ventilation, however, no significant effect on need for assisted ventilation or survival between the two groups was demonstrated.

Autopsy on seven hydrocortisone and seven non-treated infants showed no difference in lung, liver, adrenal, thymus, heart and spleen pathology attributable to steroid treatment but a statistically significant association between IVH and steroid treatment.[18] Twenty-four survivors (12 in each group) had the same mean developmental quotient (Griffiths Developmental Scale) at the age of one year, but analysis of the subtests showed a significant difference in the results for gross motor development with a lower mean score for the steroid group.[19]

Initial trials in the eighties showed short-term improvement in pulmonary function and weaning from the ventilator in preterm infants with BPD after administration of DXM,[20;21] resulting in an increased popularity of DXM in NICUs all over the world. One retrospective study examining the outcome of neonates with a BW between 500 and 749 g found that 43% of infants born from1990 to 1992 received DXM, compared with as many as 84% of those born from1993 to 1995.[22] This almost routine use of DXM continued until 1998, when Yeh et al published the results of a large multicenter follow-up study that demonstrated a significant increase in neurodevelopmental dysfunction in neonates treated with DXM compared with controls.[3] In 1999 O'Shea described an increased risk of CP in VLBW infants, who received a 42-day tapering course of DXM, started at day 15-25 of life.[4]

Because of these alarming publications on DXM, several groups tried to find an alternative corticosteroid for treating preterm infants with BPD. In a commentary in 2001, Thebaud et al questioned the rationale for the exclusive use of DXM and advocated the use of alternative steroids.[23] Andre et al [24] published a study of 45 consecutive preterm infants at risk of chronic lung disease, who were treated at a median postnatal age of 16 d with a tapering course of methylprednisolone. Methylprednisolone has a lower anti-inflammatory activity than DXM (still 5 times higher than hydrocortisone), a negligible mineralocorticoid effect and in contrast to DXM, no sulphites are used for preservation. Those treated with methylprednisolone had a higher rate of body weight gain and a lower incidence of glucose intolerance and cystic PVL compared with 45 consecutive historic cases treated with DXM. Decastro et al compared 28 DXM-treated ELBW neonates with 20 betamethasone-treated neonates, who could not be weaned from the ventilator.[25] Betamethasone has the same anti-inflammatory activity as DXM but does not contain sulphites as preservative. A shorter course and lower dose of betamethasone was nearly as effective as DXM in weaning ventilatory support without DXM's undesirable short-term side-effects. However, no data on long-term follow-up were provided in both these studies. In a retrospective study, Van der Heide et al [26] compared hydrocortisone or DXM-treated children, matched for GA and severity of disease, with non-treated children. Improvement in respiratory status was comparable between DXM and hydrocortisone

administration. Neonatal DXM-treated children needed special school education significantly more often than controls, whereas hydrocortisone-treated children had the same outcome as controls. In our study no difference in cognitive and motor outcome was found between hydrocortisone-treated and non-treated children, which is in line with the above mentioned study.

A pilot study in 40 ELBW infants showed increased survival without BPD in hydrocortisone-treated infants during their first week of life.[27] The multicenter randomized trial that followed, had to be stopped after the enrolment of 360 patients because of an increase in spontaneous gastrointestinal perforation.[28] There seemed to be an interaction with the simultaneous use of hydrocortisone and indomethacin. The indication for hydrocortisone treatment was to *prevent* BPD by substituting hydrocortisone early in life, based on work showing evidence of early adrenal insufficiency and increased lung inflammation in preterm infants, who subsequently develop BPD.[29] However, in our study hydrocortisone was prescribed at a later stage because of its anti-inflammatory activity in order to *treat* BPD. Because of this, there was no important interaction with indomethacin, which in our unit is usually prescribed in the first week of life, only to treat a hemodynamically significant PDA.

Our findings suggest hydrocortisone to be a safer corticosteroid for treating preterm infants suffering from BPD than DXM. There may be several hypotheses why hydrocortisone might be less harmful. DXM is a synthetic glucocorticoid, which has a 25-30 times higher anti-inflammatory power than hydrocortisone. The biologic half-time of hydrocortisone is 8-12 h in contrast to the 36-72 h of DXM, reducing the risk of accumulation. The preservative agent to control microbial and oxidative degeneration in DXM is sodium bisulphite. Exposure of a neuronal cell line (rat mesencephalic cells) to high levels of sulphite induced a time-dependent decrease in viability.[30] Sulphites were shown to be toxic *in vitro* to cultures of neurons and *in vivo* to the brains of 3-5 d old mouse pups.[31] The absence of a difference in outcome despite the fact that the hydrocortisone children were younger and sicker needs some reflection. By the time hydrocortisone was started, the neonates had reached a mean postmenstrual age of 30.5 weeks. Maybe part of the absent deleterious effect of hydrocortisone is due to this increased age, when possibly a neurologically critical period has passed. Finer et al reported an increased use of hydrocortisone, very early in life, to treat refractory hypotension in VLBW infants.[32] This is a different indication and age at start of treatment compared with the children, described in this study. To contemporary NICU standards, our children were at a rather advanced age at the start of their steroid treatment. Most of the adverse sequelae of DXM on long-term neurodevelopment have been described after early start of the DXM,[2;33;34] so timing might also play a role.

In a recent review, Grier and Halliday recommended restricted use of DXM and appropriate long-term neurodevelopmental follow-up for all infants receiving corticosteroids in the neonatal period.[35] They also state that larger trials are required before corticosteroids other than DXM can be recommended. The present study, although observational, shows that hydrocortisone might be a safer alternative for DXM when treating BPD.

In conclusion, the findings in this large long-term follow-up study in a cohort of preterm children provide strong support to the view that neonatal hydrocortisone treatment for BPD does not adversely affect neurodevelopmental outcome or conventional MRI of the brain at school age. In the absence of confirmation from adequately sized randomized trials these results suggest that hydrocortisone rather than dexamethasone should be used in cases where corticoid treatment for chronic lung disease is judged to be necessary.

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Structural and functional brain development after hydrocortisone treatment for neonatal chronic lung disease

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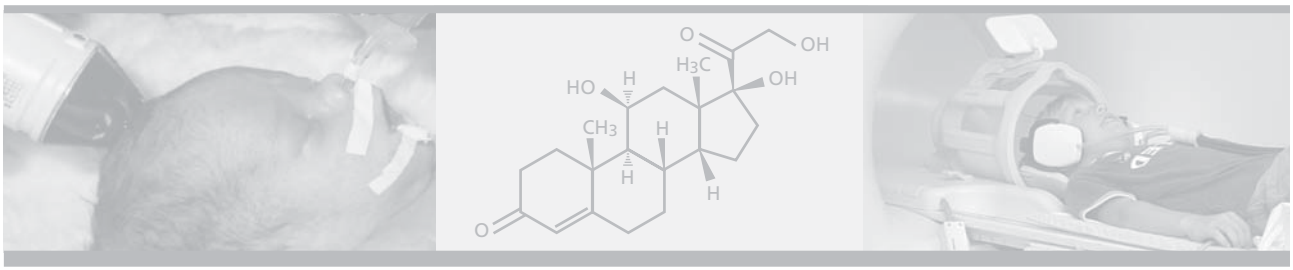

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Abstract

Objective: There is much concern about potential neurodevelopmental impairment after neonatal corticosteroid treatment for chronic lung disease. Dexamethasone is the corticosteroid most often used in this clinical setting, and it has been shown to impair cortical growth among preterm infants. This study evaluated long-term effects of prematurity itself and of neonatal hydrocortisone treatment on structural and functional brain development using three-dimensional MRI with advanced image-processing and neurocognitive assessments.

Patients and Methods: Sixty children born preterm, including 25 children treated with hydrocortisone and 35 children not treated with hydrocortisone, and 21 children born at term were evaluated, at a mean age of 8 years, with quantitative MRI and neurocognitive assessments (Wechsler Intelligence Scales for Children-Revised (WISC-R)). Automatic image segmentation was used to determine the tissue volume of cerebral gray matter, white matter, and cerebrospinal fluid. In addition, the volume of the hippocampus was determined manually. WISC-R scores were recorded as mean intelligence scores at evaluation. Neonatal hydrocortisone treatment for chronic lung disease consisted of a starting dose of 5 mg/kg per day tapered over a minimum of 3 weeks.

Results: Cerebral gray matter volume was reduced among preterm children (regardless of hydrocortisone treatment), compared with children born at term (preterm: 649 ± 4.4 ml; term: 666 ± 7.3 ml). Birth weight was shown to correlate with gray matter volume at 8 years of age in the preterm group ($r = 0.421$). Cerebrospinal fluid volume was increased among children born preterm, compared to children born at term (preterm: 228 ± 4.9 ml; term: 206 ± 8.2 ml). Total hippocampal volume tended to be lower among children born preterm with a more pronounced reduction of hippocampal volume among boys (preterm: 6.1 ± 0.13 ml; term 6.56 ± 0.2 ml). The WISC-R score was lower for children born preterm, compared with children born at term (preterm: 99.4 ± 12.4; term 109.6 ± 8.8). Children treated with neonatal hydrocortisone had very similar volumes of gray matter (preterm with hydrocortisone: 650 ± 7.0 ml; preterm without hydrocortisone: 640 ± 5.6 ml), white matter (preterm with hydrocortisone: 503 ± 6.1 ml; preterm without hydrocortisone: 510 ± 4.9 ml), and cerebrospinal fluid (preterm with hydrocortisone 227 ± 7.4 ml; preterm without hydrocortisone: 224 ± 6.0 ml), compared with non-treated infants. The hippocampal volumes were similar in the 2 groups (preterm with hydrocortisone: 5.92 ± 0.15 ml; preterm without hydrocortisone 5.81 ± 0.12 ml). The WISC-R score assessments were within the normal range for both groups, with no difference between the groups (preterm with hydrocortisone: 100.8 ± 13.0; preterm without hydrocortisone: 98.6 ± 12.3).

Conclusions: Prematurity is associated with mild brain structural differences that persist at 8 years of age, with associated lower scores in neurocognitive assessments. The data suggest that perinatal hydrocortisone given at the described dosage has no long-term effects on either neurostructural brain development or neurocognitive outcomes.

Introduction

Corticosteroids have been used widely for the prevention and treatment of chronic lung disease in the neonatal period with proven short-term benefits, including reductions of mortality rates and rates of chronic lung disease.[1] The short-term adverse effects of neonatal corticosteroids are also widely known, with increases in the incidences of hyperglycemia, arterial hypertension, gastrointestinal bleeding and cardiac hypertrophy.[2] Neonatal corticosteroid treatment has been evaluated in relation to long-term neurodevelopmental outcomes.[3-5] Barrington et al,[6] in a meta-analysis, showed an increased risk for developing cerebral palsy and neurodevelopmental disabilities after postnatal corticosteroid treatment. Most of the studies reviewed used dexamethasone as the corticosteroid treatment.[3-5] Recently, Short et al[7] described detailed neurodevelopmental outcomes at 8 years after neonatal bronchopulmonary dysplasia and found significantly poorer performance in IQ-testing among infants treated with corticosteroids, compared with the non-steroid group. The Vermont Oxford Network Steroid Group found a marginal increase in periventricular leukomalacia (PVL) among infants treated with dexamethasone.[8] These emerging long-term, neurologic, side effects prompted a statement by the American Academy of Pediatrics, which discouraged the routine use of corticosteroids, specifically dexamethasone, for the treatment of chronic lung disease among infants with very low birth weights.[9] Dexamethasone, a fluorinated glucocorticoid, was shown to deplete pyramidal and dentate granular neurons and to reduce hippocampal volume in animal studies.[10;11] At the cellular level, neonatal dexamethasone administration was shown to alter permanently the composition and function of the hippocampal N-methyl-D-aspartate receptor complex in rats.[12] Baud et al[13] described a specific neurotoxic effect of sulfites used as preservatives in intravenous dexamethasone preparations. Preliminary data on direct effects on structural brain development from three-dimensional quantitative MRI analyses showed significant reduction of cerebral cortical gray matter volume at term among preterm infants exposed to dexamethasone.[14] To date, there are few data on the use of alternative corticosteroids, such as hydrocortisone, for treatment in the newborn period.[15] A recent retrospective study, comparing hydrocortisone and dexamethasone treatment in the newborn period, showed fewer short-term and long-term adverse effects with hydrocortisone treatment.[16] The focus of this study was to determine whether neonatal systemic hydrocortisone treatment for chronic lung disease among preterm infants had any effect on structural brain development, development of the hippocampus, and neurofunctional outcomes at 8 years of age, with quantitative, volumetric, three-dimensional MRI and neuropsychological assessments.

Subjects

Subjects

Three hundred seventy-five preterm infants born between March 1, 1991, and March 1, 1993, were recruited into a long-term follow-up study. They were born in or referred to the tertiary referral neonatal intensive care unit at the Wilhelmina Children's Hospital

Table 1: Demographic details of children born preterm and controls

	Children Born Preterm (n=60)			Controls (n=21)
	Preterm Infants (n=60)	Preterm Infants not treated with HC (n=35)	Preterm Infants treated with HC (n=23)§	Term Infants (n=21)
Mean BW, g, (SD)	1280 (360)	1400 (380)	1120 (300)*	3380 (570)
Mean GA, w, (SD)	29.4 (1.9)	30.4 (1.5)	28.0 (2.0)*	40.0 (1.2)
Boys	32	17	13	12
Girls	28	18	10	9
Inotropes	13	3	9#	0
PDA	16	5	9#	0
Mechanical ventilation	47	22	23#	0
Surfactant	21	7	12#	0
Moderate to severe perinatal brain lesions	12	8	4	0
Parental social class				
I-II, n (%)	16 (27)	10 (29)	6 (26)	2 (10)
III, n (%)	21 (35)	12 (34)	8 (35)	8 (38)
IV-V, n (%)	23 (38)	13 (37)	9 (39)	11 (52)

Legend: BW, birth weight; SD, standard deviation; GA, gestational age; HC, hydrocortisone
Number of individuals are given unless otherwise indicated. Moderate to severe perinatal brain lesions include intraventricular hemorrhage III/IV, PVL grade II/III or association of PVL and IVH II, brain infarct.
§ the number of preterm infants with and without HC do not add up to 60, as 2 HC-treated children were left out in the comparison treated vs. non-treated because no data on duration of HC treatment were obtained
* $p < 0.05$ for comparison of children born preterm treated vs. not treated
# < 0.01, Fisher's exact test

(Utrecht, The Netherlands). They had a gestational age of ≤ 32 weeks and/or a birth weight of ≤ 1500 g. Sixty-four children (17%) died, 28 (7,5%) were excluded because of congenital abnormalities and/or chromosomal disorders. Of the remaining 283 children, 22 children (7,8%) could not be traced and the parents of 25 children (8,8%) refused to participate. A total of 236 of the 283 children participated, yielding an inclusion rate of 83%. MRI was performed for all children and was successful for 226 children. During the last 6 months of the study period, quantitative volumetric, three-dimensional MRI was added to the MRI protocol. The study presents the observations for this subgroup of 61 children who were evaluated with quantitative, three-dimensional, volumetric MRI. One child born preterm was excluded because of the presence of a large arachnoid cyst discovered on MRI scans.

At a mean age of 8 years 7 months (SD: 8.6 months), the prematurely born children were invited back to the hospital to undergo a cerebral MRI investigation and a detailed neurodevelopmental assessment. A group of 21 healthy term-born children were included in the study as control group. At assessment, they had a mean age of 8 years 5 months (SD: 8.1 months). Of the 60 preterm children included in the MRI analysis, 25 children (mean GA: 28 ± 1.6 weeks; mean BW: 1120 ± 290 g) had been treated with hydrocortisone for chronic lung disease in the neonatal period, and 35 children (mean GA: 30.4 ± 1.5 weeks; mean BW: 1400 ± 380 g) had not received any corticosteroids during the neonatal period (Table 1). Criteria for starting hydrocortisone treatment were ventilator dependency and increasing oxygen requirements.

Neonatal hydrocortisone treatment consisted of a starting dose of 5 mg/kg per day, divided into 4 doses, for 1 week. Treatment was introduced at a median age of 18 days (minimum: 4 days; maximum: 43 days), followed by a tapering course with a median duration of treatment of 26 days (minimum: 22 days; maximum: 171 days). For 2 of the 25 infants, we were unable to obtain data on the duration of hydrocortisone treatment; therefore, the 2 infants were excluded from the analysis comparing preterm infants with hydrocortisone treatment versus no treatment. Twelve preterm children with moderate/severe perinatal brain lesions (intraventricular hemorrhage (IVH) of grade III or IV, PVL of grade II and III,[17] association of PVL and IVH of grade II, or focal brain infarction) were distributed equally between the 2 groups. Neurological examinations at the time of treatment initiation were not different between hydrocortisone-treated and untreated preterm infants.

The study was approved by the local ethics committee. Written informed parental consent was obtained for all children included in the study

Methods

MRI acquisition

MRI scanning was performed with a 1.5-T Gyroscan ACS-NT system (Philips Medical Systems, Best, The Netherlands). For the acquisition of the primary MRI data, 2 different imaging modes were applied, i.e., transverse dual turbo spin echo (proton density and T2-weighted; first echo: repetition time: 4000 ms; echo time: 17 ms; slice thickness: 5.0 mm; gap: 1.0 mm; second echo: repetition time: 4000 ms, echo time: 110 ms; slice thickness: 5.0 mm; gap: 1.0 mm) and coronal inversion recovery sequences for the hippocampus (repetition time: 2933 ms; echo time: 13 ms; inversion time: 400 ms; slice thickness: 2.0 mm, without gap).

MRI processing

Postacquisition processing was performed on workstations (Sun Microsystems, Mountain View, CA) with specifically designed software, namely, MEDx (Sensor System, Sterling, VA) and Slicer (www.slicer.org). All brain measurements were made with a rater blinded to group affiliations. The axial slices were reformatted with MEDx in order to produce a three-dimensional data set, with inclusion of the gap of 1 mm. The fully automatic Brain

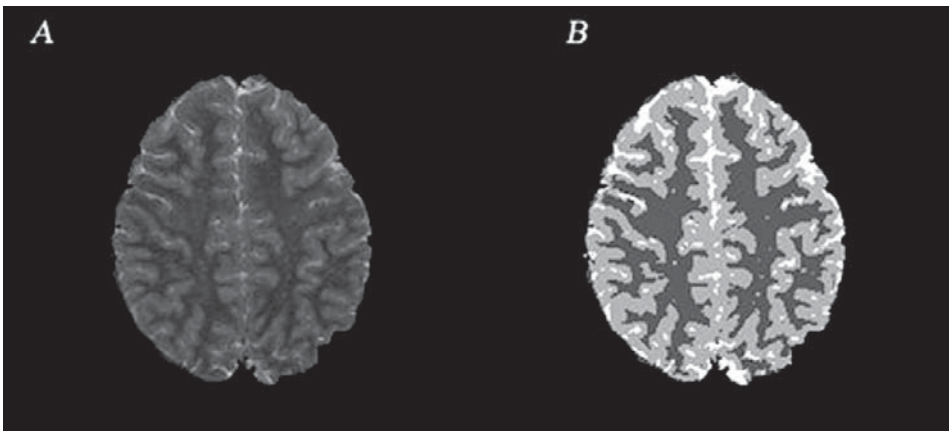

Fig 1: Brain tissue segmentation. A, an axial turbo spin echo T2-weighted scan for an 8-year-old child born at term, after extraction of the skull with the Brain Extraction Tool. B, brain tissue classes extracted from the image in A with the FAST algorithm. White represents cerebrospinal fluid. Light gray represents gray matter. Dark gray represents white matter

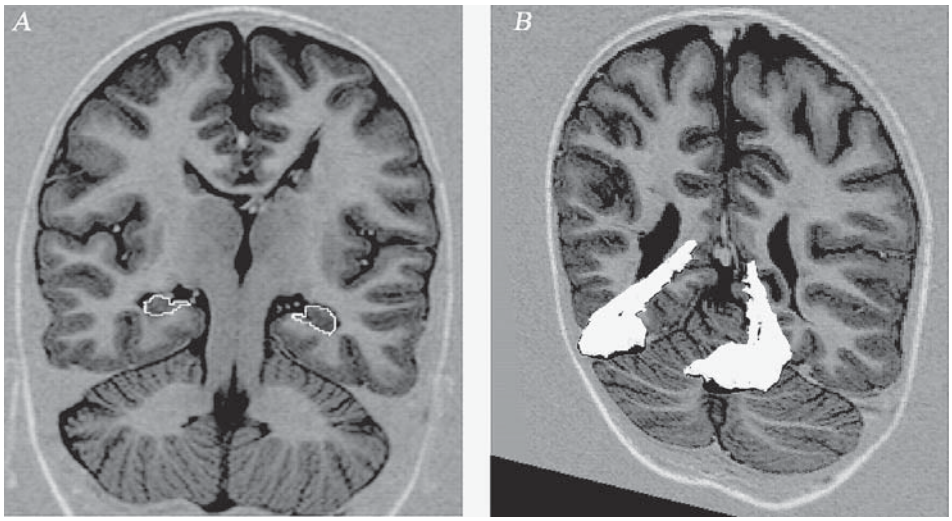

Fig 2: Hippocampal segmentation. A, a coronal inversion recovery MRI scan for an 8-year-old child, with contours of both hippocampi traced manually. B, a coronal inversion recovery MRI scan for the same child, with both hippocampi reconstructed three-dimensionally

Extraction Tool included in MEDx was used to exclude non-brain tissue (skin, skull, and eyes) from the brain tissue assessment (Fig 1, A). The FAST algorithm (FMRIB Automated Segmentation Tool) included in MEDx was used to segment the brain into 3 separate brain tissue classes, i.e., gray matter, white matter, and cerebrospinal fluid (Fig 1, B). The FAST algorithm is based on a hidden Markov random field model and an associated expectation-maximization algorithm.[18] The hippocampus was segmented manually on inversion recovery coronal slices of 2-mm thickness with 3D Slicer software (www.slicer.org). The segmentation was started on coronal slices and then completed on sagittal slices. A three-dimensional reconstruction of both hippocampi was performed to check the quality of the segmentation (Fig 2).

Our measurement of the hippocampus included the hippocampus proper, the dentate gyrus, and the subiculum and excluded fimbria and alveus. Because the hippocampus, subiculum, and dentate gyrus are indistinguishable on the basis of tissue signal intensity on MRI scans, they were segmented as a single structure. The amygdala, parahippocampal gyrus, and crus of the fornix were excluded. The boundary between the amygdala and the head of the hippocampus and the boundary of the tail of the hippocampus were traced mainly on the sagittal plane. The tracing guidelines for the hippocampus used in

this study were based on published guidelines by Obenaus et al,[19] Pantel et al,[20] and Duvernoy et al.[21] The total hippocampal volume analyzed in this study was calculated with the summation of voxels of the left and the right hippocampi. Hippocampal volumes were determined by 1 rater. The mean intra-observer variability for 4 right hippocampi that were segmented twice was 2.72%. The segmentation of the brain into 3 different tissue classes was achieved with a sequence of fully automated algorithms; therefore, no intra-observer variability was determined.

Segmentation of the brain into 3 tissue classes was not possible in 3 cases because of image artifacts in the double echo image series. Segmentation of the hippocampus was not performed for 2 children because the inversion recovery image series could not be completed.

Neurocognitive assessment

Neurocognitive assessment included several subtests of cognitive functioning of the Wechsler Intelligence Scales for Children-Revised (WISC-R) (Dutch version). An estimate of the full-scale WISC-R IQ score was calculated on the basis of the subtest scores for vocabulary and block design. With the procedures and tables published by Kaufman,[22] the scaled scores were converted to an estimated IQ score, which was within the 95% confidence interval of the full-scale IQ score, with a standard error of the estimate of 6.3. A psychologist experienced in conducting standardized assessments with children performed all neuropsychological examinations.

Statistical analyses

The hippocampal volume, total intracranial volume, gray matter volume, white matter volume, cerebrospinal fluid volume and the WISC-R score showed Gaussian distributions. Therefore, a univariate additive model with gender as a fixed factor and intracranial volume as a covariate was chosen for analysis of cerebral gray matter, cerebral white matter, and hippocampal volumes among the 3 groups (control subjects, children born premature and treated with hydrocortisone, and children born premature and not treated with hydrocortisone). This model was established to analyze the group effect on brain tissue volume by taking into account the intrinsic variation attributable to intracranial volume and gender.

The Student's *t*-test ($\alpha = 0.05$) was used to analyze the differences of the WISC-R scores among the groups. The Pearson correlation coefficient and linear regression analyses were also used. All statistical procedures were performed with SPSS version 11 (SPSS, Chicago, Illinois, USA).

Results

Results of quantitative, volumetric, MRI analyses performed at 8 years of age and neurocognitive outcomes are presented for a group of 60 prematurely born infants and 21 infants born at term. Differences in structural and functional brain development at 8 years among preterm infants, compared with term infants, were as follows.

Effects of prematurity

Total intracranial volume

Children born preterm had a similar intracranial volume, compared with children born at term, after adjustment for gender differences (mean adjusted volume: preterm: 1379 ± 16 ml; term: 1398 ± 26 ml; F = 0.378, df = 1,78, R^2 = 0.293, p = 0.541).

Gray matter volumes (cerebral and cerebellar cortex)

Children born preterm had significantly reduced gray matter volumes, compared with control children (mean adjusted volume: preterm: 649 ± 4.4 ml; term: 666 ± 7.3 ml; F = 4.1, df = 1,74, R^2 = 0.782, p = 0.046) (Table 2). After the exclusion of 12 children with brain lesions, the difference in gray matter volumes remained significant.

There was a modest but significant correlation between birth weight and gray matter volume at 8 years in the preterm group (r = 0.421, p = 0.001; regression equation: gray matter volume = 0.07 * birth weight + 558.76) (Fig 3). There was no correlation between gestational age and gray matter volume (r = 0.124, p = 0.358).

Table 2: Quantitative 3-dimensional MRI volumes of cerebral tissues and WISC-R scores at 8 years of age of children born preterm and at term

	Children born preterm (n=60)	Children born at term (n=21)	P value*
Gray matter	649 (4.4)	666 (7.3)	0.046
White matter	512 (3.8)	513 (6.2)	0.9
CSF	228 (4.9)	206 (8.2)	0.027
Hippocampal volume	5.86 (0.09)	6.16 (0.15)	0.094
WISC-R score	99.4 (12.4)	109.6 (8.8)	0.001#

Legend: CSF, cerebrospinal fluid. Data (except the WISC-R score) are volumes in millimeters and are adjusted means (standard error of the estimated values)

*Analysis of covariance, including group and gender as factors and intracranial volumes as covariate

Student's *t*-test

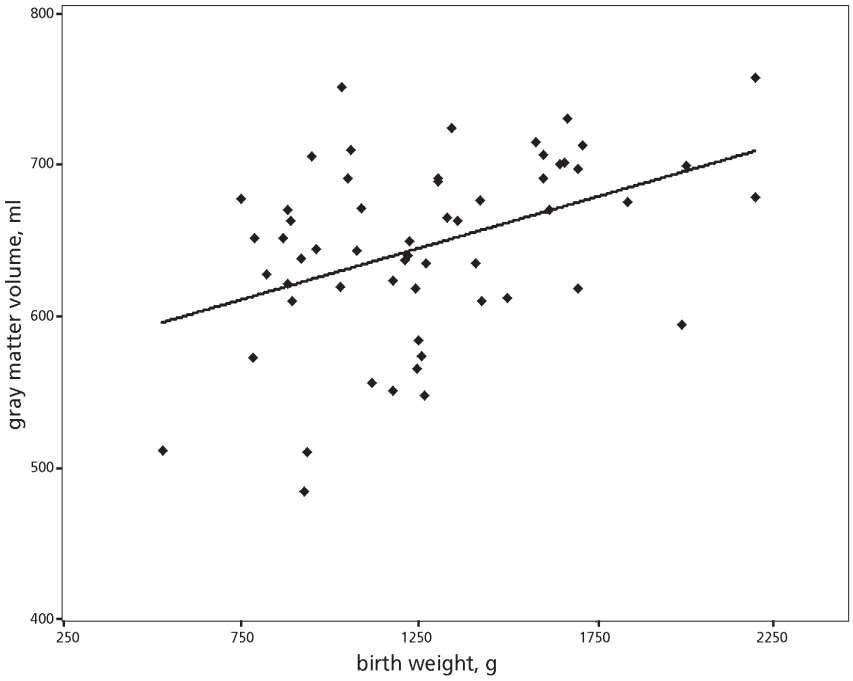

Fig 3: Scatterplot of the birth weight effect for gray matter volume in the group of preterm children, with a regression line (gray matter volume = 0.0681 birth weight + 558.76; R^2 = 0.1773*

Cerebral white matter volumes

Cerebral white matter volumes were similar between children born at term and children born preterm (mean adjusted volume: preterm: 512 ± 3.8 ml; term: 513 ± 6.2 ml; F = 0.017, df = 1,74, R^2 = 0.811, p = 0.9).

Cerebrospinal fluid volumes

Cerebrospinal fluid volumes were significantly increased among children born preterm, compared with children born at term (mean adjusted volume: preterm: 228 ± 4.9 ml; term: 206 ± 8.2 ml; F = 5.112, df = 1,77, R^2 = 0.341, p = 0.027).

Hippocampal volumes

The total hippocampal volume was decreased slightly among children born preterm, compared with children born at term (mean adjusted volume: preterm: 5.86 ± 0.09 ml;

term: 6.16 ± 0.15 ml; F = 2.87, df = 1,75, R^2 = 0.337, p = 0.094), with a more pronounced reduction of hippocampal volume among boys (mean adjusted volume: preterm: 6.1 ± 0.13 ml; term: 6.56 ± 0.2 ml; F = 3.696, df = 1,40, R^2 = 0.25, p = 0.06). A comparison of absolute hippocampal volumes for boys without adjustment for intracranial volume showed a significantly reduced hippocampal volume for prematurely born boys (mean volume: preterm: 6.07 ± 0.69 ml; term: 6.64 ± 0.91 ml; p = 0.03).

Neurocognitive outcomes

WISC-R scores were found to be lower for children born preterm, compared with children born at term (WISC-R score: preterm: 99.4 ± 12.4; term: 109.6 ± 8.8; p = 0.001). Modest but significant correlations for the group of children born preterm were found between the gray matter volume and the WISC-R score (r = 0.361, p < 0.01; regression equation: WISC-R score = 0.074 * gray matter volume + 51.08) and between the hippocampal volume and the WISC-R score (r = 0.282, p < 0.05; regression equation: WISC-R score = 4.49 * hippocampal volume + 73.19).

Effects of postnatal hydrocortisone treatment

Total intracranial volume

Total intracranial volumes were similar for preterm infants with and without postnatal hydrocortisone treatment (mean adjusted volume with gender as a covariate: preterm with hydrocortisone: 1373 ± 24 ml; preterm without hydrocortisone: 1378 ± 19 ml; F = 0.034, df = 1,0, R^2 = 0.255, p = 0.854).

Table 3: Quantitative 3-dimensional MRI volumes of cerebral tissues and WISC-R scores at 8 years of age of children born preterm with and without hydrocortisone

	Children born preterm with HC (n=23)	Children born preterm without HC (n=35)	P value*
Gray matter	650 (7.0)	640 (5.6)	0.31
White matter	503 (6.1)	510 (4.9)	0.42
CSF	227 (7.4)	224 (6.0)	0.77
Hippocampal volume	5.92 (0.15)	5.81 (0.12)	0.56
WISC-R score	100.8 (13)	98.6 (12.3)	0.53#

Legend: CSF, cerebrospinal fluid; HC, hydrocortisone. Data (except the WISC-R score) are volumes in millimeters and are adjusted means (standard error of the estimated values)

*Analysis of covariance, including group and gender as factors and intracranial volumes as covariate

Student's *t*-test

Gray matter volumes

Gray matter volumes were similar for preterm infants with and without postnatal hydrocortisone treatment (mean adjusted volume: preterm with hydrocortisone: 650 ± 7.0 ml; preterm without hydrocortisone: 640 ± 5.6 ml; F = 1.05, df = 1,0, R^2 = 0.724, p = 0.31) (Table 3).

Cerebral white matter volumes

White matter volumes were not different after postnatal hydrocortisone treatment among children born preterm (mean adjusted volume: preterm with hydrocortisone: 503 ± 6.1 ml; preterm without hydrocortisone: 510 ± 4.9 ml; F = 0.649, df = 1,0, R^2 = 0.790, p = 0.424).

Cerebrospinal fluid volumes

Cerebrospinal fluid volumes were not different after postnatal hydrocortisone treatment among children born preterm (mean adjusted volume: preterm with hydrocortisone: 227 ± 7.4 ml; preterm without hydrocortisone: 224 ± 6.0 ml; F = 0.084, df = 1,0, R^2 = 0.397, p = 0.77).

Hippocampal volumes

Hippocampal volumes were similar for preterm infants with and without postnatal hydrocortisone treatment (mean adjusted total hippocampal volume: preterm with hydrocortisone: 5.92 ± 0.15 ml; preterm without hydrocortisone: 5.81 ± 0.12 ml; F = 0.939, df = 1,0, R^2 = 0.259, p = 0.563).

When analyzed separately, boys and girls did not show any difference in any brain tissue volume as a function of hydrocortisone treatment.

Neurocognitive outcomes

Postnatal hydrocortisone treatment had no effect on the WISC-R scores (preterm with hydrocortisone: 100.8 ± 13; preterm without hydrocortisone: 98.6 ± 12.3, p = 0.53).

Discussion

This study, with quantitative MRI techniques, documents mild structural brain differences among children that are attributable to premature birth and persist at 8 years of age, with associated slightly lower scores in neurocognitive assessments. The structural alterations are demonstrated specifically in a reduction of cortical gray matter, with a

compensatory increase of cerebrospinal fluid. Similar results were reported by Nosarti et al[23] for adolescents born very preterm. The specific reduction in brain tissue volume of cortical gray matter was also observed at term age for prematurely born infants.[24;25] Our results also show a significant correlation of birth weight, rather than gestational age, and cortical gray matter volume at 8 years of age. This finding may suggest that prenatal factors affecting fetal growth, rather than gestational age itself, influence cortical gray matter development.[26]

The hippocampus has been shown to be a cortical gray matter structure of particular vulnerability to prematurity-associated insults, resulting in hippocampal volume reduction.[23;27;28] Isaacs et al[27] demonstrated a significant association of hippocampal volume reduction and deficits in everyday memory capacity for a group of adolescents born before 30 weeks of gestation. In our population, overall hippocampal volume among premature infants was reduced only marginally, compared with term infants, with a more marked, significant reduction in hippocampal volume among preterm boys, compared with term boys. A male disadvantage was reported in several outcome studies of children born preterm.[29;30] Johnson and Breslau[31] described specific learning difficulties present predominantly among male preterm infants. Isaacs et al[32] showed the importance of the size of the hippocampus in relation to developmental amnesia, indicating that hippocampal volume had an effect on specific memory functions. Interestingly, we found significant correlations of both the cortical gray matter volume and the overall hippocampal volume with the overall IQ (measured as the WISC-R score), which emphasizes a certain structure-function relationship in brain development.

The overall IQ (measured as the WISC-R score) for our population of children born preterm was lower than the score for the children born at term. Despite this significant reduction, the absolute mean value of the IQ measured for the children born preterm remained within 2 SD of the normal range. This finding might be influenced by the age at which the children are evaluated. Ment et al[33] showed possible cognitive improvement throughout childhood after premature birth. The limited number of preterm children born between 24 and 26 weeks of gestation included in this study could also explain the rather high IQ score for this group of preterm infants.

No differences in total intracranial volume, cerebral gray matter, white matter volume, and cerebrospinal fluid volume were observed after hydrocortisone treatment. Brain tissue volumes in the treated and untreated groups were similar despite differences in gestational age, birth weight, and the number of infants treated with mechanical ventilation, surfactant, and inotropes, favoring the untreated group. This is in contrast to a study of perinatal dexamethasone exposure among preterm infants at term, which

found a reduction of 30% in cortical gray matter volume after dexamethasone treatment for chronic lung disease.[14]

The increased sensitivity of the hippocampus to corticosteroids and chronic psychosocial stress is well known.[34;35] The exposure to hydrocortisone in our study did not have any lasting effect on hippocampal volume at 8 years of age. There are no other studies addressing directly the effect of postnatal corticosteroid treatment on hippocampal volume among human subjects.

In our study, the preterm infants received hydrocortisone at a starting dose of 5 mg/kg per day, equivalent to one third of the glucocorticoid activity of a dexamethasone dosage of 0.5 mg/kg per day, as used in most published studies. Moreover, the biologic half-life of hydrocortisone is 5 times shorter than that of dexamethasone, which reduces the risk of cumulative dosing.[36] Aside from the differences in glucocorticoid activity and half-life of hydrocortisone, several mechanisms could explain the absence of significant effects of hydrocortisone on brain development. Both hydrocortisone and dexamethasone can cross the blood-brain barrier.[37;38] Hydrocortisone, however, binds preferentially to the mineralocorticoid receptors in the brain,[38;39] whereas dexamethasone binds preferentially to the glucocorticoid receptor. In neuronal cells of the dentate gyrus, this binding to the glucocorticoid receptor was shown to induce the expression of the proapoptotic molecule Bax.[40] The exacerbation by dexamethasone of neuronal cell death through apoptosis in the dentate gyrus was also described by Hassan et al,[41] who demonstrated a neuroprotective effect of corticosterone, the physiological form of hydrocortisone, in rats.

Both the structural development at 8 years of age and the neurofunctional outcomes measured with a standardized neurocognitive assessment scale did not differ for the children treated with hydrocortisone. This is in agreement with the outcome data of the recently published comparison study of postnatal hydrocortisone and dexamethasone treatment, with favorable outcome for hydrocortisone-treated infants,[16] and is in contrast to several studies that examined neurocognitive outcomes after dexamethasone treatment, which showed significant associations with neurodevelopmental delays.[6;42]

In conclusion, we were able to show that prematurity affects long-term structural and functional brain development. Furthermore, this study showed that postnatal hydrocortisone treatment for chronic lung disease has no effect on cerebral brain tissue volumes, no effect on hippocampal development, and no negative effect on neurocognitive outcomes at 8 years of age. These findings have potentially important implications for the treatment of chronic lung disease in the neonatal period.

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6

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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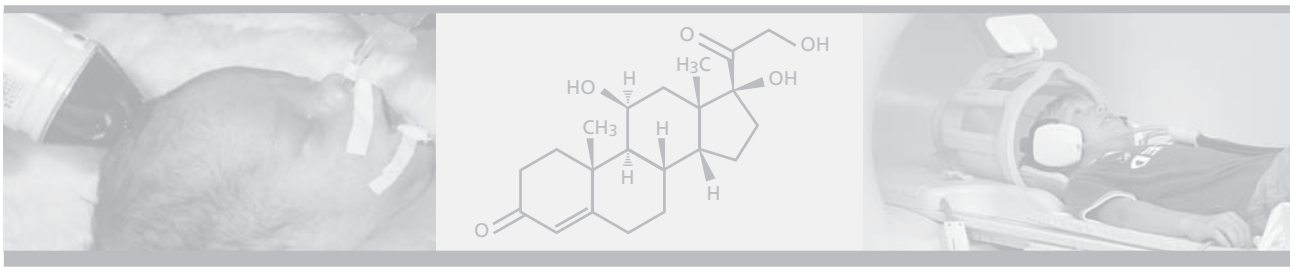

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Abstract

Background: 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.

Aim: 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.

Patients and Methods: In this observational study 37 preterm-born children (gestational age ≤ 32 weeks (range 25.0-33.0) and/or 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.

Results: Hydrocortisone-treated children were younger, lighter and sicker than their non-steroid-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.

Conclusion: 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.

Introduction

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 neurological 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 postnatally 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.

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) ≤ 32 wk (range 25.0-33.0) and/or a birth weight (BW) ≤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 months 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 prior to extubation (n=2) were excluded from this study.
The Medical Ethics Committee of the University Medical Center Utrecht approved the study and parental informed consent was obtained.

Cranial US

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).

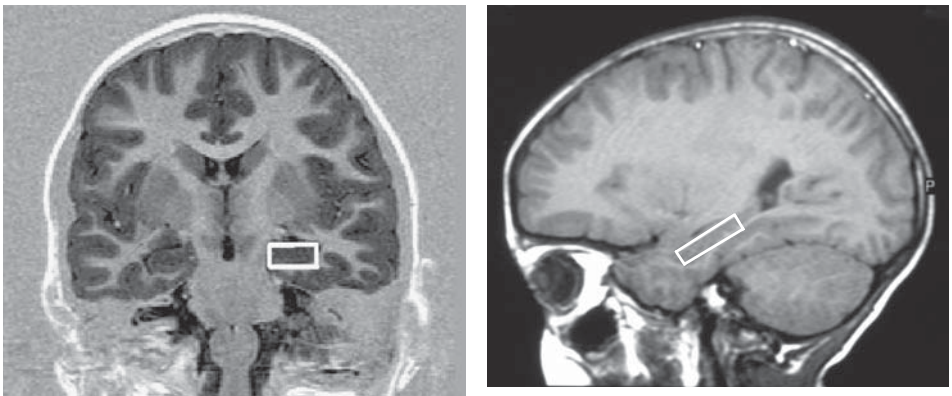

Figure 1: Image of the Volume of Interest (VOI) placed in the hippocampus

MRI and ^{1}H-MRS

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).

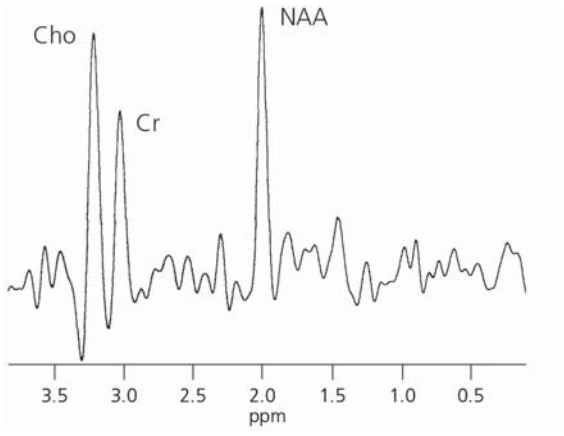

Figure 2: Proton spectroscopy of the hippocampus, echo time 144 msec.
NAA: N-acetyl-aspartate, Cr: (phospho)Creatine, Cho: Choline

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 25x15x10 mm^3 was placed in the hippocampus, avoiding contact with cerebrospinal fluid and white matter (Figure 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) (Figure 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%.

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 minutes and without further presentation, delayed recall is assessed. The 15 words 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 minutes 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 standard error 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 Chi-square 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 (SPSS, Chicago, Il, USA) 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 ventilation. 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 6 of the 18 steroid children were treated with a complete course of betamethasone (2 x 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 week and the child was ventilator-dependent with increasing oxygen requirements, which could not be explained by infection or a hemodynamically 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

Table 1: Patient characteristics

	No Steroids (n=19)	Steroids (n=18)	P value
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

Legend: GA, gestational age; BW, birth weight; PDA, patent ductus arteriosus; US, ultrasound; MRI, magnetic resonance imaging; 1 m, one ultrasound missing; handedness l, left-handed; handedness r, right-handed; group 1, normal findings; group 2, minor lesions; group 3, major lesions (see methods section)

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

Table 2: Mean NAA/(Cho+Cr) ratio in preterm infants at school age with and without prolonged use of steroids

	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) ratio adj (SEM)	0.63	(0.02)	0.67	(0.02)	0.19

Legend: SEM, standard error of mean; adj: adjusted for gender

compared with the non-treated group (0.67 versus 0.63), as shown in Table 2. Adjustment for gender did not influence the difference in the ratio. There was 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 non-steroid groups ($-6.55*10^{-2}$, p = 0.09).

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
Recall adj I (SEM)	6.16	(0.47)	6.66	(0.49)	0.47
Recall adj II (SEM)	6.32	(0.48)	6.49	(0.50)	0.81
Recall adj III (SEM)	6.25	(0.48)	6.57	(0.49)	0.64
IQ (SEM)	95	(2)	97	(3)	0.67

Legend: SEM, standard error of mean; adj I, adjusted for gender; adj II, adjusted for NAA/(Cho+Cr) ratio; adj III, adjusted for IQ

15-word recall

The hydrocortisone group scored in the same range on the 15-word memory test (delayed recall after 20 minutes) in comparison with the non-steroid 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 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 y 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 cerebrospinal 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 = 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 leaves the possibility of confounding. 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 neurological 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 hours in contrast to the 36-72 hours 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 ≥ 10 mg per day for ≥ 6 mo) were found to have smaller hippocampal volumes, lower NAA/Cho and NAA/(Cho+Cr) ratios and lower scores on the Rey's Auditory Verbal Learning Test compared with controls.[28] Although less potent than dexamethasone, prednisone is still 4 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 non-steroid 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 to 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 administration. 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]

In conclusion, 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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7

Postnatal hydrocortisone treatment in the preterm newborn: clinical indications and long-term neurodevelopmental follow-up

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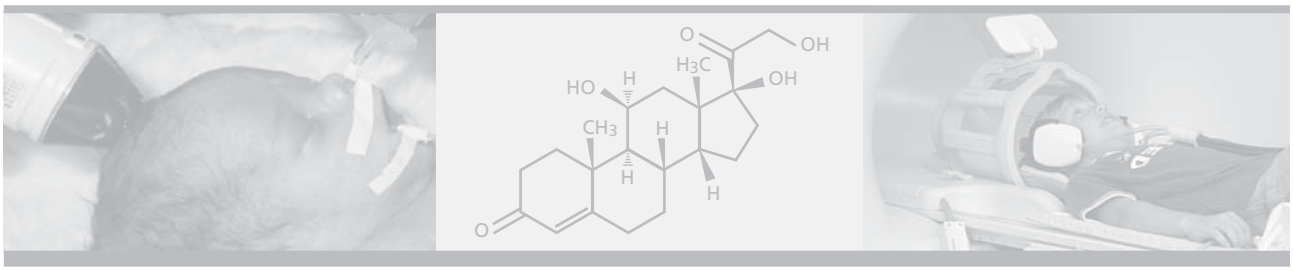

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Abstract

Two main indications for postnatal hydrocortisone treatment in preterm-born infants can be distinguished: prevention or treatment of chronic lung disease and refractory hypotension. This paper gives an overview of the current literature on postnatal hydrocortisone treatment and evaluates the available long-term outcome data.

Introduction

In contrast with the consensus about the benefits of maternal steroid treatment to accelerate fetal lung maturation,[1] there is an ongoing debate about the pros and cons of postnatal corticosteroid administration to preterm-born infants.[2-6] After initial reports in the nineteen eighties suggesting short-term benefits of steroids in ventilator-dependent infants, dexamethasone (DXM) became the widely and almost exclusively used drug for preventing or treating chronic lung disease in preterm infants.[7] One retrospective study examining the outcome of neonates with a birth weight between 500 and 749 g, showed that 43% of infants born between 1990 and 1992 received DXM, compared with as many as 84% of those born between 1993 and 1995.[8] The almost routine use of DXM continued until 1998, when Yeh et al published the results of a large multicenter follow-up study that demonstrated a significant increase in neurodevelopmental dysfunction in neonates treated with DXM compared with controls.[9] More alarming publications on the long-term negative effects of DXM appeared,[10;11] and as a result a gradual decrease in postnatal steroid prescription was noted.[12] The American Academy of Pediatrics stated in 2002 that, outside of clinical trials, postnatal steroid use should be reserved for "exceptional clinical circumstances" only.[13] However, a recent prospective evaluation of postnatal steroid administration in California from April 2002 to March 2003 showed, that 19.3% of the children ≤ 1500 g still received steroids: 3.6% for chronic lung disease alone, 11.8% for other indications (mainly hypotension) and 4% for both indications.[14] Of the infants weighing 500 to 749 g, as many as 41.8% were treated with postnatal steroids.

Whereas it is strongly advocated not to prescribe DXM for treatment of chronic lung disease any more, hydrocortisone (HC) is increasingly used in neonatal medicine for prevention of chronic lung disease and treatment of refractory hypotension. Explicit negative long-term neurodevelopmental sequelae following neonatal DXM treatment have been reported over the past years.[9-11;15;16] HC could be a suitable alternative for DXM if adverse long-term effects are less but studies on long-term outcome after postnatal HC use in preterm infants are scarce.

The aim of this review is to summarize the literature on postnatal HC treatment in preterm infants by taking into account the clinical indications for its use and the available data on long-term neurodevelopmental outcome.

Hydrocortisone and chronic lung disease

Five reports on postnatal HC administration for prevention (n=4) or treatment (n=1) of chronic lung disease have been published: details of which are shown in Table 1. The first randomized placebo-controlled trial of HC therapy already appeared in 1972.[17] The study was conducted to evaluate the ability of postnatally administered HC to alter the course of outcome in infants with hyaline membrane disease. Forty-four infants with a mean gestational age of 32.5 weeks were treated with HC or a lactose placebo within 24 hours after birth. There was no significant effect on $PaO_{2,}$ $PaCO_2$, need for assisted mechanical ventilation or survival.

No further studies on HC and respiratory disease were published hereafter until 1999, when Watterberg et al enrolled forty preterm infants into a randomized pilot study to test whether early treatment with low dose HC for 12 days, started within 48 hours after birth, would increase the likelihood of survival without bronchopulmonary dysplasia.[18] The rationale for this study was that many extremely low birth weight infants (< 1000 g) show biochemical evidence of adrenal insufficiency in the first week of life, correlating with subsequent development of chronic lung disease.[19] Adrenal insufficiency is also associated with amplified inflammatory responses, because cortisol is essential for resolution of inflammation. Infants who develop chronic lung disease have been shown to have increased indicators of both prenatal and postnatal inflammation.[20] Sixty percent of the HC-treated infants survived without supplemental oxygen at 36 weeks postmenstrual age in contrast to 35% in the placebo group. HC treatment decreased the number of days on > 40% oxygen, days on > 25% oxygen, days on ventilator and oxygen at discharge. Although fewer children in the HC group were subsequently treated with DXM, there was no difference in median days of DXM administration between the two groups. Adverse short-term neonatal complications were similar for the two groups.

A retrospective study comparing 25 preterm infants who were treated for chronic lung disease with a much higher dose of HC with 25 controls from the same center, showed equal reduction in the need for extra oxygen and successful weaning from the ventilator as shown when comparing 23 patients receiving DXM with 23 controls in another center.[21] There was no difference in mean arterial blood pressure, blood glucose, weight gain or intestinal problems between the HC and a non-steroid control group.

The multicenter trial following the 1999 pilot study,[18] enrolled mechanically ventilated infants with a birth weight of 500 to 999 g between 12 and 48 hours of life.[22] Patient enrolment was stopped at 360 patients because of an increase in spontaneous gastrointestinal perforation in the HC-treated group. For the total population, prophylaxis of early adrenal insufficiency did not improve survival without chronic lung disease nor

mortality at 36 weeks. However, in the patients exposed to histologic chorioamnionitis (representing a large proportion: 149 out of 180 patients receiving HC), HC did significantly decrease mortality and increase survival without chronic lung disease. From the study, an interactive effect between simultaneous administration of HC and indomethacin was suggested as in these children a significantly higher percentage suffered from spontaneous gastrointestinal perforation.
Finally, Peltoniemi et al investigated the effect of early HC treatment on survival without bronchopulmonary dysplasia (BPD) in infants ≤ 30 weeks and noticed a tendency towards lower incidence of BPD in the HC group.[23] This study was also discontinued early at an inclusion of 51 infants due to a higher incidence of gastrointestinal perforation in the HC group. Three of the four children in the HC group who suffered from this complication had been treated simultaneously with indomethacin/ibuprofen. The HC-treated infants with serum cortisol concentrations above the median had a high risk of gastrointestinal perforation. Infants with cortisol values below the median, who were treated with HC, showed increased survival without bronchopulmonary dysplasia.
Four of the five studies mentioned here, aimed at prevention of (chronic) lung disease by early administration of HC, whereas in the only retrospective study HC was prescribed to treat chronic lung disease. Dose and duration of HC treatment varied considerably and three of the five studies were contaminated by open-label steroids prescription (DXM) during and after HC treatment (Table 1).

Hydrocortisone and refractory hypotension

Systemic hypotension is a common problem in critically ill preterm infants and is known to have a diverse and multifactoral etiology.[24] In some patients a volume- and pressor-resistant hypotension exists: increasing the amount of fluid expanders and dosage of inotropes does not lead to restoration of adequate mean arterial blood pressure. In these infants postnatal steroids and in particular HC have been used to treat hypotension as the pressor resistance may reflect relative adrenal insufficiency, often noted in VLBW infants.[25]
The immature hypothalamo-pituitary-adrenal axis is not capable of maintaining higher corticosteroid production, so adrenergic receptor down-regulation and desensitization of the cardiovascular system to catecholamines will develop during critical illness. Steroids can regulate cardiovascular adrenergic receptor expression through their genomic effects resulting in a decrease in inotrope requirements after 6-12 hours. Steroids also have non-genomic properties like increasing intracellular calcium availability in the heart and vascular smooth muscle and inhibiting both catecholamine metabolism and release

Table 1: Hydrocortisone and chronic lung disease

Study no	First author Ref no	Year	Type of study	Number of patients	Treatment allocation	mean GA	mean BW	HC indication
1	Baden[17]	1972	Randomized, placebo controlled	44	22 HC 22 placebo	32.5 31.8	1730 1767	prophylaxis
2	Watterberg[18]	1999	Randomized, double-masked, placebo-controlled pilot	40	20 HC 20 placebo	25.2 25.4	732 770	prophylaxis
3	Van der Heide[21]	2003	Retrospective non-randomized	50	25 HC 25 control	28.3 28.4	1040 1090	treatment
4	Watterberg[22]	2004	Randomized, double-masked, placebo-controlled	Enrolment stopped at 360*	180 HC 180 placebo	25.2 25.3	731 734	prophylaxis
5	Peltoniemi[23]	2005	Randomized, placebo-controlled	Enrolment stopped at 51*	25 HC 26 placebo	26.7 26.5	888 903	prophylaxis

Legend: Ref no, reference list number; no, number; GA, gestational age; SD, standard deviation; BW, birth weight; HC, hydrocortisone; CLD, chronic lung disease; *, enrolment stopped due to an increase in spontaneous gastrointestinal perforation in the HC-treated group; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia

Table 1: Hydrocortisone and chronic lung disease, continued

Study no	Dose	Duration	Cumulative dose	Postnatal age at start	Effects on pulmonary function	Open-label systemic steroids (dexamethasone)
1	15 mg/kg 2x	1 d	30 mg/kg	< 24 hours	No significant effect on PaO_2, $PaCO_2$, oxygen need, need for assisted ventilation and survival	no
2	1 mg/kg 9 d 0.5 mg/kg 3 d	12 d	10.5 mg/kg	< 48 hours	HC treatment decreased days on > 40% and > 25 % oxygen, days on ventilator and oxygen at discharge	yes
3	5 mg/kg 7 d 3.75 mg/kg 5 d 2.5 mg/kg 5 d 1.25 mg/kg 5 d	22 d	72.5 mg/kg	2.1 weeks (SD 1.5)	From day 7 no significant difference in amount of extra oxygen needed between HC-treated infants and controls	no
4	1 mg/kg 12 d 0.5 mg/kg 3 d	15 d	13.5 mg/kg	12-48 hours	No difference in survival without CLD and mortality. For patients exposed to histologic chorioamnionitis (n=149), HC treatment significantly decreased mortality and increased survival without CLD compared with placebo	HC: 18% during treatment 38% during/after treatment Placebo: 28% during treatment 41% during/ after treatment
5	2.0 mg/kg 2 d 1.5 mg/kg 2 d 0.75 mg/kg 6 d	10 d	11.5 mg/kg	< 36 hours	Incidence of BPD tended to be lower and PDA was lower in the HC group	HC: 28% Placebo: 46%

Legend: Ref no, reference list number; no, number; GA, gestational age; SD, standard deviation; BW, birth weight; HC, hydrocortisone; CLD, chronic lung disease; *, enrolment stopped due to an increase in spontaneous gastrointestinal perforation in the HC-treated group; PDA, patent ductus arteriosus; BPD, bronchopulmonary dy splasia

Table 2: Hydrocortisone and refractory hypotension

Study no	First author [Ref no]	Year	Type of study	Number of patients	Treatment allocation	Mean GA	Mean BW	Medication at start HC
1	Helbock[27]	1993	observational	6	n.a.	25.5	672	Dopamine/Dobutamine 24-60 µ/kg/m
2	Ramanathan[28]*	1996	unknown	34	19 HC 15 DXM	25 25	705 659	Dopamine/Dobutamine 10-20 µ/kg/m
3	Bourchier[29]	1997	randomized	40	21 HC 19 dopamine	26.6 27.5	923 1043	none
4	Rajah[30]*	1998	observational	20	n.a.	25	n.m.	none
5	Krediet [33]*	1998	randomized	26	13 HC 13 placebo	n.m.	n.m.	Dopamine/Dobutamine > 20 µ/kg/m
6	Seri[31]	2001	retrospective	21	n.a.	26.9	952	Dopamine/Dobutamine/Epinephrine
7	Heckman[32]*	2002	retrospective	30	n.a.	26.0	n.m.	16/30 Dopamine 5 µ/kg/m
8	Noori[34]*	2005	prospective	14	n.a.	29.3	n.m.	Dopamine >15 µ/kg/m +/- Dobutamine
9	Efird[35]	2005	prospective randomized	Enrolment stopped at 34 #	16 HC 18 placebo	26 26	775 790	none
10	Ng[36]	2006	prospective randomized	48	24 HC 24 placebo	27.2 26.0	918 920	Dopamine ≥10µ/kg/m

Legend: *, abstract or letter; Ref. no, reference number; n.a., not applicable; GA, gestational age; BW, birth weight; n.m., not mentioned; HC, hydrocortisone; #, enrolment stopped because of unexpectedly slow rate of enrolment and pending national collaborative study; VLBW, very low birth weight; d, days; DXM, dexamethasone

Table 2: Hydrocortisone and refractory hypotension, continued

Study no	HC indication	Dose	Duration	Postnatal age at start (hours)	Effects
1	treatment	1.5-6 mg/d	4/6 < 2 weeks 2/6 retreatment	8.5 (4-14)	↑ Blood pressure, discontinuation of vasopressors within 30 hours
2	treatment	n.m.	n.m.	n.m.	In all infants inotropes could be stopped within 12-48 hours after steroids. ↑ incidence of Candida infection in HC group
3	treatment	2 x 2.5 mg/kg 1 d tapered off	7 d	HC 11.4 (13)	All 19 Dopamine infants responded, 17 of 21 (81%) of HC responded (p=0.11)
4	prophylaxis	1.5 mg/kg/6 hours	2-3 d, then tapered off		Since the introduction of prophylactic HC, no cases of refractory hypotension
5	treatment	5 mg/kg/d	n.m.	n.m.	In the HC –treated patient significantly rapid increase of MAP
6	treatment	16: 2 mg/kg/d 5: 3-6 mg/kg/d	n.m.	11.3 d (13.1)	Rapid normalization of the cardiovascular status and sustained decreases in volume and pressor requirement
7	treatment	2-3 mg/kg	n.m.	1.6 d (0.6)	Mean blood pressure increased significantly by 1 and 2 hours after first HC dose
8	treatment	2 mg/kg, 1mg/kg q12 hours x 4 doses	n.m.	18.5 d (14.9)	HC improves blood pressure without compromising cardiac function and organ perfusion
9	prophylaxis	2 mg/kg/d, tapered off	5 d	< 3 hours	Prophylactic treatment with HC reduced the incidence of hypotension defined by treatment with vasopressors during the first 2 days
10	treatment	3 mg/kg d	5 d	11 (8-15) 12 (9-15)	A stress dose of HC was effective in treating refractory hypotension in VLBW infants

Legend: *, abstract or letter; Ref. no, reference number; n.a., not applicable; GA, gestational age; BW, birth weight; n.m., not mentioned; HC, hydrocortisone; #, enrolment stopped because of unexpectedly slow rate of enrolment and pending national collaborative study; VLBW, very low birth weight; d, days; DXM, dexamethasone

of local vasoactive factors, resulting in a rapid (1-2 hours) increase in cardiovascular responsiveness to catecholamines.[26] Finally, steroids suppress the inflammatory response and improve capillary integrity, which will result in the maintenance of an effective circulating blood volume and cardiac output.

The first publication on HC treatment for hypotension in the human newborn appeared in 1993, when Helbock reported six preterm newborns who showed an increase in mean arterial blood pressure following administration of HC after failure of volume expanders and vasopressors.[27] The dose of HC was calculated to approximate the expected adrenal output of cortisol associated with stress. After this initial observation, more reports on the effect of HC on blood pressure were published: [28-35] details are shown in Table 2. These studies were mainly observational, retrospective and results often non-peer reviewed. Dose of HC, postnatal age at start and duration of treatment varied considerably.

Only very recently, the first larger prospective double-blind, randomized, placebo-controlled study of a stress dose of HC for rescue treatment of refractory hypotension in preterm infants was reported in which 48 VLBW preterm infants requiring ≥ 10 ug/kg/min of dopamine were randomly assigned to receive HC or placebo.[36] Significantly more HC-treated infants weaned off vasopressor support after starting treatment. The trend towards an increased mean arterial blood pressure was also significantly higher in HC-treated infants.

In conclusion, the results from published research consistently show a blood pressure raising effect of HC, also at low doses. Because of the mineralocorticoid properties of HC, HC offers a theoretical advantage over DXM, which could not be demonstrated in the single available study that compared HC and DXM for treating refractory hypotension in VLBW infants.[28]

Long-term follow-up

Two follow-up reports based on the initial 1972 HC trial to alter the course or outcome in infants with respiratory distress syndrome were published. The autopsy of 14 of the 16 children, who died within two months of birth (7 in the HC and 7 in the placebo group) revealed no differences in lung, liver, adrenal, thymus, heart and spleen pathology, attributable to steroid treatment. However, a statistically significant association was found between the occurrence of intraventricular hemorrhage and HC treatment.[37] At the age of one year, 24 survivors (12 in the HC and 12 in the placebo group) were examined. There was no difference in rate of growth or in ultimate size. HC therapy was not associated with an increased rate of infection and tests for immune competence were normal in both groups. Infants who received HC tended to have a slightly increased incidence of gross neurological and electroencephalographic abnormalities but the Griffiths Developmental Scale showed a normal developmental quotient in both groups. On analysis of the subtests there was a significant difference in the results for the gross motor development with a lower mean score for the HC group.[38]

Van de Heide et al retrospectively studied a group of 25 preterm infants treated with high dose HC and found no difference in neurological outcome, psychomotor development or school performance at the age of 5-7 years compared with a non-treated control group, matched for GA, BW, severity of IRDS, IVH and period of admission. In the same study a group of DXM-treated infants required more special school education and had worse neurological outcome compared with controls.[21]

The first follow-up data on the 360 children, who participated in the prophylactic HC trial of Watterberg et al, were presented at the 2006 spring meeting of The American Pediatric Societies. Significantly more placebo infants received systemic steroids (DXM) during study treatment (18% in the HC versus 28% in the placebo group, $p = 0.02$). At the age of 20.0 ± 2.1 months, 252 of 294 survivors (86%) were evaluated by certified examiners, masked to treatment assignment. There were no differences in length, weight, head circumference, percentage on bronchodilators and inhaled/systemic steroids between the HC and the placebo group. Incidence of cerebral palsy was similar, as was the mean Mental and Physical Developmental Index, as estimated with the Bayley Scales of Infant Development II (BSID-II). However, a significantly smaller percentage of HC-treated infants had a Mental Developmental Index below 70 (27% in the HC group versus 37% in the placebo group, $p = 0.02$).[39]

In a follow-up study of our own institute, 23 preterm-born children (mean GA 28 ± 2 weeks), who received neonatal HC treatment for chronic lung disease (starting dose of 5 mg/kg/d, tapered over a minimum of 3 weeks) and 35 children (mean GA 30.4

± 1.5 weeks), not treated with HC during the neonatal period, were evaluated with quantitative MRI and neurocognitive assessment at the age of 8 years. HC treatment was introduced at a median age of 18 d (range 4-43 d) and none of the children were treated with DXM at a later stage, avoiding contamination of the outcome results. HC-treated and non-treated children were found to have similar volumes of gray matter, white matter, cerebral fluid and hippocampus. The WISC-R scores were within the normal range for both groups, with no difference between the groups.[40] In a subgroup of these patients proton magnetic resonance spectroscopy of the hippocampus was performed.[41] Eighteen HC-treated infants (mean GA 27.9 ± 1.7 weeks) were compared with 19 non-treated preterm infants (mean GA 30.6 ± 1.7 weeks). Although the HC-treated children were younger, lighter and sicker than their non-steroid treated counterparts, there was no difference in N-acetyl aspartate/ (choline and (phospho) creatine) ratios between the two groups at a median age of 8.4 years. Moreover, performance on the 15-word memory test was similar.

Recently, an extended group of preterm-born children, including the above mentioned population, was evaluated.[42] Sixty-two preterm-born children, who were treated with HC for chronic lung disease during the neonatal period, were compared with 164 children, who never received steroids during their NICU admission. HC-treated children had a lower GA as well as BW, and were sicker than the non-steroid children. To better deal with these group differences, adjustment for GA, BW, gender, need for mechanical ventilation and small for gestational age was made. Adjusted mean IQ, Visual-Motor Integration and memory test results were the same for the HC and non-treated group. The incidence of cerebral palsy was similar. There was also no difference in motor function as assessed with the Movement Assessment Battery for Children between the two groups. All children had an MRI of their brain and occurrence of brain lesions as well as mean midsagittal corpus callosum areas were the same in HC-treated children, compared with non-treated children.

At the 2006 spring meeting of the American Pediatric Societies, our group reported the results of a retrospective study on long-term effects on behavior and motor skills in school age (7-10 years) children, who received either DXM or HC for chronic lung disease. A non-treated control group and a group treated exclusively antenatally with betamethasone were included in the analysis. All groups were matched for gestational age, birth weight, gender, grade of respiratory distress syndrome and rate of peri/ intraventricular hemorrhage. Dexamethasone-treated children had more neuromotor problems compared with the control and betamethasone group, while HC-treated children did not differ in outcome from these two groups.[43]

Discussion

The available data as summarized in this paper, suggest that HC is a safer drug for treating neonates with chronic lung disease than DXM. No differences in neurocognitive or motor outcome nor in incidence of brain abnormalities on MRI were found after HC treatment for bronchopulmonary dysplasia in the long-term follow-up studies at 5-8 years of age.[21;40-43] Importantly, these children were treated exclusively with HC and no contamination by later prescription of DXM had taken place. In the one follow-up study of prophylactic HC for preventing chronic lung disease, a large percentage of children was treated with open-label DXM during or after the study period.[39] Open-label contamination may result in the treatment and placebo groups becoming more similar than intended, making it complicated to detect a difference in outcome among the two groups. Besides, open-label contamination will also increase the steroid dose received by babies in the index treatment arm, making interpretation even more difficult.

In contrast to the emerging long-term follow-up reports on children treated with HC for chronic lung disease, long-term follow-up data on children treated with HC for refractory hypotension are not available until now. Despite the absence of information on safety and efficacy at this early age and for this indication, HC has become the choice of treatment for preterm neonates with vasopressor-resistant hypotension.[14;44;45] The total dose of HC in hypotension treatment is generally lower than the dose used for preventing and especially for treating chronic lung disease. However, a major problem is that many of the hypotension infants will be treated with DXM for chronic lung disease later on, which makes interpretation of possibly adverse neurodevelopmental sequelae exclusively due to HC very difficult. In the study of Ng as many as 25% of the HC-treated and 29% of the placebo-treated infants for refractory hypotension eventually received postnatal DXM for bronchopulmonary dysplasia.[36]

There could be several explanations why HC therapy may not be associated with long-term neurological deficits, whereas DXM is. DXM is a synthetic glucocorticoid, which has an anti-inflammatory power 25-30 times higher than HC. The typical dose of HC is much lower than that of DXM in most studies. This is also reflected in fewer neonatal short-term complications with the use of HC, compared with DXM.[21]

In brain DXM binds preferentially to the glucocorticoid receptor,[46] while HC binds preferentially to the mineralocorticoid receptor. Animal studies have shown that activation of the glucocorticoid receptor leads to adverse neuronal effects.[47;48] In a neuronal cell culture model, stimulation of the glucocorticoid receptor, such as occurs with (high-dose) DXM treatment, promotes apoptosis of granule cells in the hippocampus, whereas stimulation of the mineralocorticoid receptor, as with (low-dose) HC treatment, is

protective against apoptosis. The opposing actions of mineralocorticoid receptor and glucocorticoid receptor on neuronal survival result from their ability to differentially influence the expression of members of the bcl-2 gene family (major regulatory components of the apoptotic pathway).[49]

The biologic half-time life of DXM is 36-72 hours in contrast to the 8-12 hours of HC. There may be less risk of accumulation of medication with the use of HC. The preservative agent to control microbial and oxidative degeneration in DXM is sodium bisulphite. Exposure of a neuronal cell line (rat mesencephalic cells) to high levels of sulphite induced a time-dependent decrease in viability.[50] Sulphites were shown to be toxic *in vitro* to cultures of neurons and *in vivo* to the brains of 3-5 day old mouse pups.[51]

The question is why such excess of medication like DXM should be used when a much milder drug is also effective in reducing oxygen requirement. A recent study showed that a lower dose of DXM than generally used (0.89 mg/kg/10 days) is also effective in facilitating extubation and shortening duration of intubation among ventilator-dependent ELBW infants at a median treatment age of 23 days.[52] There was little evidence for a reduction in either mortality rate or the rate of oxygen dependency at 36 weeks. Hopefully, follow-up data will be available within several years, elucidating whether adverse neurodevelopmental effects are less at a lower dose of DXM.

One could argue that the infants in the HC follow-up studies were at a more advanced GA, when receiving the medication than in most DXM studies. However, the first report on the negative long-term effects of postnatal DXM by Yeh et al [9] was about children with a mean GA of 29.8 ± 2.3 weeks, the study of Shinwell was also on infants with a mean GA of 29.2 ± 2.6 weeks when receiving DXM.[10] A possible factor could be that in the HC follow-up studies, the infants were already two weeks postnatal, whereas in these DXM studies the infants received the medication shortly after birth. Still in one study, there were considerably more cases of cerebral palsy and abnormal neurological examinations at 1 year of age after a 42-day course of DXM, started after 2 weeks of age.[11] Another study described 22 infants (BW < 1250 g and GA < 30 weeks) who survived till 15 years and who were ventilator-dependent at 2 weeks of age. Nine received a 42-day course of DXM, 8 an 18-day course of DXM and 5 infants did not receive steroids. The authors concluded that the 42-day course was associated with improved long-term neurodevelopmental outcome, however the number of patients in each subgroup was very small.[53]

We think that there is a rationale for treating infants, who can not be weaned from the ventilator after the second week of life, with HC. The fact that the infant can be extubated earlier (without negative short-term side effects like hyperglycemia, hypertension, decreased weight gain) improves quality of life during NICU admission considerably. The

infant does not need endotracheal suction anymore, can be handled much more easy by nurses and parents and no additional baro- or volutrauma by mechanical ventilation is applied.

In two HC studies patient enrolment was stopped because of an increased incidence of spontaneous gastrointestinal perforation in combined HC-indomethacin treatment.[22;23] A cohort study of adult patients who were treated with corticosteroids combined with NSAIDs reported a more than 2-fold increased risk of gastrointestinal bleeding compared with the use of corticosteroid alone.[54] In VLBW infants, low-dose HC alone (in the absence of co-treatment with prophylactic indomethacin) did not lead to gastrointestinal perforation.[55] Treatment with HC after two weeks of postnatal age will avoid the interactive effect of HC with indomethacin, therefore reducing the risk of gastrointestinal perforation considerably. Although two publications reported an increased risk of disseminated Candidal infections in HC-treated infants,[28;56] this was not confirmed in other studies.[22;36]

We should aim for the lowest dose and shortest course of the least toxic steroid that facilitates weaning off the ventilator and protects against chronic lung disease. Taking into account the reassuring reports on postnatal HC treatment versus the alarming reports on postnatal DXM treatment regarding long-term neurodevelopment, a change in prescribing corticosteroids in neonatal practice in favor of HC after two weeks of postnatal age for treatment of chronic lung disease seems hard to criticize. Still, additional long-term follow-up studies are needed, especially in preterm-born infants of a lower gestational age and of an earlier postnatal age at the start of treatment.

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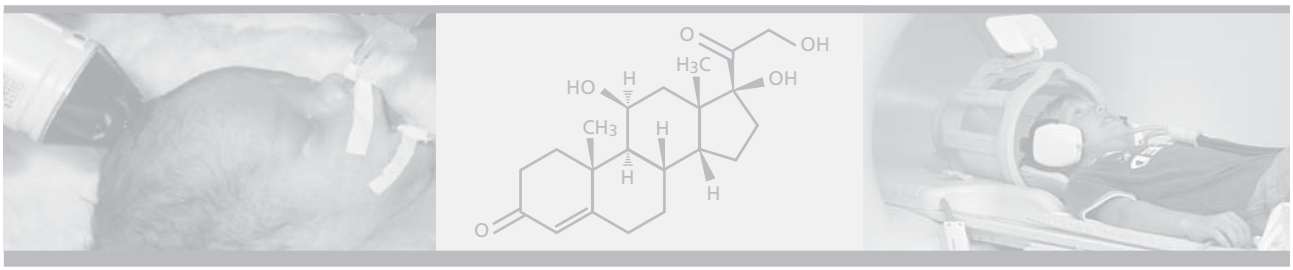
8

Summary and future directions



Summary

Preterm delivery, defined as delivery before 37 completed weeks of gestation, occurs in 7 to 10% of all pregnancies and is the most important cause of infant morbidity and mortality. Modern neonatal intensive care techniques have resulted in an increased survival of very low birth weight infants. However, long-term outcome of these high-risk infants remains a matter of serious concern. This thesis describes neurodevelopmental outcome at school age of a cohort of 236 preterm-born children with a gestational age (GA) ≤ 32 weeks and/or a birth weight (BW) ≤ 1500 g without congenital abnormalities and/or chromosomal disorders, born between March 1, 1991, and March 1, 1993, and admitted to the Neonatal Intensive Care Unit (NICU) of the Wilhelmina Children's Hospital in Utrecht, The Netherlands. This unit is one of the 10 level III NICUs in the country and is part of the University Medical Center Utrecht. The 236 children comprise 83.4% of the surviving population of the mentioned GA and BW that had been admitted during this time period. *Chapter 1* describes the aims and outline of the thesis.

All preterm infants had their brains evaluated by serial cranial ultrasound (US) as part of routine care. In *Chapter 2* neonatal cranial US scans of 221 children (78% of the original cohort) were compared with school age MRIs of the same children. Mean GA of the children was 29.4 weeks (standard deviation (SD) 2.0) and mean BW 1197 g (SD 315).
Cranial US findings were classified into three groups: normal when no or minor abnormalities like germinal layer/plexus cysts, subependymal pseudocysts or calcifications as exclusive findings were present (group 1), mildly abnormal when an intraventricular hemorrhage (IVH) grade I/II, periventricular leukomalacia (PVL) grade I or germinal layer necrosis or a combination of these features were present (group 2), severely abnormal when one or more of the following features were present: IVH grade III/IV, cystic-PVL grade II/III, thalamic lesion, focal infarction or convexity hemorrhage (group 3). Ventricular dilatation (VD) as a single feature was assigned to the mildly abnormal group. VD following a hemorrhage (posthemorrhagic VD) with need for therapeutic intervention was listed in the severely abnormal group.
MRI findings were also classified into 3 groups: normal when no abnormalities were present or when a solitary finding like an arachnoid cyst was found (group1), mildly abnormal when mild gliosis, mild VD, irregular shape of the ventricles, corpus callosum thinning or a combination of these were present (group 2), severely abnormal when extensive gliosis or gliosis combined with marked VD was present (group 3). Thalamic lesions, abnormal retrochiasmatic part of the visual system, cerebellar and cortical atrophy were also classified as major abnormalities.

Overall there was poor correspondence between neonatal US and school age MRI. Those in US groups 1 and 2 had an approximately 50% chance of being in the corresponding MRI groups. Despite poor overall correspondence, over 70% of those with major lesions on US had major lesions on MRI. There was only a 1% chance among those with a normal US of having a major lesion on MRI.
We also investigated which imaging technique correlated best with IQ (assessed with subtests of the WISC-R, Dutch edition) and motor performance (assessed with the Movement Assessment Battery for Children (ABC)). Mean IQ overall was 100. Mean IQ in US group 1 was marginally higher than in group 2 but substantially and significantly higher than in group 3. Mean IQ in MRI group 1 was marginally but significantly higher than in group 2, however substantially and significantly higher compared with group 3. The proportion of children with an IQ ≤ 85 was not different between US groups 1 and 2 but significantly higher in US group 3. For MRI groups the same pattern was seen. Movement ABC tests resulted in a median overall total impairment score (TIS) of 5.5. Median TIS in US group 1 was not significantly different from group 2, but substantially and significantly different between US groups 1 and 3. In the MRI groups, median TIS between groups 1 and 2 and between groups 1 and 3 were both significantly different. The proportions of children with definite motor problems (TIS < p5), borderline problems (TIS p5-p15) and normal motor performance (TIS > p15) were not significantly different between US and MRI groups 1 and 2. However a significant difference between groups 1 and 3, both for US and MRI was found.
Cerebral palsy (CP) was present in 20 children: only one child, with cerebellar ataxia, had a normal neonatal cranial US, but a severely abnormal MRI. Of the remaining 19 CP children, 4 had a mildly abnormal US and 15 had a severely abnormal US. Not one of the CP children had a normal MRI, 3 had a mildly and 17 a severely abnormal MRI.
A normal neonatal cranial US, if obtained in a systematic way within regular time intervals, excludes a severely abnormal MRI at school age in 99% of all cases. However, half of the children with normal US do have minor abnormalities on MRI. MRI findings correlated better with mean IQ and median TIS at school age than US. Although statistically significant, these differences appear not to be clinically relevant for normal and mildly abnormal MRI groups.

Only a relatively small number of high risk preterm infants proceeds to develop CP but many will later show a developmental coordination disorder referred to as clumsiness. *Chapter 3* evaluates the relation between the size of the corpus callosum, the main white matter gateway between the two hemispheres, and the occurrence of motor problems in 204 preterm-born children, who at the time of evaluation were 7 or 8

years old. Frontal, middle, posterior and total areas (mm^2) of the corpus callosum were measured on midsagittal MRI. The preterm group consisted of 15 children with CP and 189 children without CP. A reference group of 21 term-born children of the same age, was also investigated. On visual analysis, the shape of the corpus callosum was abnormal in 67% of the preterm children with CP and in 21% of the preterm children without CP ($p < 0.0001$). The shape of the corpus callosum was found to be normal in all controls. All measured midsagittal areas of the corpus callosum were significantly smaller for the entire group of preterm children compared with term controls. All measured areas of the children with CP were also smaller compared with the preterms without CP. However, in the preterm children without CP, all areas except the frontal part of the corpus callosum were also significantly smaller compared with term-born controls. As expected, the CP children performed poorly on the Movement ABC: 87% had a TIS < p5, compared with 11% of the preterms without CP. There was a statistically significant inverse association between the TIS and the area of the corpus callosum. The higher the TIS (indicating poorer motor performance), the smaller the area of the corpus callosum. This association was found for all parts of the corpus callosum but clearly increased in the direction of the posterior part. There was also a positive linear association for all measured areas of the corpus callosum and the VMI: a larger area of the corpus callosum was associated with a better outcome on the VMI. This study provides strong support for a critical role of corpus callosum size in predicting motor performance.

Despite improved mechanical ventilatory strategies and administration of exogenous surfactant, bronchopulmonary dysplasia (BPD) remains a problem in neonatal intensive care practice. The most commonly and almost exclusively prescribed drug to prevent and to treat BPD is dexamethasone (DXM), which has been used worldwide for over twenty years. Corticosteroids improve short-term respiratory function, leading to a reduction in supplemental oxygen requirements and earlier extubation. However, many side effects (short-term as well as long-term) have been reported. The adverse long-term effects on neurodevelopment are particularly alarming. Instead of DXM, the Wilhelmina Children's Hospital, historically has always used the milder hydrocortisone (HC) for treatment of BPD. In the next three chapters long-term outcome of preterm-born children, treated with HC during the neonatal period, is presented.

Chapter 4 describes the neurodevelopmental outcome at school age of 226 preterm-born children: 62 were treated with HC for BPD and 164 did not receive corticosteroids. HC was started at a median age of 19 d (inter quartile range (IQR): 14 d). Mean age of the steroid group had advanced to 30.5 postmenstrual weeks at the start of treatment,

which was not significantly different from the GA at birth of the non-treated group. Neonatal HC treatment generally consisted of a starting dose of 5 mg/kg/d, divided into 4 doses for one week, followed by a tapering course of 3, 2 and 1 dose(s) each for 5 d. Median length of administration of HC was 27.5 d (IQR: 12 d). Cognitive development, motor performance and occurrence of brain lesions on conventional MRI were assessed at a median age of 8.1 years, which was the same for the HC and the non-treated group. HC-treated children were younger, lighter and sicker than their non-steroid counterparts. Because of these group differences outcome was adjusted for GA, BW, gender, need for mechanical ventilation and small for gestational age using a propensity score.
There were no statistically significant differences between the HC-treated children and the non-treated children in mean IQ (99 vs. 101, p = 0.62), VMI (97 vs. 99, p = 0.49) and short-term memory results (15-word Test 7.9 vs. 7.5, p = 0.42). There was no significant difference in the occurrence of CP between the two groups either (11% vs. 7%, p = 0.34). Motor performance of the non-CP children was the same for the two groups: median TIS for both was 5.5. The midsagittal area of the corpus callosum was also identical and HC-treated children did not show more brain lesions on conventional MRI than non-treated children. We concluded that HC in the mentioned dose, administered in the neonatal period for BPD, did not appear to have long-term effects on neurodevelopment.

Chapter 5 evaluates long-term consequences of prematurity itself and of neonatal HC treatment on structural and functional brain development, using 3D-MRI with advanced image-processing and neurocognitive assessment. Sixty children born preterm (25 children treated with HC, 35 children not treated with HC) and 21 children born at term were evaluated at a mean age of 8 years with quantitative MRI and the WISC-R Dutch edition. Automatic image segmentation was used to determine the tissue volume of cerebral gray matter, white matter and cerebrospinal fluid. In addition the volume of the hippocampus, an organ very susceptible to corticosteroids, was determined manually. Neonatal HC treatment for BPD consisted of the same regime as mentioned in chapter 4.
Cerebral gray matter volume was reduced in preterm children (regardless of HC treatment) when compared with children born at term (649 ± 4 ml vs. 666 ± 7 ml, p = 0.046). Birth weight was shown to correlate with gray matter volume at 8 years of age in the preterm group (r = 0.421, p = 0.001). Cerebrospinal fluid volume was increased in children born preterm compared with children born at term (228 ± 5 ml vs. 206 ± 8 ml, p = 0.027). Total hippocampal volume tended to be lower in children born preterm, with a more pronounced reduction of hippocampal volume in boys (6.1 ± 0.1 ml vs. 6.56 ± 0.2 ml, p = 0.06). The WISC-R score was lower in children born preterm compared with children born at term (99 ± 12 vs. 110 ± 9, p = 0.001). Children treated with neonatal HC had

very similar volumes of gray matter, white matter, CSF and hippocampus compared with non-treated infants. The WISC-R score was within normal range in both groups, with no difference between the groups (101 ± 13 vs. 99 ± 12, p = 0.53).
Postnatal HC treatment in the mentioned dose had no effect on brain volumes, including hippocampal volume, in preterm-born infants measured at school age. However, regardless of HC treatment, brain volumes of all preterm-born infants were smaller in comparison with brain volumes in term-born infants.

In *Chapter 6* Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) was used to measure brain metabolites *in vivo* in the hippocampus. Animal studies have shown that corticosteroids (dexamethasone) lead to neuronal loss in the hippocampus and deficits in short-term memory.
We investigated whether postnatal administration of HC in preterm-born children changes the metabolism in the hippocampus, measured at school age and whether hippocampal metabolism and short-term memory and neurodevelopmental outcome are related.
Thirty-seven preterm children underwent proton spectroscopy of the hippocampus at school age. Eighteen children were treated with HC 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 + (phospho)creatine (NAA/(Cho+Cr)) ratios were determined. A 15-word recall memory test and an IQ measurement were obtained on the same day. HC-treated children were younger, lighter and sicker than their non-steroid-treated counterparts. Mean NAA/(Cho+Cr) ratios in the hippocampus were not significantly different in the HC 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.
Hydrocortisone in the mentioned dose, administered in the neonatal period for BPD, did not appear to have any long-term effects on memory and/or hippocampal metabolism.

In *Chapter 7* the clinical indications for postnatal HC administration in current neonatal practice and the available long-term neurodevelopmental outcome data are presented after a search in the literature. Two main indications for HC prescription during the NICU period are recognized: firstly prevention or treatment of chronic lung disease (CLD) and secondly prevention or treatment of refractory hypotension (persistent hypotension despite increased volume suppletion and vasopressors). Only 5 studies on HC prescription for CLD and about 10 studies on hydrocortisone for refractory hypotension have been published.

Four hydrocortisone studies aimed at prevention and one study aimed at treatment of CLD. Not all studies showed a positive effect of HC administration shortly after birth on prevention of CLD. In the patients exposed to histologic chorioamnionitis, HC did significantly decrease mortality and increase survival without CLD. However, 2 of the 4 studies had to be stopped due to an increased incidence of gastrointestinal perforation in the hydrocortisone-treated group. A relation with simultaneous use of indomethacine or ibuprofen was noted. As for treatment of refractory hypotension, all published research shows that HC is capable of exerting a systemic blood pressure raising effect, even at small doses.

Long-term follow-up data on postnatal HC treatment are not available for the infants who were treated with HC for refractory hypotension. A complicating factor in interpreting outcome is that the data can be contaminated by so-called open-label prescription of mainly DXM.

The neurodevelopmental studies of children who were treated with HC for BPD at the Wilhelmina Children's Hospital, where DXM is never prescribed for BPD, fail to show any negative effect of HC on neurocognitive or motor outcome nor on incidence of brain abnormalities on MRI. Only very recently, the first outcome data of the large American prophylactic HC multicenter trial have been presented and no negative sequelae of HC on cerebral palsy and mental and physical developmental indices were found. The infants in this study were at a younger GA than the Dutch children at the start of their HC treatment. They were also still at a young age (20.0 ± 2.1 months) when assessed for possibly subtle negative effects of the prescribed medication.

We concluded that the available data suggest hydrocortisone to be a safer drug for treating neonates with BPD but additional long-term follow-up studies are needed, especially in preterm-born infants of a lower gestational age and of an earlier postnatal age at the start of treatment.

Future directions

"What about imaging?"

We set out to investigate whether findings on conventional brain MRI, at a time when myelination is more or less completed (at the age of 2 years - in this thesis children of 7 to 10 years old were investigated, to avoid anesthesia-), would predict neurodevelopmental outcome at school age. Does MRI give more and better information about future motor and cognitive performance in preterm-born infants than serial neonatal cranial ultrasound examinations, which are performed anyway as part of routine care? Although

MRI findings were found to correlate better with mean IQ and motor performance than cranial ultrasound findings, these differences, while statistically significant, were clinically not very relevant. Besides, the age at which myelination is completed (2 years), is rather late to speak in terms of predicting outcome. It would be far more helpful if children at risk of an adverse outcome could be identified much earlier in life, to allow early introduction of intervention therapies. During the time period of completion of this thesis, MRI techniques and facilities ensuring safe conditions for very young patients during MRI acquisition (like special MRI-proof incubators and monitoring devices), have improved considerably.

MRI studies have now pointed out the value of the presence of the myelinated posterior limb of the internal capsule and the aspect of the peduncles at term equivalent age, in predicting motor problems in preterm infants with parenchymal hemorrhages. Subtle white matter lesions such as diffuse excessive high signal intensities (DEHSI) are clearly visible on term MRI, and these are especially related to cognitive outcome. A recent MRI study showed that at term equivalent age moderate to severe cerebral white matter abnormalities were present in 21% of the infants (gestational age ≤ 30 weeks), and these were predictive of adverse outcomes at two years of age (cognitive delay, motor delay, cerebral palsy and neurosensory impairment). Gray matter abnormalities, which are more difficult to detect with cranial ultrasound, were present in 49% of the infants and were also associated, though less strongly, with cognitive delay, motor delay, and cerebral palsy. These studies are most often performed at one fixed moment, i.e. term age equivalent, and findings are not compared with serial ultrasound examinations according to a standardized protocol.

The value and strength of ultrasound examinations are directly related to the frequency of the examinations. Because of the serial character of cranial ultrasonography, the evolution of brain lesions can be followed during the neonatal intensive care treatment which may lead to early intervention, for example in post hemorrhagic ventricular dilatation. A day-to-day monitoring of the size of the lateral ventricles (which determines the amount of cerebrospinal fluid to be punctured from an intraventricular reservoir) is only feasible with ultrasound. However, due to high pressure on the availability of intensive care incubators, infants are currently transferred to local hospitals sooner than some years ago, which may result in underestimation of certain cerebral lesions that take longer to develop, such as localized cystic lesions.

Cranial ultrasound should remain the method of first choice to detect brain lesions in preterm-born infants, but the number of MRIs at term age in selected patients has already increased considerably. MRI, at this age, however, should be seen as complementary to ultrasound and not as a replacement. An additional conventional MRI at 2 years of age

will probably not lead to much more information, although gliosis cannot be appreciated until 18 to 24 months.
Even newer MRI techniques, like diffusion tensor imaging, cortical folding analysis, functional MRI, and advanced three-dimensional volumetric MRI analyses are developing at a fast rate. These highly sophisticated techniques will certainly provide more and better insight into the anatomical basis of brain function. However, it remains to be seen whether preterm infants will benefit from these newer techniques in terms of early prognosis of neurodevelopmental outcome. To date, no extensive long-term follow-up data of patients, subjected to these newer techniques are available that show a better prediction of outcome compared with serial cranial ultrasonography and conventional term MRI alone.

"What about steroids?"

The American Academy of Pediatrics strongly recommends to restrict the use of systemic dexamethasone to carefully designed randomized, double-masked controlled trials. Another statement of the Academy is that clinical trials investigating the use of alternative anti-inflammatory corticosteroids, both systemic and inhaled, are required before additional recommendations can be made. Despite this recommendation, dexamethasone is still the drug of choice to treat severe chronic lung disease with many practicing neonatologists in many countries. In the trials in which hydrocortisone was used shortly after birth for prevention of chronic lung disease, neonatologists always prescribed dexamethasone at a later stage, when chronic lung disease developed in spite of initial prophylactic hydrocortisone treatment. This bears the risk of "contamination" of hydrocortisone treatment effects due to later dexamethasone prescription in some children.
This thesis presents long-term neurodevelopmental outcome data on the largest group of preterm infants, treated with postnatal hydrocortisone for chronic lung disease, described thus far. Our studies do not show adverse effects of hydrocortisone on functional and structural brain development in preterm-born children evaluated at school age. However, it should be noted that the children were of a higher gestational age than in most dexamethasone studies and that they were at a rather advanced postnatal age when receiving the hydrocortisone treatment. In The Netherlands, preterm infants with a gestational age of 24 weeks are only very rarely subjected to neonatal intensive care treatment but 25-weekers are nowadays admitted to the NICU on a regular base. We can therefore not be certain that at a younger gestational age, perhaps at a more vulnerable or susceptible period of brain development, hydrocortisone treatment similarly has no impact on later neurodevelopment.

Most of the follow-up studies on dexamethasone were placebo-controlled randomized studies, whereas the studies in this thesis were observational, in which adjustment for confounding factors like indication for treatment was made.

The question is how to move on from here. Although many adverse long-term effects of dexamethasone have been described and hydrocortisone consequently could offer an alternative, dexamethasone advocates are reluctant to change their prescription policy on the basis of our observational studies. Hydrocortisone advocates, on the other hand, are reluctant to participate in randomized studies with dexamethasone therapy in the alternative treatment arm, as they are convinced that hydrocortisone is a safer alternative. Both groups agree that the use of systemic steroids should be restricted to ventilator-dependent preterm infants, in whom other therapeutic interventions like fluid restriction, diuretics, and bronchodilation therapy have failed, and who are unlikely to survive otherwise.

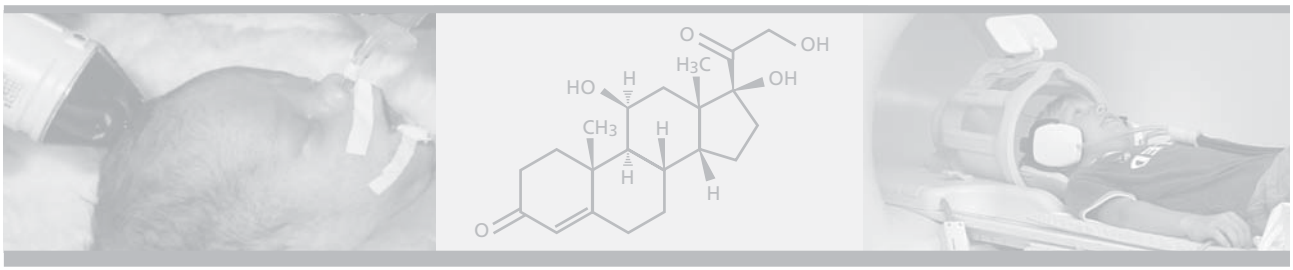
However, there is clearly a dispute that will presumably not be solved by exchanging current stand-points. Probably, the evidence needed to convince both "parties" will have to be obtained from a direct comparison of the two treatment strategies, preferably in a randomized controlled trial in which ventilator-dependent children with chronic lung disease are allocated to treatment with hydrocortisone or dexamethasone. Based on the experience described in this thesis, we are convinced of the relative benefits of hydrocortisone compared with dexamethasone to such an extent that a direct comparison of the two in a study would not be feasible locally.

Due to the growing reluctance in neonatal practice to use corticosteroids, it may be difficult to recruit a sufficient number of patients. Despite an increased number of admissions, systemic hydrocortisone treatment for bronchopulmonary dysplasia in patients with a GA ≤ 32 weeks and/or a BW ≤ 1500 g went down to 10 patients in our own unit in the year 2005, compared with over 35 per year in the early nineteen nineties! It goes without saying, that an extended period of follow-up of the participants in such a study is very important, as minor neurodevelopmental sequelae may only become evident when the child is faced with increased demands on an intellectual and motor level.

A well-designed trial offers the option to solve this issue once and for all, but this can only be done with the cooperation of many neonatal centers. Continuing treatment with dexamethasone does not seem wise; a complete shift to hydrocortisone prescription, including children of a very early gestational age, without a properly conducted trial, could create the risk of repeating mistakes made in the past. Currently, the clinical choice of steroids, dexamethasone or hydrocortisone, is largely based on cultures and training, rather than on sufficient evidence obtained from direct comparisons. However, in terms of quantitative published evidence, there is equipoise. Claims for either of the

steroids that randomized comparison would expose children to excessive (avoidable) risks or would presumably withhold the best treatment to some children are not based on direct evidence. As there will remain clinical indications for the administration of steroids to preterm-born infants, it is in the best interest of these children to provide such quantitative evidence. Therefore, neonatology as a discipline should aim to make a randomized comparison between dexamethasone and hydrocortisone possible.

Nederlandse samenvatting en toekomst perspectieven



Samenvatting

Vroeggeboorte, gedefinieerd als geboorte voor 37 complete zwangerschapsweken, komt voor in 7 tot 10% van alle zwangerschappen en is de belangrijkste oorzaak van morbiditeit en mortaliteit op de zuigelingenleeftijd. Moderne neonatale intensive care technieken hebben geresulteerd in een toegenomen overlevingskans voor kinderen met een zeer laag geboortegewicht. De ontwikkeling op de lange termijn van deze kinderen blijft echter iets dat serieuze aandacht vereist. Dit proefschrift beschrijft de uitkomst op cognitief en motorisch gebied, op de schoolleeftijd, van een cohort van 236 te vroeg geboren kinderen met een zwangerschapsduur ≤ 32 weken en/of een geboortegewicht ≤ 1500 gram, zonder aangeboren en/of chromosomale afwijkingen, geboren tussen 1 maart 1991 en 1 maart 1993, en opgenomen op de Neonatale Intensive Care Unit (NICU) van het Wilhelmina Kinderziekenhuis te Utrecht. Deze afdeling is een van de tien NICU's in Nederland en is onderdeel van het Universitair Medisch Centrum Utrecht. De 236 kinderen vormen 83.4% van de hierboven beschreven, nog in leven zijnde, populatie. *Hoofdstuk 1* beschrijft het doel en de opzet van het proefschrift.

Alle kinderen ondergingen schedelechografisch onderzoek als onderdeel van de routine klinische zorg tijdens hun opname op de NICU. In *Hoofdstuk 2* werden neonatale schedelecho's van 221 kinderen (78% van het oorspronkelijke cohort) vergeleken met MRI's van de hersenen van dezelfde kinderen op de schoolleeftijd. De gemiddelde zwangerschapsduur was 29.4 weken (SD 2.0) en het gemiddelde geboortegewicht bedroeg 1197 gram (SD 315).
De schedelechografische bevindingen werden ingedeeld in drie groepen: *normaal* indien er geen of minimale afwijkingen aanwezig waren zoals germinale laag/plexus cystes, subependymale pseudocystes of calcificaties als enige bevinding (groep 1), *licht afwijkend* indien sprake was van een intraventriculaire bloeding (IVH) graad I/II, periventriculaire leukomalacie (PVL) graad 1 of germinale laag necrose of een combinatie van deze verschijnselen (groep 2), *ernstig afwijkend* indien sprake was van IVH graad III/IV, cysteuze PVL graad II/III, thalamus laesie, focaal infarct of een bloeding aan de convexiteit van de hersenen (groep 3). Ventrikeldilatatie (VD) als enige verschijnsel werd geclassificeerd in de licht afwijkende groep. VD na een bloeding (posthemorrhagische ventrikeldilatatie), met de noodzaak tot therapeutisch ingrijpen werd in de ernstig afwijkende groep ingedeeld.
MRI bevindingen werden eveneens in drie groepen onderverdeeld: *normaal*, indien geen afwijkingen of een solitaire bevinding zoals een arachnoidale cyste werd gevonden (groep 1), *licht afwijkend*, indien sprake was van milde gliose, milde VD, een onregelmatige

ventrikelvorm, een dun corpus callosum of een combinatie hiervan (groep 2), *ernstig afwijkend* indien sprake was van uitgebreide gliose of gliose in combinatie met evidente VD (groep 3). Thalamus laesies, een abnormaal retrochiasmatisch deel van de visuele witte stof of cerebellaire en corticale atrofie werden eveneens ingedeeld bij de ernstige afwijkingen.

Over het geheel genomen bestond er weinig overeenkomst tussen neonatale schedelechografie en MRI op de schoolleeftijd. Diegenen in echogroep 1 en 2, hadden ongeveer een kans van 50% om zich in de corresponderende MRI groep te bevinden. Ondanks deze matige correlatie, hadden ruim 70% van de kinderen met ernstige afwijkingen op de neonatale schedelecho ook ernstige afwijkingen op hun latere MRI. Belangrijk was, dat voor kinderen met een normale neonatale schedelecho slechts een kans van 1% bestond op ernstige MRI afwijkingen.

Vervolgens hebben we onderzocht welke beeldvormende techniek het beste correleerde met twee uitkomstparameters: IQ (gemeten met subtesten van de WISC-R, Nederlandse versie) en motorische functie (gemeten met de Movement Assessment Battery for Children (ABC)). Het gemiddelde IQ van de hele groep was 100. Het gemiddelde IQ in echogroep 1 was marginaal hoger dan in groep 2, maar substantieel en significant hoger vergeleken met groep 3. Het gemiddelde IQ in MRI groep 1 was marginaal maar significant hoger dan in groep 2, echter substantieel en significant hoger vergeleken met groep 3. Het aandeel kinderen met een IQ $\leq$ 85 was niet verschillend tussen echogroep 1 en 2 maar wel significant groter in echogroep 3. Voor de MRI groepen werd eenzelfde patroon gezien.

De Movement ABC testen resulteerden in een mediane "total impairment score" (TIS) van 5.5. De mediane TIS in echogroep 1 was niet significant verschillend van groep 2, maar substantieel en significant verschillend tussen echogroep 1 en 3. Voor de MRI groepen gold dat de mediane TIS tussen groep 1 en 2 en tussen groep 1 en 3 beiden significant verschillend waren. Het aandeel kinderen met evidente motorische problemen (TIS < p5), borderline problemen (TIS p5-p15) en normale motorische functie (TIS > p15) was niet verschillend tussen echo en MRI groepen 1 en 2. Er bestond echter een significant verschil tussen groep 1 en 3, zowel bij de echo als de MRI.

Infantiele encephalopathie (IE) werd vastgesteld bij 20 kinderen: slechts één kind, met een cerebellaire ataxie had een normale neonatale schedelecho, echter een ernstig afwijkende MRI op de schoolleeftijd. Van de overige 19 IE kinderen hadden 4 een licht afwijkende en 15 een ernstig afwijkende schedelecho. Niet één van de IE kinderen had een normale MRI op de schoolleeftijd: 3 hadden een licht afwijkende en 17 hadden een ernstig afwijkende MRI.

Een normale neonatale schedelecho, verkregen op systematische wijze volgens een vast

protocol, sloot een ernstig afwijkende MRI op de schoolleeftijd uit in 99% van de gevallen. De helft van de kinderen met een normale echo hadden echter lichte afwijkingen op hun latere MRI. MRI bevindingen correleerden beter met gemiddeld IQ en mediane TIS op de schoolleeftijd dan schedelechografie. Hoewel statistisch significant, waren deze verschillen klinisch niet relevant voor de normale en licht afwijkende MRI groepen.

Slechts een minderheid van de te vroeg geboren high-risk kinderen ontwikkelt uiteindelijk een infantiele encephalopathie, maar velen vertonen later een coördinatiestoornis, welke motorische onhandigheid wordt genoemd. *Hoofdstuk 3* evalueert de relatie tussen de afmeting van het corpus callosum (de belangrijkste witte stof verbinding tussen de twee hersenhelften) en het vóórkomen van motorische problemen bij 204 te vroeg geboren kinderen, die ten tijde van het onderzoek 7 of 8 jaar oud waren. Het voorste, middelste, achterste en totale oppervlakte (mm^2) van het corpus callosum werd gemeten op midsagittale MRI opnames. De groep bestond uit 15 kinderen *met* en 189 kinderen *zonder* IE. De motorische functie werd gemeten met de Movement ABC; tevens werd de Visuele-Motorische Integratie test (VMI) afgenomen. Dezelfde onderzoeken werden verricht bij 21 a term geboren kinderen van dezelfde leeftijd, welke geen neonatale problemen hadden gekend.
De vorm van het corpus callosum was afwijkend in 67% van de prematuur geboren kinderen *met* en in 21% van de prematuur geborenen *zonder* IE ($p < 0.0001$). De vorm van het corpus callosum was normaal bij alle controle kinderen. Alle gemeten midsagittale oppervlaktes van het corpus callosum waren significant kleiner voor de gehele groep prematuur geboren kinderen vergeleken met de a term geboren controles. Alle gemeten oppervlaktes van de kinderen *met* IE waren eveneens kleiner vergeleken met de premature kinderen *zonder* IE. Echter: in de premature groep *zonder* IE, waren ook alle oppervlaktes, behalve die van het voorste gedeelte van het corpus callosum, kleiner vergeleken met de a term geboren controles. Zoals te verwachten, presteerden de IE kinderen matig op de Movement ABC: 87% hadden een TIS < p5, vergeleken met 11% van de ex-prematuren zonder IE. Er bestond een statistisch significante omgekeerde associatie tussen de TIS en het oppervlakte van het corpus callosum. Des te hoger de TIS (hetgeen inhoudt een slechtere motorische functie), des te kleiner het oppervlak van het corpus callosum. Deze associatie gold voor alle verschillende delen van het corpus callosum, maar nam duidelijk toe in de richting van het achterste gedeelte. Er bestond eveneens een lineaire associatie tussen alle gemeten oppervlaktes van het corpus callosum en de VMI: een groter corpus callosum oppervlakte was geassocieerd met een betere uitkomst op de VMI. Deze studie ondersteunt de belangrijke rol van de grootte van het corpus callosum bij het voorspellen van het latere motorisch functioneren.

Ondanks verbeterde beademingstechnieken en de toediening van surfactant, blijft bronchopulmonale dysplasie (BPD) een probleem binnen de neonatale intensive care. De prevalentie van BPD is hoog en de aandoening is een belangrijke oorzaak van mortaliteit en morbiditeit bij te vroeg geboren kinderen. Het meest frequent en bijna exclusief voorgeschreven middel om chronische longschade te voorkomen en BPD te behandelen, is dexamethason (DXM), dat wereldwijd al meer dan 20 jaar wordt gebruikt. Corticosteroïden verbeteren op korte termijn de respiratoire functie, wat leidt tot een afname van de extra zuurstofbehoefte en een snellere extubatie van beademde kinderen. Van DXM zijn inmiddels vele bijwerkingen beschreven; vooral de negatieve effecten van het middel op de lange termijn uitkomst geven aanleiding tot zorg. Het Wilhelmina Kinderziekenhuis heeft altijd het veel mildere hydrocortison (HC) gebruikt voor de behandeling van BPD. De volgende drie hoofdstukken presenteren de lange termijn uitkomsten van te vroeg geboren kinderen, welke tijdens hun neonatale intensive care periode behandeld werden met HC.

Hoofdstuk 4 beschrijft de ontwikkeling op de schoolleeftijd van 226 te vroeg geboren kinderen: 62 werden behandeld met hydrocortison en 164 werden niet met corticosteroïden behandeld. HC voor de behandeling van BPD was op de NICU gestart op een mediane leeftijd van 19 dagen met een interquartile range (IQR) van 14 dagen. Bij aanvang van de behandeling was de gemiddelde leeftijd van de HC kinderen gevorderd tot 30.5 postmenstruele weken, hetgeen niet significant verschilde van de zwangerschapsduur bij de geboorte van de niet behandelde groep. Neonatale HC behandeling bestond in het algemeen uit een startdosis van 5 mg/kg/dag, verdeeld over 4 giften gedurende een week, gevolgd door een geleidelijk afnemende kuur van 3, 2 en 1 gift(en), elk gedurende 5 dagen. De mediane lengte van de HC kuur bedroeg 27.5 dagen (IQR: 12 dagen). Voor 58 van de 62 kinderen kon de cumulatieve hydrocortison hoeveelheid per kilo gemiddeld lichaamsgewicht (gemiddeld gewicht: het gewicht aan het eind van de behandeling plus het gewicht aan het begin van de behandeling, gedeeld door 2) berekend worden, wat uitkwam op 70 mg/kg gemiddeld gewicht (IQR: 21 mg/kg).
Cognitieve ontwikkeling, motorische functie en het voorkomen van afwijkingen op een conventionele MRI van de hersenen werden onderzocht op een mediane leeftijd van 8.1 jaar (zowel van de HC groep als van de niet behandelde groep). HC behandelde kinderen waren na de geboorte jonger, lichter en zieker dan de niet met steroïden behandelde kinderen. Vanwege deze groepsverschillen werden de uitkomsten geadjusteerd voor zwangerschapsduur, geboortegewicht, geslacht, noodzaak tot beademing, en dysmaturiteit, met behulp van een zogenaamde "propensity score".

Er waren geen statistisch significante verschillen tussen de met HC behandelde en de niet behandelde kinderen in gemiddeld IQ (99 vs. 101, p = 0.62), VMI scores (97 vs. 99, p = 0.49) en korte termijn geheugen resultaten (15-woorden test 7.9 vs. 7.5, p = 0.42). Het optreden van infantiele encephalopathie was eveneens niet significant verschillend tussen de twee groepen (11% vs. 7%, p = 0.34). De motorische functie van kinderen zonder IE was exact hetzelfde voor de twee groepen: de mediane TIS bedroeg voor beiden 5.5. De midsagittale oppervlakte van het corpus callosum was ook identiek en HC behandelde kinderen hadden niet meer afwijkingen op de MRI van hun hersenen dan niet behandelde kinderen. Wij concludeerden dat hydrocortison, in de genoemde dosering, toegediend tijdens de neonatale periode voor de behandeling van BPD, geen nadelige effecten op de lange termijn ontwikkeling van deze kinderen veroorzaakt had.

Hoofdstuk 5 evalueert de lange termijn effecten van prematuriteit op zich en van neonatale hydrocortison behandeling in het bijzonder op de structurele en functionele ontwikkeling van de hersenen, gebruik makend van driedimensionele MRI, met geavanceerde beeldbewerking en neurocognitieve onderzoeken. Zestig te vroeg geboren kinderen (25 behandeld met HC, 35 niet behandeld met HC) en 21 a term geboren kinderen werden onderzocht op een gemiddelde leeftijd van 8 jaar met kwantitatieve MRI en de WISC-R. Om het volume van de cerebrale grijze stof, witte stof en liquor te bepalen werd automatische-beeld-segmentatie gebruikt. Daarnaast werd het volume van de hippocampus (een orgaan dat zeer gevoelig is voor corticosteroïden) handmatig bepaald. Neonatale hydrocortison behandeling voor BPD bestond uit hetzelfde regime als beschreven onder hoofdstuk 4.
Onafhankelijk van hydrocortison behandeling, was het volume van de cerebrale grijze stof kleiner bij te vroeg geboren kinderen in vergelijking met a term geboren kinderen (649 ± 4 ml vs. 666 ± 7 ml, p = 0.046). Bij de te vroeg geboren groep bleek op de leeftijd van 8 jaar het geboortegewicht te correleren met het grijze stof volume (r = 0.421, p = 0.001). Het liquorvolume was toegenomen bij te vroeg geboren kinderen vergeleken met a term geboren kinderen (228 ± 5 ml vs. 206 ± 8 ml, p = 0.027). Het totale hippocampusvolume was bijna significant kleiner bij te vroeg geboren kinderen, met een meer uitgesproken afname van het hippocampusvolume bij jongens (6.1 ± 0.1 ml vs. 6.56 ± 0.2 ml, p = 0.06). De WISC-R score was lager voor te vroeg geboren kinderen in vergelijking met a term geboren kinderen (99 ± 12 vs. 110 ± 9, p = 0.001).
Met hydrocortison behandelde kinderen hadden vrijwel identieke volumes van grijze stof, witte stof, liquor en hippocampus vergeleken met niet behandelde te vroeg geboren kinderen. De WISC-R score viel voor beide groepen binnen de normale range, zonder verschil tussen de groepen (101 ± 13.0 vs. 99 ± 12, p = 0.53).

We concludeerden dat postnatale hydrocortison behandeling in de genoemde dosering geen effect had op hersenvolumes van te vroeg geboren kinderen, gemeten op de schoolleeftijd. Behalve het witte stof volume, bleken echter alle gemeten hersenvolumes van alle te vroeg geboren kinderen, ongeacht hydrocortison behandeling, kleiner te zijn dan de hersenvolumes van op tijd geboren kinderen.

In *Hoofdstuk 6* wordt de toepassing van Proton Magnetische Resonantie Spectroscopie (^{1}H-MRS) om hersenmetabolieten in de hippocampus *in vivo* te meten beschreven. Dierstudies hebben aangetoond dat corticosteroïden (dexamethason) leiden tot verlies van neuronen in de hippocampus en tot verslechtering van het korte termijn geheugen. Wij onderzochten of toediening van hydrocortison in de neonatale periode aan te vroeg geboren kinderen de stofwisseling in de hippocampus, gemeten op de schoolleeftijd, veranderd had. Ook onderzochten we of er een relatie bestond tussen het metabolisme van de hippocampus en korte termijn geheugen en IQ.
Zevenendertig te vroeg geboren kinderen ondergingen protonspectroscopie van de hippocampus op de schoolleeftijd: achttien waren behandeld met HC voor BPD, en negentien waren niet behandeld met steroïden. N-acetyl-aspartate/(choline + (phospho)creatine) (NAA/(Cho+Cr)) ratio's werden bepaald en een 15-woorden geheugentest en een IQ test werden afgenomen op dezelfde dag.
De met HC behandelde kinderen waren jonger, lichter en zieker dan de niet met steroïden behandelde kinderen. De gemiddelde NAA/(Cho+Cr) ratio's in de hippocampus waren niet significant verschillend tussen de behandelde en niet behandelde groep. De resultaten voor de geheugentest en de IQ test waren hetzelfde voor de twee groepen. Er bestond geen relatie tussen NAA/(Cho+Cr) ratio's en geheugen, noch tussen NAA/(Cho+Cr) ratio's en IQ.
We concludeerden dat HC in de genoemde dosering, toegediend in de neonatale periode voor BPD, geen nadelige lange termijn effecten had veroorzaakt op het geheugen en op het metabolisme van de hippocampus.

In *Hoofdstuk 7* worden de klinische indicaties voor postnatale hydrocortison medicatie in de huidige neonatologische praktijk en de beschikbare data betreffende uitkomst op de lange termijn besproken, na een zoektocht in de literatuur. Twee belangrijke redenen voor HC medicatie tijdens de NICU periode worden genoemd: de preventie of behandeling van chronische longziekte (CLD) en als tweede de preventie of behandeling van refractoire hypotensie (persisterende hypotensie ondanks verhoging van volume suppletie en inotrope medicatie). Er zijn slechts 5 studies betreffende HC toediening voor CLD en ongeveer 10 studies betreffende HC toediening voor refractoire hypotensie gepubliceerd.

Vier HC studies richtten zich op de preventie en één richtte zich op behandeling van CLD. Niet alle studies betreffende HC toediening kort na de geboorte, lieten een positief effect zien op het voorkómen van CLD. Hydrocortison verlaagde wel significant de mortaliteit en verhoogde de overlevingskans zonder CLD voor kinderen, die in utero bloot gesteld waren aan histologische chorioamnionitis. Twee van de vier studies moesten worden afgebroken in verband met een toegenomen aantal gevallen van gastrointestinale perforatie in de met HC behandelde groep. Er werd een relatie met gelijktijdig gebruik van indomethacine of ibuprofen vastgesteld. Ten aanzien van hydrocortison behandeling voor refractoire hypotensie lieten alle gepubliceerde studies zien dat HC, zelfs in lage dosering, in staat is tot een bloeddruk verhogend effect.

Lange termijn uitkomsten betreffende kinderen die behandeld zijn met HC voor hypotensie zijn tot nu toe niet beschikbaar. Een complicerende factor hierbij is, dat uitkomst resultaten gecontamineerd kunnen zijn door eventuele latere open label behandeling met dexamethason voor BPD.

De ontwikkelingsonderzoeken bij te vroeg geboren kinderen, die met HC behandeld waren in het Wilhelmina Kinderziekenhuis, waar nooit dexamethason wordt voorgeschreven voor BPD, toonden geen enkel negatief effect van hydrocortison op neurocognitief of motorisch vlak. Ook werd geen toegenomen incidentie van hersenafwijkingen op de MRI vastgesteld. Recentelijk zijn de eerste follow-up resultaten van de grote Amerikaanse profylactische multicenter HC trial gepresenteerd: er werden geen nadelige effecten van HC op neurocognitief functioneren noch op de incidentie van IE gevonden. De kinderen in deze studie waren van een kortere zwangerschapsduur dan de Nederlandse kinderen, ten tijde van hun HC behandeling. Op het moment van de follow-up waren de kinderen echter nog relatief jong (20.0 ± 2.1 maanden) om eventuele subtiele negatieve effecten van het voorgeschreven medicament goed te kunnen beoordelen.

De tot nu toe gepubliceerde follow-up gegevens suggereren dat hydrocortison een veiliger alternatief kan zijn voor de behandeling van kinderen met BPD. Echter, additionele lange termijn follow-up studies zijn nodig, vooral bij te vroeg geboren kinderen met een kortere zwangerschapsduur en bij kinderen van een jongere postnatale leeftijd bij de start van de behandeling.

Toekomst perspectieven

"Hoe nu verder met beeldvorming?"

Wij begonnen dit onderzoek met de vraag of bevindingen op een conventionele hersen-MRI, op het moment dat myelinisatie min of meer compleet is (de leeftijd van 2 jaar- om narcose te vermijden werden in dit proefschrift kinderen tussen de 7 en 10 jaar onderzocht-), de ontwikkeling op de schoolleeftijd kunnen voorspellen. Geeft MRI-onderzoek meer en betere informatie over toekomstig motorisch en cognitief functioneren van te vroeg geboren kinderen dan regelmatig neonataal schedelechografisch onderzoek, dat als onderdeel van de routine klinische zorg verricht wordt? Hoewel MRI bevindingen sterker correleerden met gemiddeld IQ en motorisch functioneren dan schedelechografische bevindingen, waren deze verschillen, weliswaar statistisch significant, klinisch niet echt relevant. De leeftijd waarop myelinisatie min of meer compleet is (2 jaar), is eigenlijk ook aan de late kant om nog echt in termen van "voorspelling" van uitkomst te spreken. Het zou veel waardevoller zijn indien kinderen, at risk voor een slechte uitkomst, eerder geïdentificeerd kunnen worden, zodat vroegtijdige introductie van interventie therapieën kan volgen.

In de periode van het schrijven van dit proefschrift, zijn MRI technieken en mogelijkheden voor bewaking van zeer jonge patiënten tijdens het maken van een MRI (zoals MRI compatibele couveuses en monitoren) aanzienlijk verbeterd.

MRI studies hebben aangetoond, dat de mate van myelinisatie van het achterste been van de capsula interna en het aspect van de cerebrale pedunkels op de a terme leeftijd, van voorspellende waarde zijn voor het eventuele optreden van motorische problemen bij te vroeg geboren kinderen met een parenchymbloeding. Subtiele witte stof afwijkingen, zoals "diffuse excessive high signal intensities" (DEHSI), zijn duidelijk zichtbaar op een MRI op de a terme leeftijd, en zijn vooral gerelateerd aan cognitieve uitkomst. Een recente MRI studie liet zien dat op de a terme leeftijd matige tot ernstige witte stof afwijkingen voorkwamen bij 21% van de kinderen (zwangerschapsduur ≤ 30 weken) en dat deze voorspellend waren voor een slechte uitkomst op de leeftijd van twee jaar (cognitieve en motorische achterstand, IE en neurosensorische handicaps). Grijze stof afwijkingen, welke moeilijker vast te stellen zijn met schedelechografie, waren aanwezig bij 49% van de kinderen en waren ook geassocieerd, zij het minder sterk, met cognitieve en motorische achterstand en IE. Deze studies worden vaak uitgevoerd op een bepaald vast moment, in het bijzonder op de a terme leeftijd, en de bevindingen worden vaak niet vergeleken met regelmatig verrichte schedelecho's, volgens een vast protocol.

De waarde en de kracht van echografisch onderzoek is juist direct gerelateerd aan het

aantal onderzoeken en aan de periode waarover de onderzoeken worden verricht. Door het regelmatige herhalen van de schedelechografie, kan de ontwikkeling van hersenafwijkingen tijdens de neonatale intensive care behandeling nauwlettend worden gevolgd. Zo nodig kan vroegtijdige interventie, zoals bij posthemorrhagische ventrikeldilatatie, plaatsvinden. Een dagelijkse meting van de ventrikelgrootte (zodat in voorkomende gevallen de hoeveelheid uit een intraventriculair reservoir te puncteren liquor bepaald kan worden) is alleen mogelijk met behulp van echografie. Als gevolg van de hoge druk op beschikbare intensive care couveuses, worden kinderen tegenwoordig echter vroeger overgeplaatst dan enkele jaren geleden. Dit zou kunnen leiden tot het mogelijk niet signaleren en daardoor onderschatten van bepaalde hersenafwijkingen, die soms langer nodig hebben om zichtbaar te worden, zoals gelokaliseerde cysteuze laesies.

Schedelechografie hoort het beeldvormend onderzoek van eerste keus te blijven om hersenafwijkingen bij te vroeg geboren kinderen op te sporen, maar het aantal MRI's op de a terme leeftijd in geselecteerde patiënten is reeds aanzienlijk toegenomen. Een MRI op deze leeftijd moet echter niet gezien worden als een vervanging van schedel-echografisch onderzoek, maar als een aanvulling hierop. Een additionele conventionele MRI op de leeftijd van 2 jaar levert waarschijnlijk niet veel extra informatie op, al wordt gliose meestal pas echt zichtbaar vanaf de leeftijd van 18-24 maanden.

Nog nieuwere MRI technieken, zoals diffusion tensor imaging, cortical folding analysis, functionele MRI en geavanceerde drie-dimensionele volume MRI beeldvorming, worden momenteel in een hoog tempo ontwikkeld. Deze zeer geavanceerde technieken zullen zeker meer en beter inzicht bieden in de anatomische basis van hersenfuncties. Het valt echter nog te bezien of te vroeg geboren kinderen van deze technieken zullen profiteren in de vorm van een vroegere prognose voor hun uiteindelijk functioneren. Tot op dit moment zijn geen uitgebreide, lange termijn follow-up gegevens bekend van patiënten die met deze nieuwe technieken onderzocht zijn. Het is dus nog onduidelijk of hiermee een betere voorspelling van uitkomst mogelijk is dan met frequente schedelechografie en conventionele a terme MRI alleen.

"Hoe nu verder met steroïden?"

De "American Academy of Pediatrics" adviseert dringend het gebruik van systemisch dexamethason te beperken tot zorgvuldig opgezette gerandomiseerde, dubbelblinde gecontroleerde trials. Een andere stelling van de "Academy" is, dat klinische trials, die het gebruik van alternatieve ontstekingsremmende corticosteroïden (zowel systemische als inhalatie) onderzoeken, nodig zijn, voordat aanvullende adviezen gegeven kunnen worden. Ondanks deze aanbevelingen, is dexamethason wereldwijd nog steeds het

middel van eerste keus voor vele neonatologen om chronische longziekte bij te vroeg geboren kinderen te behandelen. Ook in de trials waarin hydrocortison kort na de geboorte werd toegediend om CLD te voorkomen, schreven neonatologen op een later moment (als ondanks de initiële HC behandeling toch chronische longzieke was ontstaan), altijd dexamethason voor. Dit brengt het risico met zich mee van "contaminatie" van de behandelingseffecten van hydrocortison als gevolg van de latere behandeling met dexamethason.

Dit proefschrift beschrijft de lange termijn uitkomsten van de tot nu toe grootste groep prematuur geboren kinderen, welke behandeld zijn met hydrocortison voor chronische longziekte. Onze studies konden geen nadelige gevolgen van hydrocortison medicatie op functionele en structurele hersenontwikkeling aantonen bij te vroeg geboren kinderen, onderzocht op de schoolleeftijd. Echter, opgemerkt dient te worden dat de kinderen van een langere zwangerschapsduur waren dan in de meeste dexamethason studies en ook dat ze al op een tamelijk gevorderde postnatale leeftijd waren, op het moment dat de hydrocortison medicatie gestart werd. In Nederland worden kinderen met een zwangerschapsduur van 24 weken slechts zelden blootgesteld aan een intensive care behandeling maar kinderen met een zwangerschapsduur van 25 weken worden tegenwoordig regelmatig op de NICU opgenomen. We kunnen daarom niet met zekerheid stellen, dat bij een kortere zwangerschapsduur, wellicht tijdens een meer gevoelige of kwetsbare periode van de hersenontwikkeling, een behandeling met hydrocortison eveneens geen nadelig gevolgen heeft voor de latere ontwikkeling.

De meeste dexamethason follow-up studies waren placebo gecontroleerde studies, terwijl de studies in dit proefschrift observationele studies waren, waarin uitkomsten geadjusteerd werden voor "confounding factors", zoals de indicatie voor behandeling.

De vraag is, hoe we nu verder moeten gaan. Hoewel er vele nadelige effecten van dexamethason zijn beschreven en hydrocortison dus een alternatieve behandelingsmogelijkheid zou kunnen bieden, zijn voorstanders van dexamethason niet geneigd hun medicatiebeleid te wijzigen op grond van onze observationele studies. Voorstanders van hydrocortison daarentegen, hebben grote bedenkingen bij deelname aan gerandomiseerde studies met dexamethason medicatie als een van de behandelingsarmen, omdat zij ervan overtuigd zijn dat hydrocortison een veiliger alternatief is. Beide groepen zijn het met elkaar eens dat het gebruik van systemische corticosteroïden beperkt moet worden tot die beademingsafhankelijke patiënten, bij wie andere therapeutische interventies zoals vochtbeperking, diuretica en verneveling niet helpen en die zonder corticosteroïden waarschijnlijk niet zouden overleven.

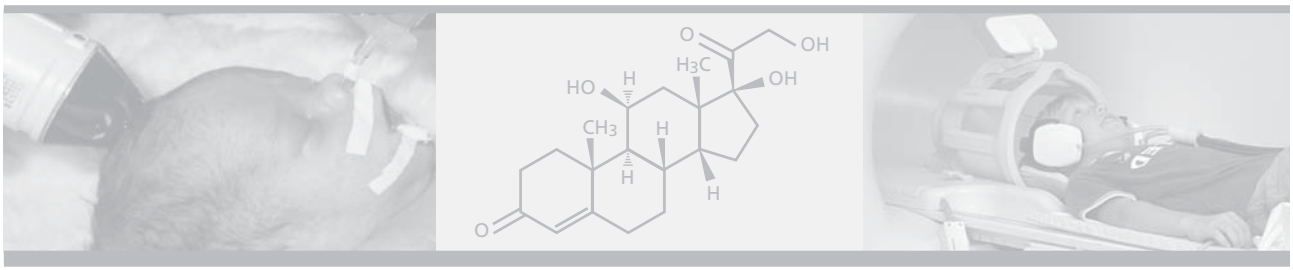
Er bestaat dus een duidelijk verschil van mening, dat vermoedelijk niet opgelost gaat worden door het uitwisselen van de huidige standpunten. Het nodige bewijs om beide

"partijen" te overtuigen, zal waarschijnlijk verkregen moeten worden uit een directe vergelijking van de twee behandelingsstrategieën, bij voorkeur in een gecontroleerde trial, waarin beademingsafhankelijke kinderen met chronische longziekte worden gerandomiseerd voor behandeling met hydrocortison of dexamethason. Op grond van de ervaringen in dit proefschrift beschreven, zijn wij echter dermate overtuigd van de relatieve voordelen van hydrocortison ten opzichte van dexamethason, dat een directe vergelijking van de twee behandelingen in een dergelijke studie in ons ziekenhuis in feite niet meer mogelijk is.

Vanwege de toenemende weerstand in de neonatologische praktijk om corticosteroïden te gebruiken, zou het wel eens moeilijk kunnen worden voldoende patiënten te includeren in een dergelijke studie. Ondanks een sterk toegenomen aantal opnames, is behandeling met hydrocortison voor bronchopulmonale dysplasie van patiënten met een zwangerschapsduur ≤ 32 weken en/of een geboortegewicht ≤ 1500 gram op onze eigen afdeling afgenomen tot slechts 10 patiënten in 2005 vergeleken met meer dan 35 per jaar in de vroege negentiger jaren. Verder spreekt het voor zich, dat in een dergelijke studie de kinderen over een langere periode gevolgd moeten worden, omdat subtiele nadelige effecten vaak pas zichtbaar worden op een moment waarop hogere eisen op intellectueel en motorisch vlak aan het kind gesteld worden.

Een goed opgezette trial biedt de mogelijkheid om deze zaak voor eens en voor altijd op te lossen, maar dit kan uitsluitend bereikt worden met de medewerking van vele neonatologische centra. Het zondermeer continueren van dexamethason voor de behandeling van chronische longziekte lijkt geen wijze keuze; een complete omslag naar hydrocortison zonder een correct uitgevoerde trial, ook aan kinderen van een zeer jonge zwangerschapsduur, draagt het risico met zich mee van herhaling van in het verleden gemaakte fouten. De klinische keuze voor één van beide steroïden is tegenwoordig meer gebaseerd op locale cultuur en opleiding, dan op voldoende bewijs vanuit directe vergelijkingen. In termen van kwantitatief bewijs bestaat momenteel geen duidelijkheid. Beweringen ten aanzien van elk van de steroïden, dat een gerandomiseerde vergelijking kinderen bloot zou stellen aan een excessief (vermijdbaar) risico of hen de veronderstelde beste behandeling zou onthouden, zijn niet gestoeld op direct bewijs. Omdat er klinische indicaties zullen blijven bestaan voor steroïdgebruik bij te vroeg geboren kinderen, is het voor deze kinderen van het grootste belang om een dergelijk kwantitatief bewijs te leveren. Daarom zou de neonatologie als vakgebied de mogelijkheid moeten scheppen voor een gerandomiseerde vergelijking van dexamethason met hydrocortison.

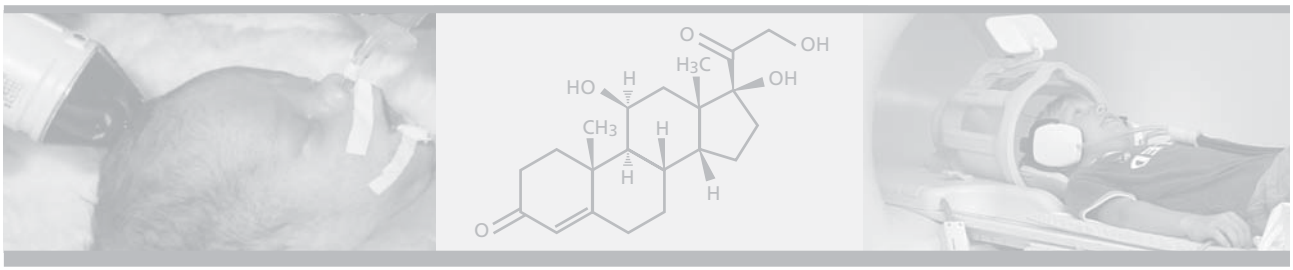
Abbreviations



BPD	bronchopulmonary dysplasia
BW	birth weight
CC	corpus callosum
Cho	choline
CI	confidence interval
CLD	chronic lung disease
CP	cerebral palsy
Cr	(phospho)creatine
CSF	cerebrospinal fluid
DEHSI	diffuse excessive high signal intensity
DXM	dexamethasone
FLAIR	fluid attenuated inversion recovery
GA	gestational age
HC	hydrocortisone
^{1}H-MRS	proton magnetic resonance spectroscopy
IRDS	infant respiratory distress syndrome
IQ	intelligence quotient
IQR	inter quartile range
IR	inversion recovery
IVH	intraventricular hemorrhage
lrc	linear regression coefficient
Movement ABC	movement assessment battery for children
MRI	magnetic resonance imaging
NAA	N-acetyl aspartate
NICU	neonatal intensive care unit
OR	odds ratio
PDA	patent ductus arteriosus
PHVD	posthemorrhagic ventricular dilatation
PVL	periventricular leukomalacia
SD	standard deviation
SEM	standard error of mean
SGA	small for gestational age
SS	standard scores
TIS	total impairment score
TSE	turbo spin echo
US	ultrasound
VD	ventricular dilatation

VLBW	very low birth weight
VMI	visual-motor integration
VOI	volume of interest
WISC-R	Wechsler intelligence scales for children-revised

List of publications



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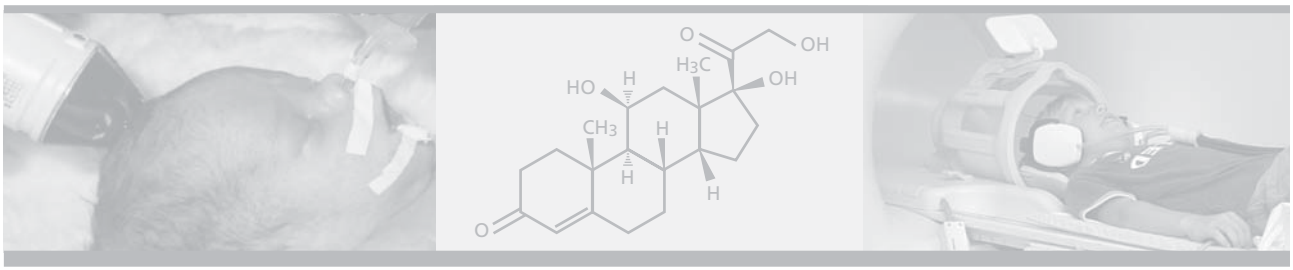
Dankwoord



Promoveren doe je nooit alleen, heel veel mensen hebben mij geholpen bij het schrijven van dit proefschrift en op deze plaats wil ik hen graag bedanken.

Allereerst wil ik de kinderen en hun ouders, die zo enthousiast aan dit onderzoek hebben meegewerkt, bedanken. Bijna alle kinderen had ik zelf, aanvankelijk als fellow neonatologie en later als beginnend staflid, mee behandeld, in de tijd dat ze op de NICU lagen. Het was indrukwekkend om ze terug te zien: van kwetsbare prematuren uitgegroeid tot basisschool kinderen. Natuurlijk waren het niet voor iedereen altijd even gemakkelijke jaren geweest. Ik bewonder de enorme veerkracht en positieve instelling van veel kinderen, vooral van diegenen, bij wie het niet allemaal mee zat.

Ook veel dank aan de controle kinderen, die samen met hun ouders zomaar een hele dag naar het ziekenhuis kwamen om een steentje bij te dragen aan dit onderzoek. Heel aardig dat jullie dit gedaan hebben.

Prof.dr. L.S. de Vries: beste Linda. Om vanuit een vriendschap naar een promotie toe te werken, is niet altijd eenvoudig geweest. We hebben niet voor niets hetzelfde sterrenbeeld en verstaan elkaar vaak met een half woord. Je moet af en toe gedacht hebben, dat het nooit af zou komen. Dat heb ik eerlijk gezegd zelf ook regelmatig gedacht, maar het is je toch gelukt een fervente clinicus enthousiast te maken voor het doen van onderzoek. Ik heb diep respect voor je ongelofelijke kennis en fenomenaal geheugen. Bij ieder afwijkend echoplaatje, weet jij altijd minstens drie kinderen van de afgelopen vijftien jaren bij naam, die hetzelfde gehad hebben. Heel erg bedankt voor je begeleiding. Ik hoop dat we nog lang in vriendschap zullen samenwerken en ik beloof je dat ik door zal gaan met het doen van onderzoek (en het samen bezoeken van leuke congressen).

Prof.dr. D.E. Grobbee: beste Rick. Een proefschrift, dat uiteindelijk toch minder epidemiologisch is geworden dan zich in eerste instantie liet aanzien. Bedankt voor je positieve, kritische begeleiding. Je opmerking: "Alles wat je schrijft, dat niet publiceerbaar is, is verspilling van tijd en energie" zal ik proberen te onthouden.

Dr. C.S.P.M. Uiterwaal: beste Cuno. Ik zou iedere promovendus een begeleider toewensen als jij. Met eindeloos geduld heb je samen met mij de analyses gedaan. SPSS was een volslagen mysterie voor me, ik ben er nog steeds niet goed in, maar dankzij jou begrijp ik er een stukje meer van. "Wat is nu precies de vraag" en "Hou het simpel" waren voor mij lichtbakens in het soms moeilijke schrijfproces. Ik hoop oprecht, dat ik in de toekomst

een beroep op je mag blijven doen. Heel leuk dat ons cohort prematuren ook nog een bijdrage heeft kunnen leveren aan jouw interessegebied betreffende (pathologische) linkshandigheid.

Dr. F. Groenendaal: beste Floris. Wie had dit ooit gedacht, toen je zestien jaar geleden samen met Anja een avond bij ons op bezoek kwam om te informeren hoe de neonatologie in Utrecht was. Ik ben nog steeds heel blij, dat je toen de stap hebt genomen om in het WKZ te komen werken. We hebben zelfs als twee ex-Rotterdammers (al was ik in jouw ogen natuurlijk geen echte) de eerste jaren een kamer gedeeld in het nieuwe WKZ. Jij hebt alle wervingstelefoontjes met ouders, die soms heel lang duurden, aan moeten horen. Ik bewonder je scherpte, je humor en je grote kennis op veel terreinen. Verder ben ik je dankbaar, dat je een soort wegenwacht voor acute computerproblemen hebt willen zijn, bijvoorbeeld als ik weer eens dacht mijn hele reference manager bestand kwijt te zijn.

Prof.dr. F. van Bel: beste Frank. Een proefschrift, waarin geleidelijk aan steeds meer hydrocortison verscheen. Jij, als de onomstreden "Mr. Steroids", hebt dat nauw gevolgd en gestimuleerd. Dank voor de ruimte en gelegenheid, die je als afdelingshoofd aan al die drukke moeders (en vaders!) binnen je staf schenkt, om onderzoek te kunnen doen. Dat het aantal promoties binnen de neonatologie de laatste jaren zo gestegen is, komt vooral ook door jouw positieve benadering van onderzoek.

De leden van de beoordelingscommissie: Prof.dr.ir. M.A. Viergever, Prof.dr. W.P. Fetter, Prof.dr. C.J. Heijnen, Prof.dr. O. van Nieuwenhuizen en Dr. F.M. Cowan dank ik voor het kritisch doornemen van dit proefschrift. A special word of gratitude to Dr. Frances Cowan, who makes the effort to come from London to participate in the defence ceremony of the thesis.

Dank aan de WKZ neonatologen van het eerste uur (Bob Senders, Leo Gerards en Ingrid van Ertbruggen), die tegen de toen gangbare trend in gingen, door aan BPD kinderen hydrocortison in plaats van dexamethason voor te schrijven, in een tijd dat het woord evidence-based waarschijnlijk nog niet eens bestond. Indien zij anders besloten hadden, had een groot deel van dit proefschrift niet geschreven kunnen worden.

Mijn huidige collegae neonatologen en fellows wil ik bedanken voor de interesse voor en steun tijdens het schrijven van dit proefschrift. Gedurende de soms lange bureaudagen

was een telefoontje van de NICU voor "een consultje arterielijn" altijd meer dan welkom. Ik ben erg blij dat ik in deze groep mag werken; ondanks alle individuele verschillen vormen we een hecht team, waarin gelukkig ook veel gelachen wordt. Ik wens Willem de Vries en Petra Lemmers veel succes met het afronden van hun proefschrift.

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Jacqueline Termote: collega, kamergenoot en dierbare vriendin geworden in al die jaren die we nu samen werken. Heel veel dank voor alle gesprekken over het leven, onze "continuing" Frankrijk - Italië strijd (maar over Griekenland worden we het vast wel eens met elkaar!) en de kilo's drop.

Onze secretaresses Daniëlle Nijssen, Ineke Krijgsman, Hanneke Dietz, Annemieke van de Vorst, Fiona van den Berg-Snijders, Edith Copier en Mariska Lagerweij dank ik voor het typen van alle wervingsbrieven, uitslagbrieven en het aannemen van ontelbare telefoontjes.

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Maarten Rijpert: als student heb je de spectroscopie gegevens nauwkeurig uitgewerkt en met je verslag uiteindelijk de WKZ studentenwetenschapsprijs gewonnen. Ik wens je veel succes met je eigen promotieonderzoek. Jeanine Lam bedank ik voor de corpus callosum metingen.

Gregory Lodygensky and Petra Hüppi: thank you for the Geneva-Utrecht collaboration, which resulted in a nice publication. It was wonderful to visit you in Geneva and I hope we will continue working together in the near future.

Dear Made Ramadhani: it was so nice to work with you on pathological left handedness in preterm-born infants and I thoroughly enjoyed the ESPR meeting in Siena, in which we both participated. I wish you lots of happiness together with Aleš in your new home country. Next year, the ESPR meeting will be held in Prague!

Inge-Lot van Haastert: het was een voorrecht om samen met jou de Movement ABC af te mogen nemen bij alle kinderen. De kwantitatieve score is niet zo moeilijk te leren, maar jouw enorme opmerkingsgave betreffende de kwaliteit van de motoriek zal ik niet snel evenaren. Prof.dr. Marian Jongmans: veel dank voor het af en toe inspringen als ik op vakantie was, zodat het onderzoek gewoon door kon lopen, en voor de bemoedigende woorden, als ik het even niet meer zag zitten. Eric Beek bedank ik voor het samen beoordelen van alle MRI scans (en daarbij het bespreken van de laatste nieuwtjes). Arno Lieftink dank ik voor het doen van het psychologisch onderzoek. Monica Uniken Venema: bedankt voor je begeleiding en luisterend oor, ook voor niet-proefschrift gerelateerde onderwerpen.

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Dien Zumbrink: lieve Dien, al bijna twintig jaar de derde ouder en duizendpoot in ons gezin. Het is maar al te waar, dat vaders en moeders alleen onbezorgd kunnen werken als het thuis goed geregeld is. Onze kinderen boffen enorm, dat ze al die jaren jou als vertrouwd gezicht hebben gezien tijdens onze afwezigheid. Ik hoop oprecht dat je nog heel lang bij ons blijft komen. Ook Jan veel dank, dat je Dien altijd naar haar "andere" gezin liet gaan.

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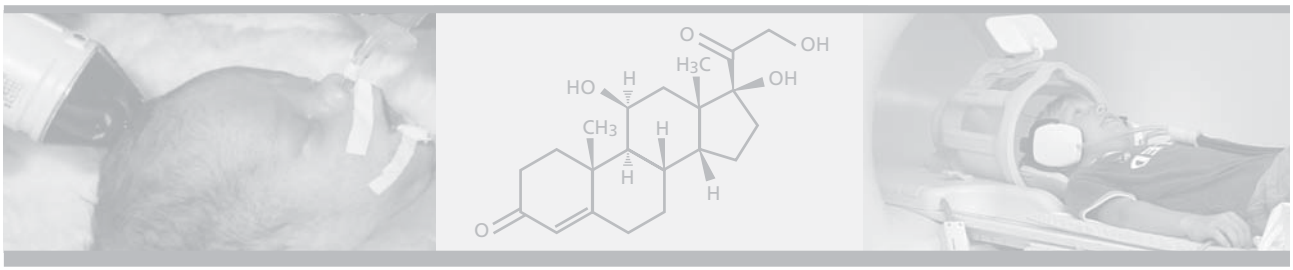
En Sander, promoveren met een voetbalclub is toch iets anders dan in de geneeskunde, maar het is allebei een feestje waard.

Curriculum vitae



De schrijfster van dit proefschrift werd op 6 februari 1957 geboren te Veendam. In 1975 behaalde zij het Atheneum B diploma aan het Zeldenrust college te Terneuzen en in datzelfde jaar startte zij met de studie geneeskunde aan de Rijks Universiteit te Utrecht. Deze studie onderbrak ze in 1979 gedurende negen maanden, om als au pair te werken in een antroposofische leefgemeenschap op het Franse platteland (St. Menoux, Frankrijk). Hierna legde ze in 1981 het doctoraal examen af en op 25 maart 1983 haalde zij haar artsexamen.

Van april 1983 tot oktober 1983 werkte zij als agnio kinderpathologie in The Hallamshire Hospital te Sheffield (Engeland), onder leiding van Dr. S.V. Variend en vervolgens werkte zij van oktober 1983 tot april 1984 op de afdeling kinderpathologie van het AZU, onder leiding van Prof. J.J. Huber.

Op 1 oktober 1984 begon zij aan de opleiding kindergeneeskunde in het Sophia Kinderziekenhuis te Rotterdam (opleider: Prof.dr. H.K.A. Visser). Tijdens deze opleiding liep zij in het laatste jaar een maand stage op de neonatologie afdeling van het Long Beach Memorial Hospital te Long Beach (Californië). De opleiding tot kinderarts rondde ze af op 1 oktober 1988, waarna ze gedurende drie maanden op de Extra Zorg afdeling (intensive care oudere kinderen) van het Sophia Kinderziekenhuis werkzaam was (hoofd: Drs. E. vd Voort). Op 1 januari 1989 begon ze aan de subspecialisatie tot neonatoloog, eveneens in het Sophia Kinderziekenhuis (opleider: Prof.dr. P.J. Sauer). Deze opleiding vervolgde ze na oktober 1989 in het Wilhelmina Kinderziekenhuis te Utrecht (opleider: Dr. L.J.Gerards). Sinds 1992 is zij als staflid verbonden aan de afdeling neonatologie van dit ziekenhuis (hoofd: Prof.dr. F. van Bel). Op deze afdeling heeft ook het onderzoek plaats gevonden, dat uiteindelijk geresulteerd heeft in dit proefschrift.