Early neuromotor development of *high risk* infants

Inge-Lot van Haastert

Colophon

Early neuromotor development of *high risk* infants
Thesis, Utrecht University, with a summary in Dutch
Proefschrift, Universiteit Utrecht, met een samenvatting in het Nederlands

Author
Ingrid Charlotte van Haastert
Illustrations cover, parts and chapters
Pim van Halem, Rotterdam
www.pimvanhalem.nl
Graphic Design
Ronald en Irene Boiten, Amersfoort
www.boitengrafischontwerpers.nl
Printed by
High Trade, Zwolle

Publication of this thesis was sponsored by the Division of Perinatology,
University Medical Center Utrecht

ISBN 978-90-393-5671-5

Early neuromotor development of *high risk* infants

– Gross motor function in preterm and full-term born infants –

Vroege neuro-motorische ontwikkeling van kinderen
met een hoog risico op ontwikkelingsproblemen
– Grof motorische functie van premature en voldragen kinderen –
(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. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen
op dinsdag 13 december 2011 des middags te 2.30 uur

door

Ingrid Charlotte van Haastert

geboren op 2 november 1950
te Hilversum

Promotoren: Prof.dr. L.S. de Vries
Prof.dr. P.J.M. Helders
Prof.dr. M.J. Jongmans

Kijk niet zolang als nodig is,
maar kijk langer,
kijk beter,
en je ziet steeds meer.

Uit: de kunst van het kijken in De Verhalen (2011) / Auteur: Mensje van Keulen

Voor mijn moeder
Denkend aan mijn vader

CONTENTS

LIST OF ABBREVIATIONS

ADC	apparent diffusion coefficient
aEEG	amplitude-integrated electroencephalography
AGA	appropriate for gestational age
AHLS	active head lifting in supine
AIMS	Alberta infant motor scale
BGL	basal ganglia lesions
BG/T	basal ganglia and thalamus
BPD	bronchopulmonary dysplasia
BSCP	bilateral spastic cerebral palsy
BSID-II-NL	Bayley scales of infant development, second edition, Dutch version
BSITD-III	Bayley scales of infant and toddler development, third edition
BW	birth weight
CA	corrected age
CBH	cerebellar haemorrhage
CI	confidence interval
CP	cerebral palsy
c-PVL	cystic periventricular leukomalacia
CS	composite score
cUS	cranial ultrasonography
DQ	developmental quotient
DWI	diffusion-weighted imaging
ELBW	extremely low birth weight
FU	follow-up
GA	gestational age
GMDS	Griffiths mental development scales
GMFCS	gross motor function classification system
GMH	germinal matrix haemorrhage
HIE	hypoxic-ischaemic encephalopathy
HPI	haemorrhagic parenchymal infarction
IVH	intraventricular haemorrhage

MCA	middle cerebral artery
MDI	mental development index
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
N	number
NICU	neonatal intensive care unit
NPV	negative predictive value
NS	not significant
OR	odds ratio
PHVD	post-haemorrhagic ventricular dilatation
PLIC	posterior limb of the internal capsule
PMA	postmenstrual age
PPV	positive predictive value
PVE	periventricular echogenicity
PVL	periventricular leukomalacia
PWML	punctate white matter lesions
SBD	spastic bilateral diplegia
SBQ	spastic bilateral quadriplegia
SCL	subcortical leukomalacia
SD	standard deviation
SGA	small for gestational age
SU	spastic unilateral
TEA	term-equivalent age
TIMPSI	test of infant motor performance screening items
UMCU	University Medical Center Utrecht
US	ultrasound
USCP	unilateral spastic cerebral palsy
VI	venous infarction
VM	ventriculomegaly

Chapter 1

INTRODUCTION

Newborns in the Netherlands who need to be admitted to one of ten neonatal intensive care units (NICU), of which eight are university-affiliated centres, can be subdivided in infants who are born very preterm (> 8 weeks too early) and full-term with perinatal complications. Infants in whom a severe congenital disorder is detected antenatally or soon after delivery may also need intensive care, diagnosis and/or treatment; the same applies to newborn infants with a suspected metabolic disorder or an infection of the central nervous system.

With the development of NICUs in the late 1960s and increased survival of newborns with progressively younger gestational ages, follow-up (FU) programs were initiated to address concerns about the developmental course, outcome and long-term health of children who survived the neonatal period.[1] However, not only very preterm birth is associated with a variety of problems across multiple neurodevelopmental domains,[2–4] also infants born at term with neonatal encephalopathy are at increased risk of adverse neurodevelopmental sequelae like cerebral palsy (CP), minor neurological dysfunction, perceptual-motor difficulties, cognitive impairments, difficulties in memory and attention/ executive functions and special educational needs.[5–9]

Following discharge from a NICU, parents and their child are offered a neonatal outpatient FU program. A neonatal FU program serves three main goals: 1. extended care for the child who survived the NICU, 2. evaluating the effects of intensive care and therapies, and 3. research to be able to identify risk factors and be able to then adjust certain clinical interventions or the FU scheme if necessary.

During the first years of life, the focus is particularly directed towards motor delays or disabilities because these are most commonly and easily detected. At older ages however, a variety of behavioural, school and other problems can be expected. Therefore it is important to choose appropriate assessment tools to evaluate a child's developmental status, interpret the findings, and provide a functional profile of the child's developmental strengths and difficulties in order to make appropriate decisions.[1,10]

In the early 1990s, we followed a FU schedule that was different for preterm and full-term born infants and children. About the same time, a national network was set up for FU outpatient clinics affiliated to neonatal centres. In 1996, a basic FU protocol for infants and children with perinatal risk factors was recommended (see Appendix A-0).[11]
At present, we still follow different schedules for preterm and full-term born infants and children in the FU outpatient clinic of our own centre, but through the years we adapted the schedule at some points for both groups. A very preterm born infant with a gestational age (GA) <30 weeks is seen at term-equivalent age, at 6, 15 and 24 months corrected age (CA) and at 3.5 and 5.5 years of age followed by an assessment of a child psychologist (see Appendix A-1). A more mature preterm born infant with a GA ≥30 weeks is offered the first four appointments. When parents and developmental specialists have no concerns about growth and development, the child is discharged from the FU outpatient clinic. A full-term born infant is followed at 3, 9 and 18 months of age and at 5.5 years of age, also followed by an assessment of a child psychologist (see Appendix A-2).

The content of this thesis is the result of 20 years of experience in the clinical and outpatient practice of neonatologists, paediatric physical therapists and other developmental specialists.
What did we know in the early 1990s? Less than we do know nowadays.

NEUROMOTOR ASSESSMENT AND DEVELOPMENT

The last two decades, we extended our knowledge considerably and learned a lot about the neurological outcome of preterm and full-term born infants and their developmental courses and outcomes, thanks to the work of pioneers with their special interest and attention to different aspects of infant and child development: Bert Touwen (prediction bands), Ronald S. Illingworth (basic developmental screening), Heinz F.R. Prechtl (neurological examination; general movements), Lilly and Victor Dubowitz (Hammersmith neonatal neurological examination), Inge

Flehmig (normal and deviant development in infancy), Václav Vojta (cerebral movement disorders in infancy), Ruth Griffiths (mental development), Claudine Amiel-Tison and Albert Grenier (neurological assessment), Mijna Hadders-Algra (general movements; variation and variability), Heidelise Als (developmental care and assessment of the newborn), Nancy Bayley (cognitive and motor development), and Martha Piper and Johanna Darrah (gross motor maturity).[12-28]

Based on this work, we used an eclectic assessment procedure in the early 1990s in order to determine if an infant or child was developing well or deviated from what was expected; also to decide if any intervention to support the development of a child was necessary. We have learned from Professor Heinz Prechtl in particular, to use our global visual 'Gestalt' perception when observing and assessing the movement repertoire of an infant. Developmental specialists working with high-risk infants need to be trained and elaborate their experiences to be able to distinguish between what is normal or not, and to recognize specific neurological signs within movement repertoires. Spontaneous movements and movement patterns, as an expression of spontaneous neural activity, are therefore excellent markers to decide if brain injury is present. Hands-on manoeuvres need to be avoided as much as possible.

Through the years, we were able to obtain and use various developmental measurement tools. However, in the studies within this thesis, only five different tools measuring or classifying gross motor development, gross motor function and cognition were used and therefore briefly described:

Motor Assessment of the Developing Infant

Also referred to as the Alberta Infant Motor Scale (AIMS), available since 1994. The scale is unidimensional: the single construct is *gross motor maturity*. Because the AIMS is non-invasive, easy to administer and requires minimal handling, it is exceptionally suited for an outpatient clinic. The total raw score, which is the sum of four positional item scores (prone, supine, sitting, and standing), ranges from 0 to 58. An item can be scored as observed (one point) or not observed (no point), according to specific criteria relating to the main components of movement: posture, weight-bearing and antigravity movements. The higher the score, the

more mature the child's gross motor pattern. The total raw score can be converted to a percentile rank or standardized *z*-score for monthly age levels from 0 to 19 months and makes it possible to determine if the gross motor development of an infant is within the norm or not.[27]

The Gross Motor Function Classification System

The Gross Motor Function Classification System (GMFCS) describes the major functional characteristics of children with CP. It is a five-level pattern-recognition system. Children classified in GMFCS level I-II have the potential to walk independently, both indoors and outdoors and in the community. In contrast, children classified in GMFCS level III-V are limited in their self-mobility. They walk with a mobility device and are potential wheelchair users.[29] Researchers from the Hammersmith Hospital in London classified gross motor impairment in children with CP as mild (GMFCS level I), moderate (level II and III) and severe (level IV and V).[30] There are four age bands: before the second year of life, between 2-4, 4-6 and 6-12 years of age. An extended version was later developed.[31] The GMFCS discriminates between children with CP syndromes according to their age-specific gross motor activity and is based on self-initiated movements.[32] The predictive value of the GMFCS between the ages of 2-12 years is relatively stable over time with a test-retest reliability of *r* 0.79.[32,33] However, the reported inter-rater reliability for infants with CP < 2 years of age is moderate (κ 0.55).[29] Overall level of agreement regarding GMFCS classification over time, i.e. between infancy (1-2 years) and early childhood (2-4 years) was 0.70 (linear weighted kappa), but stability between infancy and early childhood is good when GMFCS level I-III are combined (test-retest reliability 0.96).[34]

The Griffiths Mental Development Scales from birth to 2 years

The Griffiths Mental Development Scales (GMDS) are used in our outpatient clinic from 1990 onwards and consists of five subscales: locomotor, personal and social, hearing and language/speech, eye and hand co-ordination and performance. The test is designed to yield both global (sum of five subscales) and sub-scale developmental quotients (DQ) with a mean DQ for the general population of 100 and standard deviation (± SD) of 12. Information is obtained through direct observation and/or testing of the child.[20]

The Bayley Scales of Infant Development-II-NL

The Dutch version of the second edition of the Bayley Scales of Infant Development (BSID-II-NL) was available since 2002 and used in our outpatient clinic since 2003. The BSID-II-NL consists of a Mental and Motor Scale for infants and children in the age range 1-42 months with a mean of 100 (±15). Within this thesis, only the Mental Scale was used: total raw scores were converted to mental development index scores depending on the age of the children.[25]

The Bayley Scales of Infant and Toddler Development-III

We started to use the third edition of the Bayley Scales of Infant and Toddler Development (BSITD-III) in the beginning of 2008. It consists of cognitive, language, motor, social-emotional and adaptive behaviour subtests for infants and children in the age range 0.5-42.5 months with a mean of 100 (±15).[26] Within this thesis, only the cognitive subtest was used.

NEURO-IMAGING

The introduction of neuro-imaging techniques made it possible to visualize what was going on in the newborn brain. First of all, cranial ultrasonography (cUS) was introduced in the late 1970s; a technique that was easy to use because it is non-invasive and can be applied even if a neonate is in the incubator and ventilated. The focus was first on time of onset, evolution and risk factors of intraventricular haemorrhages. With the introduction of higher resolution transducers, it became possible to detect white matter injury as well, such as cystic periventricular leukomalacia (PVL) and focal infarction.[8] Using other acoustic windows, such as the mastoid window, cerebellar lesions can also be recognised by more experienced sonographers.[35]

Another, more advanced technique is magnetic resonance imaging (MRI), introduced in the mid 1980s. Although an advantage of MRI with regard to cUS is the ability to detect more subtle white matter lesions, there are some disadvantages: it is time consuming, expensive and the infant needs to be transported to the MR unit and sedated to avoid movement artefacts. By relating neuro-imaging findings to outcomes of neurological assessments, recognition, understanding and interpretation of different patterns of brain injury and clinical signs improved and expanded. Refinement of the aforementioned techniques and expansion of our experience improved our ability even more, to better predict neurodevelopmental outcome in preterm and full-term born infants.[8,30]

AIMS OF THE THESIS

The six studies presented in this thesis focus on neuromotor developmental pathways of children who were born preterm or with a difficult start after a full-term pregnancy, who were cared for in and discharged from our NICU.

The aims were

- To assess gross motor maturation in the first 18 months of life of infants born preterm.
- To assess the relation between cUS abnormalities and subsequent development of CP in infants born preterm.
- To dispel the myth that CP can not reliably be predicted by use of brain imaging in preterm and full-term neonates.
- To examine the incidence and severity of CP and associated factors among preterm infants who survived the NICU in our hospital in the period 1990-2005.
- To determine the association between the severity of PVL and the course and stability of gross motor abilities in infants born preterm.
- To explore the association between active head lifting in supine in the first year of life and subsequent cognitive outcome in the 2nd year of life in infants born preterm and full-term.

OUTLINE OF THE THESIS

Chapter 1 presents a general introduction on the topic, and aims and outline of the thesis.

In *Chapter 2*, we present the results on the AIMS, a standardized tool to examine the gross motor maturity in infancy, in a cohort of infants born preterm and compared the results with the norm-referenced values derived from infants born full-term.

Chapter 3 describes how brain injuries, detected by neonatal sequential high-resolution cUS, were related to the development of CP in two groups of infants born preterm.

In *Chapter 4*, we evaluated if CP could be predicted based on cUS and MRI findings in infants born preterm as well as born full-term.

Chapter 5 describes the different gross motor developmental pathways by use of the GMFCS in infants born preterm who were diagnosed with different grades of PVL.

Chapter 6 focuses on the incidence, severity and associated factors of CP over a period of 16 years in infants born preterm who were discharged from the NICU of the Wilhelmina Children's Hospital.

In *Chapter 7*, we explored if active head lifting in supine in early infancy is an early marker for non-optimal cognitive development in the 2nd year of life, and possible associated factors.

Chapter 8 summarizes the results of the studies presented in this thesis and discusses the implications for our outpatient practice and future research options.

REFERENCES

1 Synnes AR, Lefebre F, Cake HA. Current status of neonatal follow-up in Canada. Paediatr Child Health 2006;11:271-274.

2 Baar van AL, Wassenaer van AG, Briët JM, Dekker FW, Kok JH. Very Preterm Birth is Associated with Disabilities in Multiple Developmental Domains. J Pediatr Psychol 2005;30:247-255.

3 Marlow N, Hennessy EM, Bracewell MA, Wolke D, for the EPICure Study Group. Motor and Executive Function at 6 Years of Age After Extremely Preterm Birth. Pediatrics 2007;120:793-804.

4 Woodward LJ, Moor S, Hood KM, Champion PR, Foster-Cohen S, Inder TE and Austin NC. Very preterm children show impairments across multiple domains by age 4 years. Arch Dis Child Fetal Neonatal Ed. 2009;94:F339-F344.

5 Barnett A, Mercuri E, Rutherford M, Haataja L, Frisone MF, Henderson S, Cowan F, Dubowitz L. Neurological and Perceptual-Motor Outcome at 5-6 years of Age in Children with Neonatal Encephalopathy: Relationship with Neonatal Brain MRI. Neuropediatrics 2002;33:242-248.

6 Marlow N, Rose AS, Rands CE, Draper ES. Neuropsychological and educational problems at school age associated with neonatal encephalopathy. Arch Dis Child Fetal Neonatal Ed 2005;90:F380-F387.

7 Hemming K, Colver A, Hutton JL, Kurinczuk JJ and Pharoah POD. The influence of gestational Age on Severity of Impairment in Spastic Cerebral Palsy. J Pediatr 2008;153:203-208.

8 De Vries LS and Cowan FM. Evolving Understanding of Hypoxic-Ischemic Encephalopathy in the Term Infant. Semin Pediatr Neurol 2009;16:216-225.

9 De Vries LS and Jongmans MJ. Long-term outcome after neonatal hypoxic-ischaemic encephalopathy. Arch Dis Child Fetal Neontal Ed 2010;95:F220-F224.

10 Rosenbaum P. Screening tests and standardized assessments used to identify and characterize developmental delays. Semin Pediatr Neurol 1998; 5:27-32.

11 Protocol Follow-up voor kinderen met perinatale risicofactoren, Werkgroep Landelijke Neonatale Follow-up, Sectie Neonatologie van de Nederlandse Vereniging voor Kindergeneeskunde. 1996.

12 Touwen BC. A study on the development of some motor phenomena in infancy. Dev Med Child Neurol. 1971;13:435-446.

13 Touwen BCL. De neurologische ontwikkeling van de zuigeling. Utrecht: Bohn, Scheltema & Holkema, 1984.

14 Illingworth RS. Basic Developmental Screening: 0-2 years. Oxford: Blackwell Scientific publications, 1977.

15 Prechtl HFR. The Neurological Examination of the Full Term Newborn Infant. London: William Heinemann Medical Books Ltd., 1977.

16 Prechtl HFR. Qualitative changes of spontaneous movements in fetus and preterm infant are a marker of neurological dysfunction. Early Hum Dev 1990;23:151-158.

17 Dubowitz L and Dubowitz V. The Neurological Assessment of the Preterm and Full-term Newborn Infant. London: W. Heineman medical books Ltd., 1981.

18 Flehmig I. Normale ontwikkeling van de zuigeling en haar afwijkingen: vroegtijdige onderkenning en behandeling. Lochem: de Tijdstroom,1982.

19 Vojta V. Die zerebralen Bewegingsstörungen im Saüglingsalter: Frühdiagnose und Frühtherapie. Stuttgart: Ferdinand Enke Verlag, 1984.

20 Griffiths R. The Abilities of Young Children. A Comprehensive System of Mental Measurement for the First Eight Years of Life. The test agency Ltd, London, UK, 1984.

21 Amiel-Tison C and Grenier A. Neurological Assessment during the First Year of Life. Oxford: Oxford University Press, 1986.

22 Hadders-Algra M and Prechtl HF. Developmental course of general movements in early infancy. I. Descriptive analysis of change of form. Early Hum Dev. 1992;28:201-213.

23 Als H, Lawhon G, Duffy FH, McAnulty GB, Gibes-Grossman R, Blickman JG. Individualized Developmental Care for the Very Low-Birth-Weight Preterm Infant. JAMA 1994;272:853-858.

24 Hadders-Algra M en Dirks T. De motorische ontwikkeling van de zuigeling. Variëren, selecteren, leren adapteren. Houten: Bohn Stafleu Van Loghum, 2000.

25 Van der Meulen BF, Ruiter SAJ, Lutje Spelberg HC and Smirkovský. Bayley Scales of Infant and Development II, Nancy Bayley, Dutch translation. Lisse: Swets Test Publishers, 2002.

26 Bayley N. Bayley Scales of Infant and Toddler Development, third edition. San Antonio, TX, USA: Harcourt Assessment, Inc., 2006.

27 Piper MC, Darrah J. Motor assessment of the developing Infant. Philadelphia: WB Saunders; 1994.

28 Hadders-Algra M. Variation and Variability: Key Words in Human Motor Development. Physical Therapy 2010;90:1823-1837.

29 Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol. 1997;39:214-23.

30 Martinez-Biarge M, Diez-Sebastian J, Kapellou O, Gindner D, Allsop JM, Rutherford MA and Cowan FM. Predicting motor outcome and death in term hypoxic-ischemic encephalopathy. Neurol. 2011; 76:2055-2061.

31 Palisano R, Rosenbaum P, Bartlett D, Livingston M. Content validity of the expanded and revised Gross Motor Function Classification System. Dev Med Child Neurol. 2008;50, 744-50.

32 McCormick A, Brien M, Plourde J, Wood E, Rosenbaum P, McLean J. Stability of the Gross Motor Function Classification System in adults with cerebral palsy. Dev Med Child Neurol. 2007;49:265-69.

33 Wood E, Rosenbaum P. The gross motor function classification system for cerebral palsy: a study of reliability and stability over time. Dev Med Child Neurol. 2000;42:292-96.

34 Gorter JW, Ketelaar M, Rosenbaum P, Helders PJM and Palisano R. Use of the GMFCS in infants with CP: the need for reclassification at age 2 years or older. Dev Med Child Neurol. 2008;51:46-52.

35 Limperopoulos C, Benson CB, Bassan H, Disalvo DN, Kinnamon DD, Moore M, Ringer SA, Volpe JJ and du Plessis AJ. Cerebellar Hemorrhage in the Preterm Infant: Ultrasonographic Findings and Risk Factors. Pediatrics 2005; 116:717-724.

Typical gross motor development of preterm infants

Part 1

Chapter 2

EARLY GROSS MOTOR DEVELOPMENT OF PRETERM INFANTS ACCORDING TO THE ALBERTA INFANT MOTOR SCALE

Ingrid C. van Haastert
Linda S. de Vries
Paul J.M. Helders
Marian J. Jongmans

J Pediatr. 2006 Nov;149 (5):617-22.

ABSTRACT

Objective: To systematically examine gross motor development in the first 18 months of life of preterm infants.

Study design: A total of 800 preterm infants (356 boys), ages between 1 and 18 months and corrected for degree of prematurity, were assessed with the use of the Alberta Infant Motor Scale.

Results: Comparison of the mean Alberta Infant Motor Scale scores of the preterm infants with the norm-referenced values derived from term infants revealed that as a group, the preterm infants scored significantly lower at all age levels, even with full correction for degree of prematurity.

Conclusion: In general, preterm infants exhibit different gross motor developmental trajectories compared with term infants in the first 18 months of life. The gross motor developmental profile of preterm infants may reflect a variant of typical gross motor development, which seems most likely to be specific for this population. As a consequence, adjusted norms should be used for proper evaluation and clinical decision-making in relation to preterm infants.

INTRODUCTION

One of the main responsibilities of neonatologists is a systematic follow-up of infants who have been discharged from the Neonatal Intensive Care Unit (NICU).[1] Different developmental pathways, motor delays and /or motor disabilities are the most commonly detected problems among preterm children in the first years of life.[2-10] However, it is questionable whether early developmental delay is indicative of later developmental disability.[3] Abnormalities or delays diagnosed early in life may be transient and eventually fade away as the central nervous system matures.[2,11,12] Nevertheless, preterm infants are generally reported to be initially delayed in the development of gross motor abilities and therefore are often referred for developmental therapy.[13]

An important limitation of the prevailing traditional diagnostic focus on the acquisition of motor milestones is the lack of sensitivity in identifying infants with subtle movement disorders. An infant may show clinical improvement in pattern and quality of movement, but this may not be reflected in the acquisition of motor milestones. If the accuracy of early identification is to be improved, the scope of a diagnostic test of motor development for infants should be broadened to include environmental conditions, infant characteristics, and qualitative components.[6,14] Standardized tests of neuromotor development are useful in characterizing the infant's developmental status, particularly in monitoring changes in motor skills that emerge over the first years of life.[2,5,7,11] One assessment tool particularly useful for monitoring gross motor developmental change in infants during the first 18 months of life is the Alberta Infant Motor Scale (AIMS).[15] The AIMS is a norm-referenced, standardized, observational, and performance-based measure and may be performed by any health professional who has a background in infant motor development and an understanding of the essential components of movements. The AIMS is designed to examine, discriminate, and evaluate the spontaneous movement repertoire of infants from term age through independent walking. It is based on current theoretical principles of motor development that incorporate aspects of the neuro-maturational theoretical framework with relevant attributes of the dynamic systems perspective.[15]

In contrast to traditional clinical neurologic evaluations, the scale emphasizes functional skills and quality of movement. Ultimately, a child's performance on the AIMS can support the decision of whether or not an infant is eligible for referral or early intervention.[4,6,13,15,16] So far, to our knowledge, only Canadian norms are available.

The aims of the current study were to determine whether preterm infants show different patterns of early motor development than term infants, as reported in the original AIMS study, and to compare the scores with other preterm cohorts previously examined on the AIMS.

We hypothesized that the mean AIMS scores of the preterm cohort would be lower than the mean scores of the full-term cohort at all age levels, even after correction for the degree of prematurity.

METHODS

Patients

During a 12-year period (December 1993 to November 2005), 2228 preterm infants with a gestational age (GA) of ≤32 weeks who were nursed in one NICU of a regional tertiary level perinatal center survived the NICU period. Of these, 800 infants (35.9%) fulfilled our inclusion criteria. They were of a slightly shorter GA (mean = 29.4; SD = 1.7) compared with the nonincluded infants (mean = 29.7; SD = 1.9) (t = 3.75, df = 2226, $p < .0001$) and had lower birth weight (BW) (mean = 1194; SD= 292) compared with the nonincluded infants (mean = 1311; SD = 386) (t = 7.97, df = 2021, $p < .0001$). Sex distribution of the included and nonincluded samples also differed (44.5% boys and 55.5% girls in the included sample versus 58.2% boys and 41.8% girls in the nonincluded sample; $\chi^2 = 38.62$, df = 1, $p < .0001$). There were no differences between the samples in distribution of singletons versus multiplets (66.5% singleton and 33.5% multiplets in the included sample versus 70% singletons and 30% multiplets in the non-included sample; $\chi^2 = 2.97$, df = 1, $p = .085$).

Inclusion criteria were as follows: born before or at 32 weeks' GA, appropriate size for GA (defined as >10th percentile, <90th percentile),[17] and one or more total AIMS scores available performed by the same examiner.

Infants with the following conditions were excluded: a known syndrome, a neuromuscular disorder, severe abnormality of the brain as seen on ultrasound scans (for example, cystic periventricular leukomalacia, grade III or IV hemorrhage according to Papile classification,[18], focal infarction), posthemorrhagic ventricular dilatation (requiring treatment), congenital hydrocephalus, encephalitis, meningitis, bronchopulmonary dysplasia (defined as oxygen supplementation >36 weeks postmenstrual age), congenital anomalies, necrotizing enterocolitis requiring surgical procedures, prolonged tube feeding (after discharge), and severe visual or hearing disorder. The parents were offered the opportunity to let their infant participate in a standardized follow-up program, from term age until the age of 5 years.

Measurement

The AIMS is noninvasive, easy to administer, and requires minimal handling.[15] Each of the 58 items consists of a drawing of an infant in four different positions (prone, supine, sitting and standing) and is scored on a dichotomous scale as observed (one point) or not observed (no point), according to specific criteria relating to the main components of movement: posture, weight-bearing, and antigravity movements. 'Key descriptors,' which must be observed to give credit to the item, are provided on the score sheet. The manual provides more details for proper scoring. The total raw score, which is the sum of the positional item scores, can range from 0 to 58. The higher the score, the more mature the child's gross motor pattern. The total score can be converted to a percentile rank or standardized z-score for monthly age levels from 0 to 19 months.[15]

Content validity of the AIMS was performed through an extensive literature search and use of experienced pediatric physical therapists and an expert panel for item generation. The scale properties were examined through the use of multidimensional scaling, Guttman scaling, and Item Response Theory. The scale is unidimensional: The single construct is gross motor maturity.[15] For predictive purposes, the best cut-offs for the AIMS were established, using one pediatrician's assessment of development (normal, suspect, abnormal) as the outcome measure.

At 4 months of age, the 10th centile was identified as the most accurate cut-off point (sensitivity, 77%; specificity, 82%; negative predictive value, 96%). At 8 months, the 5th percentile was recommended as a cut-off point (sensitivity, 86%; specificity, 93%; negative predictive value, 98%). Low positive predictive values (4 months: 40%; 8 months: 66%) remain a concern, as many infants with low AIMS scores in early infancy subsequently present with normal motor development at 18 months.[2,6,13]

Design

Data used for this prospective, cross-sectional study were obtained during outpatient clinic appointments from 1 through 18 months, corrected for the degree of prematurity. Within the first 2 years of life, appointments were mainly scheduled at term and at 6, 12, 15, and 18 months' corrected age. The assessments were conducted by an experienced developmental specialist (a pediatric physical therapist and special educator). Although the AIMS is also suitable for children ages 0 to 1 month, we used the assessment of general movements[19] as well as the Dubowitz assessment at that particular time.[20]

Statistical analysis

Data were analyzed with the SPSS/ PC+.[21] We explored the association between GA, BW, sex, and fetal number and the AIMS total scores by using univariate analysis of variance per age group. To test the hypothesis that preterm infants' mean AIMS scores are lower than the scores of the norm-referenced term infants, one-sample *t* tests (one-sided) were performed. In addition, scores of the current preterm cohort were compared with other preterm cohorts by using one-sample *t* tests. A value of $p < .05$ was considered to be statistically significant.

RESULTS

Association between selected variables and AIMS scores

A significant association was found between GA and AIMS total score only at 5 to 6 months ($F[2,62] = 6,20$, $p = .004$). Post hoc analyses, however, revealed no significant differences between the groups (GA, 24 5/7 to 28 weeks: n = 17, mean = 15.18, SD = 3.07; GA, 28 1/7 to 30 weeks: n = 21, mean = 14.95, SD = 2.46; GA, 30 1/7 to 32 weeks: n = 24, mean = 16.83, SD = 5.10; $p = .082$). There was a significant association between BW (subdivided into infants <1250 g and ≥1250 g) and AIMS total score at 6 to 7 months and at 15 to 16 months ($F[1,343] = 4,57$, $p = .033$ and $F[1,206] = 4,88$, $p = .028$, respectively). At both ages, infants weighing <1250 g had a slightly lower AIMS total score (6 to 7 months: <1250 g, mean = 18.12, SD = 3.75 versus ≥1250 g mean = 19.09, SD = 4.28; 15 to 16 months: <1250 g mean = 55.11, SD = 3.06 versus ≥1250 g, mean = 55.52, SD = 3.45). With respect to sex, a significant difference was noted at 7 to 8 months ($F[1,55] = 5,27$, $p = .027$). Girls had higher scores (n = 30, mean = 24, SD = 6.42) than did boys (n = 25, mean = 20.72, SD = 4.18). Finally, a significant difference was found at 5 to 6 months for fetal number ($F[1,62] = 6,20$, $p = .004$). Multiplets had higher scores (n = 20, mean = 18.10, SD = 4.34) than singletons (n = 42, mean = 14.62, SD = 3.10). The absence of a systematic pattern of association between GA, BW, sex, and fetal number and AIMS total score led to exclusion of these variables in subsequent analyses. For example, the AIMS scores of boys and girls per age group were pooled (after Piper and Darrah 1994, p. 198, Table 11-4).[15]

Comparison between preterm and term infants

The mean AIMS scores of preterm infants were significantly lower compared with those of term infants at all age levels (Table I and Figure 1; see Piper and Darrah 1994 Appendix III on p. 205 for an overview of the mean scores and standard deviations of the normative sample).[15] From twelve months onward, the percentage of preterm infants that achieved a total AIMS score of 58 points (that is, passed all items in all four positions) increased from 1.5% to 78% through 18 months, showing that at an early age even a preterm infant can achieve the highest score possible.

Table I AIMS scores (1196) in 800 preterm (GA ≤ 32 weeks) infants

Months	n	Mean	SD	SE	*t*	*P* value*
1<2	28	6.6	1.42	0.27	−2.45	.011
2<3	18	7.3	1.61	0.38	−6.51	.000
3<4	36	9.7	2.24	0.37	−7.72	.000
4<5	26	11.4	2.00	0.39	−16.48	.000
5<6	62	15.7	3.88	0.49	−15.16	.000
6<7	343	18.6	4.02	0.22	−44.94	.000
7<8	55	22.5	5.71	0.77	−12.72	.000
8<9	20	33.4	8.89	1.99	−3.22	.003
9<10	27	35.2	9.06	1.74	−5.94	.000
10<11	21	39.3	9.10	1.99	−5.04	.000
11<12	12	43.4	9.38	2.71	−2.91	.007
12<13	66	48.8	5.25	0.65	−8.99	.000
13<14	41	51.0	5.89	0.92	−5.04	.000
14<15	74	53.2	3.46	0.40	−9.16	.000
15<16	206	55.3	3.23	0.23	−11.17	.000
16<17	64	55.8	3.46	0.43	−4.67	.000
17<18	48	56.7	2.55	0.37	−3.29	.001
18<19	49	56.9	2.65	0.38	−2.01	.025

*One-way *t* test (one-sided) compared with norm sample of Piper and Darrah.[15]

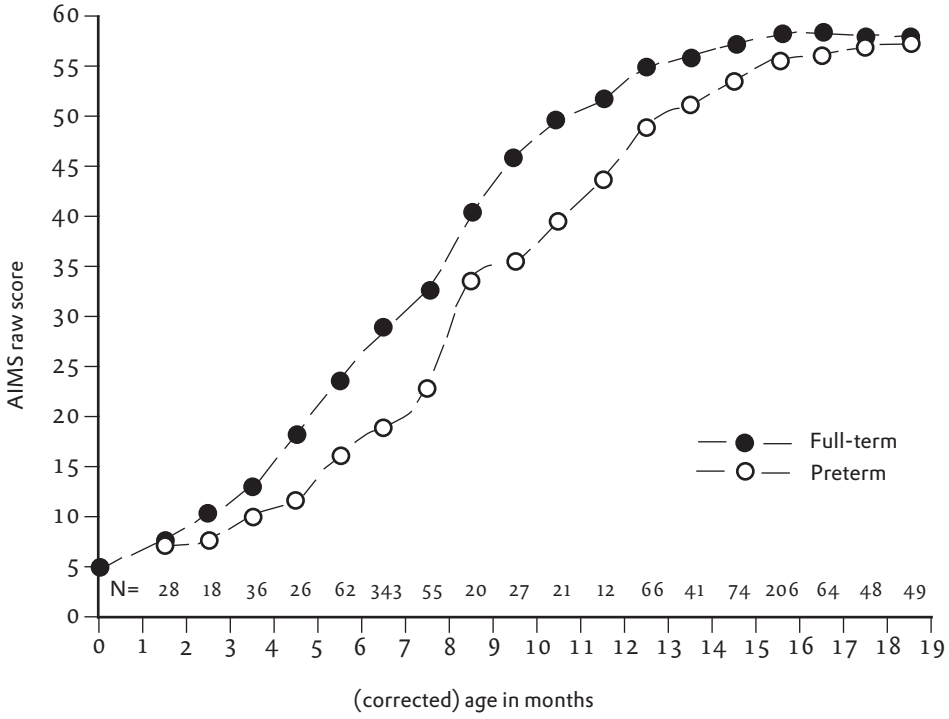

Figure 1 Mean AIMS scores of term[15] and preterm infants (GA ≤32 weeks). Numbers above the *x*-axis represent the number of observations in preterm infants. See the manual for the term infants.[15]

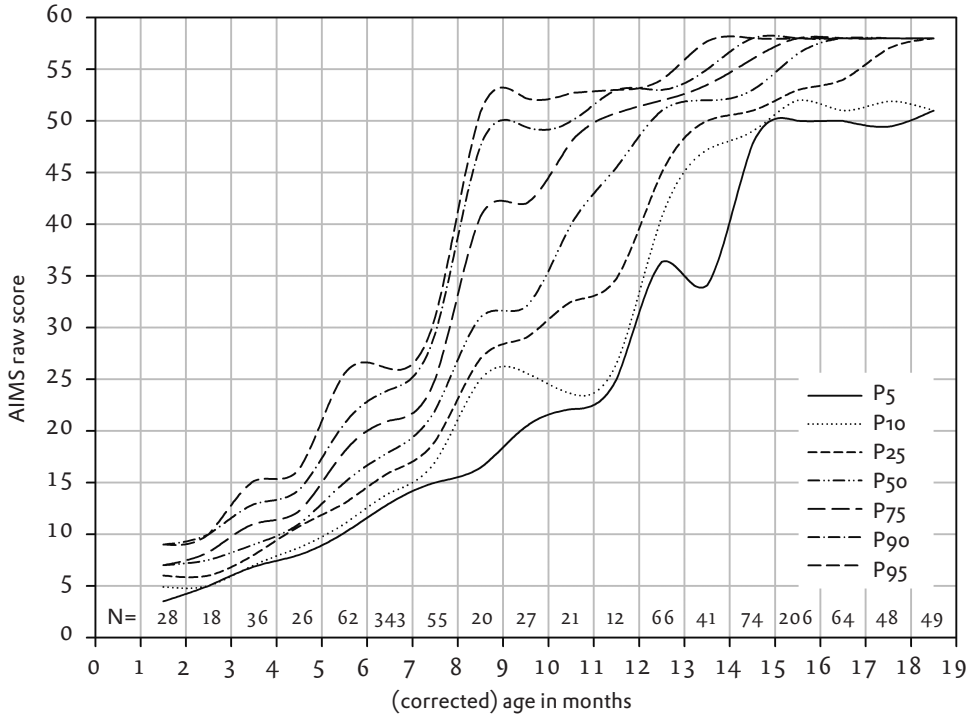

Figure 2 AIMS percentile ranks of preterm infants (n = 800). Numbers above the *x*-axis represent the number of observations.

The percentile ranks of the AIMS scores of preterm infants (including the 95th centile) are displayed in Figure 2 (see Piper and Darrah 1994 for a comparison, Appendix I on p. 203 and Appendix IV on p. 205).[15]

Comparison among different preterm cohorts

We compared the mean AIMS scores in our study with those of previously published studies including only preterm infants with similar GA and BW. Only four age categories: 6, 8, 9, and 12 months, corrected age, are described in the literature (Table II). Infants ages 6 to 7 months in our study had significantly lower mean scores compared with the populations studied by Jeng et al[6] and Jeng et al.[22] At 8 to 9 months, our results are in agreement with those of Bartlett and Fanning.[2] Infants at 9 to 10 months of age in our study had significantly lower scores compared with those included in the study of Jeng et al.[22] Finally, infants ages 12 to 13 months in our study performed equal to the infants in the Jeng et al[6] and Jeng et al[22] studies.

Table II Comparison of AIMS scores among different preterm cohorts

	Corrected age	n	Mean	SD	*t*	df	*P* value
	6-7						
Current study		343	18.6	4.0			
Jeng et al[6]		41	25.4	4.9	−31.57	342	.0001
Jeng et al [22]		92	24.3	4.6	−26.50	342	.0001
	8-9						
Current study		20	33.4	8.9			
Bartlett and Fanning[2]		60	32.5	9.7	−0.45	19	.66
	9-10						
Current study		27	35.2	9.1			
Jeng et al[22]		93	39.2	9.0	−2.32	26	.028
	12-13						
Current study		66	48.8	5.3			
Jeng et al[6]		41	49.7	7.9	−1.41	65	.16
Jeng et al[22]		95	48.7	9.3	0.14	65	.89

DISCUSSION

This study identified significant differences in early gross motor development of preterm infants compared with term infants, even after full correction for prematurity. These results were not systematically influenced by any of the variables measured in this study. Three other studies have reported similar findings at selected age levels.[2,6,22] This study presents comprehensive analyses on the differences between preterm and term infants' gross motor development on the full age range from 1 through 18 months of age.

In the last decade, a growing number of studies have used the AIMS, including both preterm and/or term infants.[2,4,6,11,13,16,22-26] To select children in need of developmental intervention, cut-off points have been introduced (for example, the 10th centile at 4 months and the 5th centile at 8 months). However, the question of false-negative and false positive identification is still an issue of debate.[13] Moreover, different studies have shown that motor development in preterm infants differs from that in term infants.[6,18,25,27,28] Therefore, it is questionable as to whether the development of preterm infants should be compared with that of term infants.[29]

It is of interest that we found a difference at 6 and 9 months but no longer at 12 months between our cohort and that of Jeng et al.[6,22] Since there seem to be no systematic differences between our cohort and Jeng et al cohorts in terms of GA, BW, sex, and fetal number, factors such as sample size and ethnicity may explain these differences. Despite these differences, the mean AIMS scores in our study increase from 1 through 18 months' corrected age, with only one noticeable outlier between the ages 7 to 8 and 8 to 9 months (Table I, and Figure 1). At these age levels, the difference between the mean scores is the highest compared with the other ages. The same applies to the normative data of the term infants, although it is less marked (see Appendix III on p. 205 of the manual).[15] It seems that this age level is of special importance in the early gross motor development of human beings. With regard to the evolution of the standard deviation (Table II), there is a gradual increase from 1 to 2 months onward until 11 to 12 months and subsequently a decrease to the end of the scale. This pattern very much mirrors the evolution of the standard deviation of the full-term infants,[15] although the standard deviation in this sample decreases 3 months earlier. One would expect lower standard deviations in this age range, when samples sizes of the preterm infants were greater. Although the percentile lines for term infants[15] converge between 15 and 18 months, this phenomenon probably occurs after 18 months of age in our preterm cohort. Therefore, extension of the scale to older ages (beyond 18 months of age) seems justified for this population.

The AIMS was constructed with the intent that it would be most sensitive around the middle of the first year of life.[15] Indeed, the test does not discriminate well between infants beyond 14 months of age.[11,15] Compared with the term infants, the preterm infants in the current study had lower mean scores (but larger standard deviations) beyond 14 months of age. This seems to be mainly due to the fact that they tended not to pass the last three items of the subscale standing ('standing from quadruped position,' 'walks alone,' and 'squat'), which primarily measure the child's ability to attain and maintain his balance.[30,31]

Preterm infants scoring in the bottom 25th centile (Figure 2) tended to fail on two of the four subscales: prone ('modified four-point kneeling' and 'reciprocal creeping') and standing ('cruising with rotation,' 'stands alone,' 'early stepping,' 'standing from modified squat,' 'standing from quadruped position,' 'walks alone,' and 'squat'). These items represent more complex anti-gravity postural control activities.[2] It is important to use cut-off points to decide if an infant will benefit from intervention.[13] However, this applies only to infants ages 4 and 8 months.[13]

We suggest the following procedure: (1) after obtaining an AIMS score, the clinician should first look up the equivalent percentile point according to the norms of the full term children[15]; (2) when the result is below the 5th centile, one should turn to the norms of the preterm sample presented here. The infants who, according to these norms, perform below the 25th centile (Figure 2) appear to be those who need careful attention and probably intervention. Because it is hard to detect infants with mild motor problems or learning difficulties in this age range, it is possible that some of the preterm infants in our study who obtained a score below the 5th centile will eventually have development of some milder disability.

One of the important biological factors possibly influencing motor development in preterm infants is insufficient postnatal growth (weight, height, head circumference).[3,7,8,10,32-35] Also, the brain maturation of preterm infants (especially the cerebellum) proceeds in a different way than in term infants.[3,4,10,29,30,32,36] Impaired growth of the cerebellum appears to be underestimated in preterm infants, although long-term neurodevelopmental disabilities may be in part attributable to this phenomenon.[10] Second, small muscle size, a lower proportion of fast-twitch muscle fibers, reduced intramuscular high-energy phosphate, and physical hypoactivity may cause the anaerobic performance of preterm infants to be lower than in term infants.[3,35] Third, inferior intermuscular coordination, poor muscle strength, poor muscle power regulation, and, as a result, inadequate postural control, can affect the quality of movement and result in a delayed onset of antigravity activities, particularly in preterm infants.[2,3,6,9,28-31,34,35,37] Moreover, there is little knowledge about the influence of inadequate motor control on the metabolic cost of locomotion and other features of movement capacity of preterm children.[34]

Finally, it is often assumed that preterm birth affects child-parent interactions and influences care-giving practices, expectations, and developmental possibilities.[3,29,36,38] For example, in term infants, it has been found that limited exposure to prone positioning[26] and high equipment use at home[24] appear to have an adverse influence on the rate and sequence of motor development. This could be equally true for preterm infants who, as a result of these early experiences, are less likely to achieve skills that involve anti-gravity activities.[6,24,26,31,37]

The present study provides evidence for the existence of specific early motor developmental trajectories of preterm infants. They exhibit a significantly different trajectory in their gross motor development in the first 18 months of life compared with term infants. Although our results cannot be generalized to all preterm infants, it is possible that this developmental pathway is characteristic for this population, reflecting a variant of typical motor development.

Standard gross motor developmental scales used for term infants should be adjusted to enable proper evaluation and clinical decision-making in relation to preterm infants.

REFERENCES

1 Spitzer AR. Follow-up of the low-birth-weight infant: Where do we go from here? (Editorial) Clin Pediatr 1998;37:547-49.

2 Bartlett DJ, Fanning JE. Use of the Alberta Infant Motor Scale to characterize the motor development of infants born preterm at eight months corrected age. Phys Occup Ther Pediatr 2003;23:31-45.

3 Marlow N. Neurocognitive outcome after very preterm birth. Arch Dis Child Fetal Neonatal Ed 2004;89:F224-8.

4 Bartlett D. Primitive reflexes and early motor development. J Dev Behav Pediatr 1997;18:151-7.

5 Rosenbaum P. Screening tests and standardized assessments used to identify and characterize developmental delays. Semin Pediatr Neurol 1998;5:27-32.

6 Jeng S, Tsou Yau K, Chen L, Hsiao S. Alberta Infant Motor Scale: reliability and validity when used on preterm infants in Taiwan. Phys Ther 2000;80:168-78.

7 Kohlhauser C, Fuiko R, Panagl A, Zadra C, Haschke N, Brandstetter S, et al. Outcome of very-low-birth-weight infants at 1 and 2 years of age. Clin Pediatr 2000;39:441-9.

8 Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. N Engl J Med 2000;343:378-84.

9 Piek JP. Is a quantitative approach useful in the comparison of spontaneous movements in fullterm and preterm infants? Hum Mov Sci 2001;20:717-36.

10 Limperopoulos C, Soul JS, Gauvreau K, Huppi PS, Warfield SK, Bassan H, et al. Late gestation cerebellar growth is rapid and impeded by premature birth. Pediatrics 2005;115:688-95.

11 Bartlett DJ. Comparison of 15-month motor and 18-month neurological outcomes of term infants with and without motor delays at 10-months-of-age. Phys Occup Ther Pediatr 2000;19:61-72.

12 Darrah J, Hodge M, Magill-Evans J, Kembhavi G. Stability of serial assessments of motor and communication abilities in typically developing infants – implications for screening. Early Hum Dev 2003;72:97-110.

13 Darrah J, Piper M, Watt M-J. Assessment of gross motor skills of at-risk infants: predictive validity of the Alberta Infant Motor Scale. Dev Med Child Neurol 1998;40:485-91.

14 Easly A. Dynamic assessment for infants and toddlers: the relationship between assessment and the environment. Pediatr Phys Ther 1996;8:62-9.

15 Piper MC, Darrah J. Motor assessment of the developing Infant. Philadelphia: WB Saunders; 1994.

16 Darrah J, Redfern L, Maguire TM, Beaulne AP, Watt J. Intra-individual stability of rate of gross motor development in full-term infants. Early Hum Dev 1998;52:169-79.

17 Gerver WJM and de Bruin R. Paediatric Morphometrics, a reference manual. 2nd extended ed. Maastricht (NL): University Press Maastricht; 2001.

18 Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529-34.

19 Einspieler C, Prechtl HFR. Prechtl's assessment of general movements: a diagnostic tool for the functional assessment of the young nervous system. Ment Retard Dev Disabil Res Rev 2005;11:61-7.

20 Dubowitz LMS, Dubowitz V, Mercuri E. The neurological assessment of the preterm and full-term newborn infant. 2nd ed. Clin Dev Med No. 148. London (UK): Mac Keith Press; 1999.
21 Statistical Package for the Social Sciences for Windows, version 12.0.1.
22 Jeng SF, Tsou Yau KI, Liao HF, Chen LC, Chen PS. Prognostic factors for walking attainment in very low-birthweight preterm infants. Early Hum Dev 2000;59:159-73.
23 Bartlett DJ, Okun NB, Byrne PJ, Watt JM, Piper MC. Early motor development of breech- and cephalic-presenting infants. Obstet Gynecol 2000;95:425-32.
24 Abbott AL, Bartlett DJ. Infant motor development and equipment use in the home. Child Care Health Dev 2001;27:295-306.
25 Campbell SK, Kolobe THA, Wright BD, Linacre JM. Validity of the Test of Infant Motor Performance for prediction of 6-, 9-, and 12-month scores on the Alberta Infant Motor Scale. Dev Med Child Neurol 2002;44:263-72.
26 Majnemer A, Barr RG. Influence of supine sleep positioning on early motor milestone acquisition. Dev Med Child Neurol 2005;47:370-6.
27 Fallang B, Saugstad OD, Hadders-Algra M. Postural adjustments in preterm infants at 4 and 6 months post-term during voluntary reaching in supine position. Pediatr Res 2003;54:826-33.
28 Mercuri E, Guzzetta A, Laroche S, Ricci D, vanHaastert I, Simpson A, et al. Neurologic examination of preterm infants at term age: comparison with term infants. J Pediatr 2003;142:647-55.
29 Samson JF, de Groot L. The influence of postural control on motility and hand function in a group of 'high-risk' preterm infants at 1 year of age. Early Hum Dev 2000;60:101-13.
30 de Groot L, de Groot CJ, Hopkins B. An instrument to measure independent walking: are there differences between preterm and fullterm infants? J Child Neurol 1997;12:37-41.
31 de Groot L. Posture and motility in preterm infants. Dev Med Child Neurol 2000;42:65-8.
32 Hack M, Fanaroff AA. Outcomes of children of extremely low birthweight and gestational age in the 1990's. Early Hum Dev 1999;53:193-218.
33 Latal-Hajnal B, Von Siebenthal K, Kovari H, Bucher HU, Largo RH. Postnatal growth in VLBW infants: significant association with neurodevelopmental outcome. J Pediatr 2003;143:163-70.
34 Hebestreit H, Bar-Or O. Exercise and the child born prematurely. Sports Med 2001;31:591-99.
35 Keller H, Bar-Or O, Kriemler S, Ayub BV, Saigal S. Anaerobic performance in 5- to 7-yr-old children of low birthweight. Med Sci Sports Exerc 2000;32:278-83.
36 Als H, Duffy FD, McAnulty GB, Rivkin MJ, Vajapeyam S, Mulkern RV, et al. Early experience alters brain function and structure. Pediatrics 2004;113:846-57.
37 Piek JP. The role of variability in early motor development. Infant Behav Dev 2002;25:452-65.
38 Davis L, Mohay H, Edwards H. Mothers' involvement in caring for their premature infants: an historical overview. J Adv Nurs 2003;42:578-86.

Prediction of neuromotor outcome based on brain imaging

Part 2

Chapter 3

ULTRASOUND ABNORMALITIES PRECEDING CEREBRAL PALSY IN HIGH-RISK PRETERM INFANTS

Linda S. de Vries
Ingrid C. van Haastert
Karin J. Rademaker
Corine Koopman
Floris Groenendaal

J Pediatr. 2004 Jun;144(6):815-20.

ABSTRACT

Objective: To assess sequential high-resolution cranial ultrasound (US) in high-risk preterm infants to predict cerebral palsy (CP).

Study design: Preterm infants were prospectively studied (n = 2139), 1636 ≤32 weeks gestational age (GA) (group A) and 503 with a GA of 33 to 36 weeks (group B). US was performed once a week until discharge and at 40 weeks postmenstrual age (PMA), using a 7.5-MHz transducer. Grade III and IV hemorrhage, cystic periventricular leukomalacia (c-PVL), and focal infarction were considered major US abnormalities. A diagnosis of CP was made at a minimum age of 24 months.

Results: Seventy-six (5%) of the 1460 survivors in group A developed CP. US abnormalities were present in 70 of 76 (92%) infants, being major in 58 (83%) and minor in 12 (17%). In 29% of the CP cases with major US abnormalities, cysts were first detected beyond day 28. A further 6 infants without US abnormalities developed CP, and 3 of these infants developed ataxic CP. Twenty-nine (6%) of the 469 survivors in group B developed CP. US abnormalities were present in 28 of 29 (96%) infants, being major in 25 (89%) and minor in 3 (11%). One infant without US abnormalities developed CP. Considering the major US abnormalities, a specificity of 95% and 99% and a sensitivity of 76% and 86% were found for group A and B, respectively. The positive predictive value was 48% in group A and 83% in group B.

Conclusion: Seventy-nine percent of our CP cases had major US abnormalities. To detect c-PVL, the most predictive US marker for CP, sequential scans with a 7.5-MHz transducer are required.

INTRODUCTION

Cranial ultrasound (US) was first introduced in the late 1970s as a non-invasive bedside technique and was considered a method of first choice to assess the brain of the high-risk preterm infant.[1] The first US studies focused on intraventricular hemorrhages (IVHs). Time of occurrence, evolution of the lesion, and risk factors were reported in the early eighties.[2,3] During this period, it also became possible to detect severe cystic periventricular leukomalacia (c-PVL) using a transducer with a better angle of insonation and of higher resolution (7.5 MHz instead of 5 MHz).[4,5]

With the introduction of neonatal magnetic resonance imaging (MRI), this technique was found to be superior for detecting subtle white matter lesions.[6-10] However, this elegant technique is expensive and time consuming, and patients need to be transported to the magnet and may need sedation. Longitudinal measurements are difficult to perform, and no long-term follow-up studies are available. It therefore would be helpful if all high-risk infants could be screened with US and then infants for a subsequent MRI.

Over the last few years, several studies were published showing that only 40% to 50% of the infants with cerebral palsy (CP) had lesions on neonatal US.[11-13] This information may lead to a decreased use of cranial US during the neonatal period. If only one or two scans are performed during the first few weeks, detection of cysts is less reliable, and unexpected cases of CP may occur.[14] The aim of this study was to evaluate sequential high-quality cranial US in high-risk preterm infants for the prediction of CP.

PATIENTS AND METHODS

All preterm infants with a gestational age (GA) ≤36 weeks, admitted to the neonatal intensive care unit of the Wilhelmina Children's Hospital (a tertiary referral center) and born between January 1990 and January 1999, were studied prospectively using cranial US. Infants with chromosomal disorders, congenital abnormalities, congenital infections, and proven metabolic disorders were excluded.

Those who survived were seen in the follow-up clinic at regular intervals. The pediatric physiotherapist was blinded to the US data. The diagnosis of CP was made according to the criteria of Hagberg at a minimum age of 24 months.[15] Maximal locomotor function of those with CP was graded according to a simplified version of the classification suggested by Palisano et al.[16] At 2 years, a distinction was made between (a) walking independently without restrictions: can take more than 10 steps without any help; (b) sits independently: infant maintains floor sitting and may pull to stand and take steps holding onto furniture; and (c) cannot sit: is unable to maintain antigravity head and trunk control in prone and sitting positions. A developmental quotient (DQ) was obtained using the Griffiths Mental Developmental Scale. A DQ >85 at 2 years corrected age was considered normal.[17]

Antenatal, perinatal, and neonatal data were maintained prospectively in a computerized database.

Ultrasound examination

Cranial US was performed as soon as possible after admission, at least once a week until discharge to the local hospital, and again at 40 weeks postmenstrual age (PMA) during the first visit to the follow-up clinic. Infants were scanned with an ATL UM-4 mechanical sector scanner with a multifrequency transducer (5-7.5-10–MHz crystals). The 7.5-MHz transducer was used whenever possible for the best possible resolution. The US abnormality was classified after its full evolution, which was either at discharge or at 40 weeks PMA. Abnormalities on cranial US for preterm infants were classified as reported previously.[18-20]

Cranial US was considered normal when there were no abnormalities or only mild echodensities, present for less than 1 week. Germinal matrix-IVH was classified according to Papile et al.[18] Periventricular leukomalacia (PVL) was graded as described previously[19]: grade I: periventricular areas of increased echogenicity present for 7 days or more; grade II: periventricular areas of increased echogenicity evolving into small localized fronto-parietal cysts; grade III: periventricular areas of increased echogenicity evolving into extensive periventricular cystic lesions involving the occipital and fronto-parietal white matter; and grade IV:

areas of increased echogenicity in the deep white matter evolving into extensive subcortical cysts. Basal ganglia lesions were diagnosed when increased echogenicity was seen on at least two sequential scans. Focal infarction was diagnosed when an area of increased echogenicity with or without cystic evolution was seen in a region supplied by one of the main cerebral arteries.[20]

Grade III and IV hemorrhage, c-PVL and subcortical leukomalacia, basal ganglia lesions, and focal infarction were considered major US abnormalities.

RESULTS

Of the 2139 children who met the entry criteria, 1636 were ≤32 weeks GA; 176 (11%) died, and 1460 infants survived. Five hundred and three infants with a GA of 33 to 36 weeks were admitted; 34 (7%) died, and 469 survived the neonatal period. More than 80% of all infants and all but 2 of those with major US abnormalities were seen in the follow-up clinic. If any of the children without major US abnormalities go on to develop CP, they are referred to our hospital, either to our neonatal follow-up clinic, to the pediatric neurologist, or to the rehabilitation center. All notes were checked for any visits to either of these specialists.

Preterm infants with a GA ≤32 weeks

Of the 1460 survivors, 76 (5%) developed CP. In 70 of the 76 children (92 %), US abnormalities were recognized in the neonatal period, being major in 58 (83%) and minor in 12 (17%) (Table I). Four of the children with a grade III hemorrhage also had grade I PVL. Two of these 4 developed mild spastic diplegia, and the other 2 developed severe spastic diplegia. Five children had an IVH grade III with associated c-PVL, 1 developed a hemiplegia, the other 4 showed an asymmetric quadriplegia. Seventeen children had a grade IV hemorrhage and developed a unilateral porencephalic cyst. Fourteen developed a hemiplegia, 1 a mild asymmetric diplegia, and 2 an asymmetric quadriplegia. Three of these 17 children required insertion of a shunt. Twelve infants had grade I PVL, and all developed a mild diplegia.

Ten had grade II PVL, 3 developed a hemiplegia, 4 a mild diplegia, and 3 a severe diplegia. Seventeen infants had grade III PVL, and all children were wheelchair dependent and showed either severe diplegia or quadriplegia. Five infants had focal infarction, 4 developed a hemiplegia, and 1 with bilateral thalamic infarcts developed a diplegia.

Table I US abnormality preceding the development of CP, GA ≤32 weeks (group A)

	N = 514	(%) Died n = 85	(%) Survivors n = 429	(%) CP n = 76	Infants without CP DQ at 24 mo corrected age (%)	
					DQ ≤ 85 (n = 80)	DQ > 85 (n = 273)
IVH grade III (+PVL I)	56	43	57	12*	38	44†
IVH grade III + c-PVL	8	25	75	83	—	17
IVH grade IV	64	44	56	47	17‡	36
PVL grade I	319	5	95	4	18	69§
PVL grade II	20	15	85	59	18	23
PVL grade III	29	38	62	94	6	—
Focal infarction	12	—	100	42	25	33
Unknown	6	—	100	100	—	—

* Four infants with associated PVL grade I.
† Two infants without follow-up.
‡ One infant blind as a result of severe retinopathy of prematurity.
§ Twenty-six infants without follow-up.

Preterm infants with a GA 33-36 weeks

Of the 469 survivors, 29 (6%) developed CP. In 28 of the 29 children (96%), US abnormalities were recognized in the neonatal period, being major in 25 (89%) and minor in 3 (11%) (Table II). Six children had a grade IV hemorrhage and developed a unilateral porencephalic cyst, and this was of antenatal onset in 5 children. Five of them developed a hemiplegia and 1 an asymmetric quadriplegia, 2 required insertion of a shunt. Three infants had grade I PVL, and these infants developed a mild diplegia. Three had grade II PVL and developed a mild diplegia. Nine had grade III PVL, and all had severe diplegia; none were able to walk unaided. Two developed

subcortical cystic leukomalacia and developed quadriplegia as well as severe cerebral visual impairment. Two had symmetric basal ganglia lesions with subsequent development of dyskinetic CP. Three infants had a focal area of infarction with subsequent development of a hemiplegia.

Table II US abnormality preceding the development of CP, GA >32 weeks (group B)

	N = 68	(%) Died n = 8	(%) Survivors n = 60	(%) CP n = 29	Infants without CP DQ at 24 mo corrected age (%)	
					DQ ≤ 85 (n = 4)	DQ > 85 (n = 27)
IVH grade III + c-PVL	1	—	100	—	—	100
IVH grade IV	9	—	100	66	—	33
PVL grade I	31	6	94	10	14	76
PVL grade II	4	—	100	75	—	25
PVL grade III	10	10	90	100	—	—
SCL	5	60	40	100	—	—
BGL	2	—	100	100	—	—
Focal Infarction	5	40	60	100	—	—
Unknown	1	—	100	100		

BGL, Basal ganglia lesions; *SCL*, subcortical leukomalacia

Time of detection of the major US abnormalities

Nineteen infants in group A developed cystic lesions in the white matter, which could be considered a marker for subsequent development of CP, beyond day 28 from birth (Table III). In 12 of the infants, the cysts were detected on the weekly scan, while the infants were still in the neonatal intensive care unit, and in 3 of these, the cysts were first seen on a pre-discharge scan at 6 and 7 weeks of age. One infant developed extensive cystic lesions after readmission at 36 weeks with an enterovirus infection. In the remaining 6 infants, the cysts were first seen on the first follow-up appointment at 40 weeks PMA. Late onset c-PVL developed in 5 children

after sepsis in 1, hypocarbia in 1, respiratory deterioration associated with a pulmonary hemorrhage in 1, and after severe recurrent apneas in 2. The cystic evolution occurred while the infant was still in the unit.

Seventeen of these 19 infants subsequently developed CP. Sixteen of these belonged to the group with grade II or III c-PVL. Only 1 of the 36 infants with a grade IV hemorrhage was first noted to have a porencephalic cyst at 40 weeks PMA without a diagnosis of a grade IV hemorrhage during his admission period. A severe clinical deterioration had occurred after discharge to the local hospital. Seventeen of 58 (29%) of the children who developed CP after major US abnormalities would not have been diagnosed if US were restricted to the first 4 weeks after birth. None of the survivors in group B developed cystic lesions beyond day 28 (Table IV).

Table III Time of occurrence of major US abnormalities and PVL grade I in the survivors ≤32 weeks (group A)

US/day	n	1-7 d	8-14 d	15-21 d	22-28 d	29-35 d	36-42 d	43-49 d	40 wks PMA
IVH grade III	32	31	1	—	—	—	—	—	—
IVH grade III + cPVL	6	0	1	2	1	2	—	—	—
IVH grade IV	36	35	—	—	—	—	—	—	1
PVL grade I	303	303	—	—	—	—	—	—	—
PVL grade II	17	—	—	3	5	6	1	1	1
PVL grade III	18	1	2	5	3	1	1	1	4
Focal infarction	12	1	6	3	2	—	—	—	—

Table IV Time of occurrence of major US abnormalities and PVL grade I in the survivors >32 weeks (group B)

US/day	n	1-7 d	8-14 d	15-21 d	22-28 d	29-35 d	36-42 d	43-49 d	40 wks PMA
IVH grade III + cPVL	1	—	—	—	1	—	—	—	—
IVH grade IV	9	9	—	—	—	—	—	—	—
PVL grade I	29	29	—	—	—	—	—	—	—
PVL grade II	4	—	—	2	2	—	—	—	—
PVL grade III	9	1	1	6	1	—	—	—	—
SCL	2	2	—	—	—	—	—	—	—
BGL	2	2	—	—	—	—	—	—	—
Focal Infarction	3	3	—	—	—	—	—	—	—

Children with normal US who developed CP

Seven of 105 infants (7%) who developed CP had normal neonatal US data. Six were born ≤32 weeks GA. Two were severely growth restricted (510 and 485 g at 27 and 29 weeks, respectively), and both had mild ataxia at 7 years of age and had achieved independent walking. MRI scans performed at 7 years of age showed mild ventricular dilatation without periventricular gliosis in 1 child and cerebellar atrophy associated with mild ventricular dilatation and periventricular gliosis in the other. One other child also developed ataxia, but also was able to walk unaided. This child had a computed tomography scan at 2 years of age that did not show any abnormalities. Two infants were each part of a monozygous twin pair, 1 developed a mild diplegia, the other a moderate hemiplegia. Both were able to walk unaided. In the remaining infant, the only US abnormality was mild ventricular dilatation. She developed a diplegia and also was able to walk unaided. Her MRI at 7 years of age confirmed the ventricular dilatation, but there was no associated periventricular gliosis.

Only 1 child belonged to group B. He was born at 34 weeks as part of a monozygous twin pair. He developed a mild hemiplegia. An MRI performed at 2 years of age showed a small unilateral periventricular infarct.

Children with major US lesions who did not develop CP

Sixty-three of the 121 (52%) surviving infants with major US abnormalities in group A did not develop CP (Table I). The majority of children with a grade III hemorrhage (26/32 survivors, 81%) did not develop CP, but 12 (38%) had a DQ ≤85 at 24 months corrected age. More than half of the infants with a unilateral parenchymal hemorrhage (19/36 survivors, 53%) did not develop CP. Whether infants developed CP or not was related strongly to the site of the parenchymal lesion, being anterior to the trigone in 16 and adjacent to the trigone in 3 in those without CP and posterior to the trigone in the 17 infants with this lesion who did develop CP. Of the 19 children without CP, 5 had a DQ ≤85, and 1 was blind as a result of severe retinopathy of prematurity. The percentage of children with c-PVL without CP was considerably lower, with 7 of 17 c-PVL grade II survivors (41%) and 1 of 18 c-PVL grade III survivors (6%).

More than half (7/12 survivors, 58%) of the infants with a focal infarction did not develop CP, but 3 (25%) had a DQ ≤85.
Only 5 of 30 (17%) children with major US abnormalities in group B did not develop CP. These children belonged mostly to the group with a unilateral parenchymal hemorrhage (3/9, 33%).

Predictive value of ultrasound for the development of CP

When considering a grade III and IV hemorrhage, cystic PVL, or focal infarction as major US abnormalities, a specificity of 95% and 99% were found for group A and B, respectively (Table V). The sensitivity was lower (76 and 86%, respectively). The positive predictive value was especially low in group A (48%) as a result of the large number of infants with a normal outcome despite major US abnormalities. This applied primarily to infants with a grade III hemorrhage. Only 4 of 32 (12.5%) surviving very preterm infants with a grade III hemorrhage developed a diplegia. If a grade III hemorrhage were considered a minor lesion and included in the normal/ minor US group, the positive predictive value would increase to 61%. Only grade III c-PVL was invariably associated with CP in all but 1 of the infants. PVL I was a very common finding, and only 15 of 331 (4.5%) infants developed a mild spastic diplegia.

DISCUSSION

Using sequential high-resolution cranial US until discharge and at 40 weeks PMA, major US abnormalities were detected in 79% of the children who developed CP during infancy. Only 7 of 105 children with CP had completely normal US findings. CP was mild in the infants with a normal US scan, and all achieved independent walking. US was unable to detect abnormalities in 3 infants who subsequently developed cerebellar ataxia. Two of these 3 infants with ataxia were severely growth retarded, and cerebellar atrophy was clearly seen on later MRI in one.[21] As the cerebellum is an echogenic structure using US, it is hard to make the diagnosis of a hemorrhage in this structure, although performing US through the posterolateral fontanel is helpful.[22,23]

Table V Predictive value (%) of major cranial US abnormalities for CP in 1460 survivors

Abnormal US	≤ 32 weeks GA	33-36 weeks GA
Sensitivity	76	86
Specificity	95	99
PPV	48	83
NPV	99	99

Three other infants with a normal neonatal US were part of a monozygous twin pair. The fluctuations in the shared circulation of the twins may cause antenatal ischemic changes, and areas of increased echogenicity (PVL grade I), if ever present, had disappeared by the time the twins were born. Almost a third (29%) of the children ≤32 weeks GA who developed CP after major US abnormalities would not have been diagnosed if US were restricted to the first 4 weeks after birth. Late detection of periventricular cysts was related to 'late onset c-PVL' in 5 infants, demonstrating the need for sequential scans after an acute deterioration.[24,25] Extensive c-PVL (grade III) was first detected at 40 weeks, without the presence of severe periventricular echogenicities at an earlier stage, in 4 infants. Eight of the remaining 10 infants who developed cysts beyond the first 4 weeks after birth were all infants who took a long time to develop localized c-PVL (grade II). In a previous study, we also reported that these small cysts take longer to develop and resolve within a few weeks after their first appearance, with ventriculomegaly (VM) as a sequel in some but not all infants.[26] Even extensive periventricular cysts (grade III) will eventually resolve with VM as a sequel. VM is sometimes reported as a separate entity as an indicator of white matter damage.[27] We preferred to classify the children according to the underlying condition, as VM can suggest atrophy after any degree of PVL but also can be seen as a sequel to an IVH with mild posthemorrhagic ventricular dilatation.

In contrast to previous studies, we also included the preterm infants with a GA of 33 to 36 weeks, who are not scanned in many neonatal units. The percentage of infants with CP in this age range in our cohort was 6%, which is even higher than the 5% of the less mature group. In all but 1 of the CP cases, an US abnormality was diagnosed during the neonatal period and always during the first 4 weeks after birth. Sequential cranial US therefore is also recommended for more mature preterm infants.

Our data are very different from studies published recently. In two cohorts, only 50% of the CP cases were detected using cranial US.[11,12] In another recent study, only 40% of the CP cases had US abnormalities.[13] In the latter study, 33% of the infants had only one US examination.

The main explanation for the differences between our results and other studies appears to be the number of scans that were performed over a period exceeding the first 4 weeks from birth. It is likely that many of the infants enrolled in the other studies were not scanned for a sufficient length of time as a result of early discharge or because further scans were not deemed necessary because of initial normal US scan findings.[11-14]

We have great concern about the recommendations given in two recent studies. One suggests that there is no need for further US scans when two normal US examinations, at least 7 days apart, have been obtained, in the absence of any further clinical deterioration.[14] However, more than half of the infants (100/198) with a normal first and second US examination did *not* have a repeat study, and no follow-up data were provided. Of more concern are the recent guidelines provided by 'the quality standards committee of the American Academy of Neurology and the practice committee of the Child Neurology Society.'[28] The recommendation is that infants be scanned at 7 to 14 days after birth and *optimally* again at 36 to 40 weeks. Our results, however, show that the diagnosis of c-PVL can only be made if infants are *also* scanned at 36 to 40 weeks PMA.

Technical issues also may play a role in explaining the differences between our results and those of others. An insufficient angle of insonation (60° instead of 90°) makes it difficult to assess the periventricular white matter, and the use of a 5-MHz instead of a 7.5-MHz transducer is not suitable for the detection of small cystic lesions (grade II PVL).[19]

The present study focused on children who developed CP. Many children did not develop CP in spite of major US abnormalities, and this was related to the site and extent of the lesion. We appreciate fully that CP is only one of the many problems that may affect the high-risk newborn infant. Other problems, such as sensorineural deficits and learning disabilities, cannot be predicted by cranial US, and these problems are more common among high-risk newborn infants than the development of CP. Volumetric MRI and magnetic resonance spectroscopy in the neonatal period may be helpful in predicting later learning disabilities.[29-31] MRI increasingly is being used in high-risk preterm infants. We and others have found a good correlation for both techniques in children with major US abnormalities[32-35] but a discrepancy between US and MRI for subtle white matter lesions.[8,10]

In conclusion, high-resolution and sequential US can detect major US abnormalities in the majority of children who develop CP during infancy. As infants often are discharged early from tertiary intensive care units to their local hospitals and usually are discharged home before 40 weeks PMA, there needs to be sufficient neurosonography experience in the referring hospitals. To avoid the occurrence of unexpected CP, it is essential that those born ≤32 weeks GA be scanned once a week until discharge and once again at term age equivalent.

REFERENCES

1 Thorburn RJ, Lipscomb AP, Stewart AL, Reynolds EO, Hope PL, Pape KE. Prediction of death and major handicap in very preterm infants by brain ultrasound. Lancet 1981;1:119-21.

2 Levene MI, Fawer C-L, Lamont RF. Risk factors in the development of intraventricular haemorrhage in the preterm newborn. Arch Dis Child 1982;57:410-7.

3 Szymonowicz W, Yu VYH, Wilson FE. Antecedents of periventricular haemorrhage in infants weighing 1250 g or less at birth. Arch Dis Child 1984;59:13-7.

4 Levene MI, Wigglesworth JS, Dubowitz V. Hemorrhagic periventricular leukomalacia in the neonate: a real-time ultrasound study. Pediatrics 1983;71:794-7.

5 Hill A, Melson GL, Clark HB, Volpe JJ. Haemorrhagic leukomalacia: diagnosis by real-time ultrasound and correlation with autopsy findings. Pediatrics 1982;69:282-4.

6 Maalouf EF, Duggan PJ, Counsell SJ, Rutherford MA, Cowan F, Azzopardi D, et al. Comparison of findings on cranial ultrasound and magnetic resonance imaging in preterm infants. Pediatrics 2001;107:719-27.

7 Childs AM, Cornette L, Ramenghi LA, Tanner SF, Arthur RJ, Martinez D, et al. Magnetic resonance and cranial ultrasound characteristics of periventricular white matter abnormalities in newborn infants. Clin Radiol 2001;56:647-55.

8 Inder TE, Anderson NJ, Spencer C, Wells S, Volpe JJ. White matter injury in the premature infant: a comparison between serial cranial sonographic and MR findings at term. Am J Neuroradiol 2003;24:805-9.

9 Debillon T, N'Guyen S, Muet A, Quere MP, Moussaly F, Roze JC. Limitations of ultrasonography for diagnosing white matter damage in preterm infants. Arch Dis Child Fetal Neonatal Edition 2003;88:F275-F9.

10 Miller SP, Cozzio CC, Goldstein RB, Ferriero DM, Partridge JC, Vigneron DB, et al. Comparing the diagnosis of white matter injury in premature newborns with serial MR imaging and transfontanel ultrasonography findings. Am J Neuroradiol 2003;24:1661-9.

11 O'Shea TM, Klinepeter KL, Dillard RG. Prenatal events and the risk of cerebral palsy in very low birth weight infants. Am J Epidemiol 1998;147:362-9.

12 Wheater M, Rennie MA. Perinatal infection is an important risk factor for cerebral palsy in very low birthweight infants. Dev Med Child Neurol 2000;42:364-7.

13 Nelson KB, Grether JK, Dambrosia JM, Walsh E, Kohler S, Satyanarayana G, et al. Neonatal cytokines and cerebral palsy in very preterm infants. Pediatr Res 2003;53:600-7.

14 Nwafor-Anene VN, DeCristofaro JD, Baumgart S. Serial head ultrasound studies in preterm infants: how many normal studies does one infant need to exclude significant abnormalities? J Perinatol 2003;23:104-10.

15 Hagberg B, Hagberg G, Olow I. The changing panorama of cerebral palsy in Sweden 1954-1970, II: analysis of various syndromes. Acta Paediatr Scand 1975;64:193-200.

16 Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39:214-23.

17 Griffiths R. The abilities of babies: a study in mental measurement. Amersham (UK): Association of Research in Infant and Child Development;1976.

18 Papile L, Burstein J, Burstein R, Koffler H. Incidence and evaluation of subependymal haemorrhage: a study of children with a birthweight less than 1500 g. J Pediatr 1978;92:529-34.

19 De Vries LS, Eken P, Dubowitz LMS. The spectrum of leukomalacia using cranial ultrasound. Behav Brain Res 1992;49:1-6.

20 De Vries LS, Groenendaal F, Eken P, van Haastert IC, Rademaker KJ, Meiners LC. Infarcts in the vascular distribution of the middle cerebral artery in preterm and fullterm infants. Neuropediatrics 1997;28:88-96.
21 Krageloh-Mann I, Toft P, Junding J, Andresen J, Pryds O, Lou HC. Brain lesions in preterms: origin, consequence and compensation. Acta Paediatr 1999;88:897-908.
22 Miall LS, Cornette LG, Tanner SF, Arthur RJ, Levene MI. Posterior fossa abnormalities seen on magnetic resonance brain imaging in a cohort of newborn infants. J Perinatol 2003;23:396-403.
23 Luna JA, Goldstein RB. Sonographic visualisation of neonatal posterior fossa abnormalities through the posterolateral fontanelle. AJR 2000;174:561-7.
24 De Vries LS, Regev R, Dubowitz LMS. Late onset cystic leukomalacia. Arch Dis Child 1986;61:298-9.
25 Andre P, Thebaud B, Delavaucoupet J, Zupan V, Blanc N, d'Allest AM, et al. Late-onset cystic periventricular leukomalacia in premature infants: a threat until term. Am J Perinatol 2001;18:79-86.
26 Pierrat V, Duqennoy C, van Haastert IC, Ernst M, Guilley N, de Vries LS. Ultrasound diagnosis and neurodevelopmental outcome of localised and extensive cystic periventricular leukomalacia. Arch Dis Child Fetal Neonatal Edition 2001;84:F151-F6.
27 Kuban K, Sanocka U, Leviton A, Allred EN, Pagano M, Dammann O, et al. White matter disorders of prematurity: association with intraventricular hemorrhage and ventriculomegaly. The Developmental Epidemiology Network. J Pediatr 1999;134:539-46.
28 Ment LR, Bada HS, Barnes P, Grant PE, Hirtz D, Papile LA, et al. Practice parameter: neuroimaging of the neonate. Report of the quality standards subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2002;58:1726-38.
29 Inder TE, Huppi PS, Warfield S, Kikinis R, Zientara GP, Barnes PD, et al. Periventricular white matter injury in the premature infant is followed by reduced cerebral cortical gray matter volume at term. Ann Neurol 1999;46:755-60.
30 Groenendaal F, van der Grond J, van Haastert I, Toet M, Rademaker K, de Vries LS. Early cerebral proton MRS and neurodevelopmental outcome in infants with cystic leukomalacia. Dev Med Child Neurol 1997;39:373-9.
31 Peterson BS, Anderson AW, Ehrenkranz R, Staib LH, Tageldin M, Colson E, et al. Regional brain volumes and their later neurodevelopmental correlates in term and preterm infants. Pediatrics 2003;111:939-48.
32 De Vries LS, Eken P, Groenendaal F, van Haastert JC, Meiners LC. Correlation between the degree of periventricular leukomalacia diagnosed using cranial ultrasound and MRI later in infancy in children with cerebral palsy. Neuropediatrics 1993;24:263-8.
33 De Vries LS, Rademaker KJ, Groenendaal F, Eken P, Van Haastert JC, Vandertop WP, et al. Correlation between neonatal cranial ultrasound, MRI in infancy, and neurodevelopmental outcome in infants with a large intraventricular haemorrhage with or without unilateral parenchymal involvement. Neuropediatrics 1998;29:180-8.
34 De Vries LS, Groenendaal F, Eken P, Rademaker KJ, Meiners LC. Asymmetrical myelination of the posterior limb of the internal capsule: an early predictor of hemiplegia. Neuropediatrics 1999;30:314-9.
35 Roelants-van Rijn AM, Groenendaal F, Beek E, Eken P, van Haastert IC, de Vries LS. Parenchymal brain injury in the preterm infant: comparison of cranial ultrasound, MRI and neurodevelopmental outcome. Neuropediatrics 2001;32:80-9.

Chapter 4

MYTH: CEREBRAL PALSY CANNOT BE PREDICTED BY NEONATAL BRAIN IMAGING

Linda S. de Vries
Ingrid C. van Haastert
Manon J.N.L. Benders
Floris Groenendaal

Semin Fetal Neonatal Med. 2011 Oct;16(5):279-87.
Epub 2011 Jun 1.

ABSTRACT

There is controversy in the literature about the value of brain imaging in neonates regarding the prediction of cerebral palsy (CP). The aim of this review was to unravel the myth that CP cannot be predicted by neuroimaging in neonates. Major intracranial lesions in the preterm infant should be recognized with sequential cranial ultrasound and will predict those with non-ambulatory CP. Magnetic resonance imaging (MRI) at term-equivalent age will refine the prediction by assessment of myelination of the posterior limb of the internal capsule. Prediction of motor outcome in preterm infants with subtle white matter injury remains difficult, even with conventional MRI. MRI is a better tool to predict outcome in the term infant with hypoxic-ischaemic encephalopathy or neonatal stroke. The use of diffusion-weighted imaging as an additional sequence adds to the predictive value for motor outcome. Sequential and dedicated neuroimaging should enable us to predict motor outcome in high risk newborns infants.

1. INTRODUCTION

The aim of this review is to refute the myth that cerebral palsy (CP) cannot be predicted by neonatal brain imaging in neonates when combining sequential cranial ultrasonography (cUS) for a sufficient length of time with conventional magnetic resonance imaging (MRI) at term-equivalent age (TEA) in the preterm infant and when using first week MRI including diffusion-weighted imaging (DWI) in the term infant.

2. THE PRETERM INFANT

Preterm birth is still increasing. The rate of neurodevelopmental impairment in survivors remains high and recent data have failed to show an improvement in neurodevelopmental outcome in infants with a gestational age (GA) of ≤25 weeks.[1,2] Others have reported a significant decrease in the rates of CP, severe cognitive impairments, and overall neurodevelopmental impairment, but these studies include infants with a GA >25 weeks and are hospital- rather than population-based studies.[3–5] Hitherto, rates of CP in preterm infants over time have been considered a good monitor of standards of perinatal and neonatal care,[6] but now this may be a less useful marker as rates and severity of CP fall and increasingly the bulk of adverse neurodevelopmental outcomes comprises cognitive and behavioural problems. Neonatal recognition of these problems is thought to be difficult. In our experience, the pathology that leads to the development of CP is largely understood and recognised with conventional neuroimaging, yet there are still several papers reporting that lesions preceding CP are identified with neonatal cUS in only 40–50% of cases.[7,8] More sophisticated imaging techniques are almost certainly needed to predict the later occurrence of cognitive and behavioral problems.[9]

Despite the decrease in rates of CP, it still occurs. Early recognition of at risk infants remains important; this is increasingly so as early neuro-behavioral intervention may be beneficial and improve later outcome.[10,11] Selection of infants who may benefit most from medical intervention is also becoming an issue, with randomised trials starting to show effect.[12]

Most parents want to be informed during the neonatal period about the expected neurodevelopmental outcome of their children. In the very vulnerable and immature infant, the presence of severe intracranial lesions may play a role when deciding whether to continue or redirect intensive care. While prognostic information used to be obtained mainly with cUS, MRI is now becoming more easily accessible and increasingly utilised. Subtle white matter lesions are best recognised with MRI, although their significance is still uncertain, whereas severe intracranial lesions which may lead to redirection of care should be recognizable with cUS.

2.1. Cranial ultrasonography

cUS was introduced into the neonatal intensive care unit (NICU) in the late 1970s.[13] The anterior fontanelle is the most commonly used acoustic window. More recently, the posterior fontanelle and the mastoid window have been used to achieve better visualization of the occipital part of the lateral ventricles, the occipital white matter and the posterior fossa.[14–17] Mechanical sector scanners replaced linear array imaging and allowed a wider angle of insonation, giving better visualization of the periventricular white matter.

Cystic periventricular leukomalacia (c-PVL) can now be diagnosed reliably as long as the examinations are performed often enough and over an appropriate time period as cysts take 2–5 weeks to develop, depending on their size.[18,19] Major intracranial lesions, such as large intraventricular haemorrhages (IVH grade III) and parenchymal haemorrhages (grade IV) or c-PVL should all be detectable with cUS, provided that a high resolution transducer with a wide angle of insonation is used. The examiner should have sufficient experience to obtain good quality images. During the last decade, awareness of cerebellar injury has increased and is routinely searched for on cUS through the posterior or mastoid fontanelles allowing improved detection of cerebellar haemorrhages (CBH) and infarction, which are especially common in the extremely preterm infant.[16,17]

All major intracranial lesions mentioned above are predictive of CP, and to a lesser degree to severe cognitive impairment, depending upon the size and site of the lesion. Despite studies reporting that lesions were identified on neonatal cUS in only 40–50% of infants who subsequently developed

CP,[7,8] we have been able to detect major cUS abnormalities in the majority of infants (83%) who developed CP by using high resolution, sequential cUS during the first 4–6 postnatal weeks and again between 36–40 weeks' postmenstrual age (PMA).[19] Recommendations for neuroimaging were given by the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society.[20] They stated that all infants with a GA ≤30 weeks should have cUS examination at 7–14 days of age and that this should optimally be repeated at 36–40 weeks' PMA. We have learned over the years that c-PVL may not have had the time to develop before discharge. Extensive cystic lesions in the white matter will still be visible using cUS at TEA, in contrast to only 50% of the small, localized cysts (grade II c-PVL). Among 41 infants in our cohort with c-PVL, cysts were only recognized beyond day 28 in 18 infants; 16 (90%) of these infants developed CP.[19] Cysts may also develop after discharge when there has been a late onset bacterial or viral infection.[21-23]

2.1.1. Interobserver agreement

Several groups have studied interobserver agreement. Hintz et al.[24] looked at cUS data from 326 infants interpreted by a central reader and compared those findings with local interpretations. Agreement was good (kappa >0.75) for severe haemorrhages, c-PVL, and the degree of ventriculomegaly (VM) but poor for lower grade IVH and non c-PVL. Local interpretations were highly accurate for grades III and IV IVH and c-PVL (sensitivity, 87–90%; specificity, 92–93%), but sensitivity was poor-to-fair for grades I and II IVH (48–68%) and PVL (20–44%). Harris et al.[25] compared reviews of cUS data of 255 infants with a birth weight <1500 g and GA <32 weeks. The original scans were copied, de-identified, and independently read by a panel of three experts using a standardized method of reviewing and reporting. There was only moderate agreement between the reviewers' reports and the original reports (kappa 0.45–0.51) and between the reviewers (kappa 0.54–0.64). The reviewers reported three to six times more white matter damage than had been reported locally. The scans had been photographed and copied, possibly adversely affecting quality.

2.1.2. Normal ultrasound scan

There is agreement about the predictive accuracy of a persistently normal cUS scan for a normal outcome first reported by Stewart et al.[26] In a more recent study of infants born between 1983 and 1988 from the same group, a correlation between neonatal cUS and outcome at 8 years of age was studied.[27] Disabling impairment was associated with a normal neonatal cUS examination in 6% of those with GA between 28 and 32 weeks and 8% for those with a GA <28 weeks. Despite the enhanced resolution of recent transducers being different from what we are used to today, making it likely that some localized c-PVL or cerebellar lesions may have been missed, these data are very similar to those of the EPIPAGE study, where 4% of children with normal cUS scans developed CP.[28]

2.1.3. Uncomplicated GMH-IVH

A germinal matrix haemorrhage (GMH) or a small IVH (grade II) are often taken together and considered to carry a low risk for CP. In the EPIPAGE study, 6.8% and 8.1% of affected infants developed CP, respectively. Especially in infants with a grade II IVH, it is of utmost importance to take changes in the white matter into account. The associated presence of echogenicity in the white matter is likely to play a more important role than the IVH itself in the development of CP, especially if it is followed by VM, indicating associated white matter loss.[29]

2.1.4. Severe haemorrhage

Both grades III and IV IVH are considered severe and are often combined for analysis. A grade III haemorrhage is defined as a bleed within the lateral ventricle with acute dilatation from blood, filling >50% of the ventricle. Associated white matter damage may be present and should be taken into account when predicting outcome. However, when post-haemorrhagic ventricular dilatation (PHVD) occurs and becomes severe, it may be difficult to assess the white matter fully within the field of view. Development of CP following an isolated grade III IVH varies considerably in the literature (12–28%) and increases with the development of PHVD.[30]
A grade IV haemorrhage is now preferably referred to as haemorrhagic parenchymal infarction (HPI) or venous infarction (VI), as the lesion is

likely to develop following impaired drainage of the medullary veins in the white matter.[31] Classically, this type of lesion evolves on the side of the larger haemorrhage into a porencephalic cyst, which communicates with the adjacent ventricle. When the HPI is smaller, it may evolve into multiple small cysts, which remain separate from the lateral ventricle, and the subsequent parenchymal appearance tends to be misclassified as PVL. Even though with an HPI there may be significant injury to the parenchyma, it is usually unilateral. Only about half of the children develop CP, and this is usually a unilateral spastic CP (USCP).[19] Whether USCP develops depends especially on the site/localization and extent of the lesion. Lesions in the parietal white matter involving the trigone are more likely to lead to USCP than those more anteriorly located.[32]

Bassan et al.[33] proposed a severity score on the basis of whether the HPI (i) involved two or more territories, (ii) was bilateral, or (iii) caused a midline shift. Among 30 infants, 18 developed CP with only 11 having a USCP. Their scoring system may be of limited use, as it is uncommon to find bilateral haemorrhages or a midline shift.[33]

Others were unable to find an association between site of the lesion and development and severity of CP.[34] In their cohort, 66% of those with HPI developed CP, but only 16% had moderate-to-severe functional impairment. Neither of these studies analysed their data with respect to the site of the lesion and relation to the trigonal area.

2.1.5. Ventricular dilation

A distinction should be made between ventricular enlargement seen following an IVH or following white matter damage. While the first tends to be classified as PHVD, the second is often referred to as VM.[29] Without sequential imaging, it is not always easy to make a distinction. In infants with PHVD, the shape of the lateral ventricles tends to be different with so-called 'ballooning' suggestive of increased pressure. Dilation is often progressive and intervention may be required. In VM following white matter damage, the occipital horns may be dilated with an irregularity to the margin in the absence of dilation of the frontal horns (Fig. 1). This is more commonly seen after several weeks in the extremely preterm infant and often occurs in the absence of preceding cUS abnormalities except for a mild and subjective increase in periventricular echogenicity.

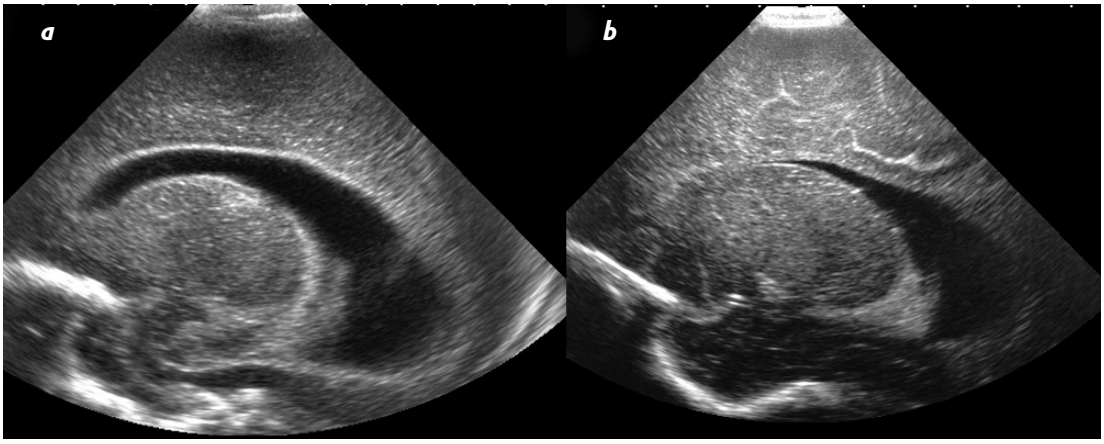

Fig. 1 cUS of two preterm infants, parasagittal views (***a***) following an IVH and (***b***) following PVE. Note the posterior dilatation following PVE, in contrast to more global VM following the IVH.

2.1.6. Cerebellar haemorrhage (CBH)

A CBH that can be diagnosed with cUS is usually large, considered severe, and is often associated with a large supratentorial haemorrhage. CUS performed through the mastoid window aids in the detection of CBH. The first large study by Limperoupolos et al.[16] reported mainly unilateral CBH in 35 preterm infants. Isolated CBH occurred in eight patients (23%); the remaining infants had associated supratentorial lesions. The overall incidence of CBH in their preterm infants was 2.8%, and the incidence of this lesion increased to 8.7% in infants born at <750 g. In a recent study, using the mastoid fontanelle routinely, the incidence of CBH in infants of ≤32 weeks' gestation was 1.3%.[35] Infants with CBH were more likely male, more preterm (24.4 vs 27.0 weeks) and of lower birth weight (692 vs 979 g). In another study of 77 infants with a GA <32 weeks,[17] seven (9%) infants were found to have CBH; in only two was the lesion seen on routine anterior fontanelle views. The lesions occurred in combination with a supratentorial haemorrhage in five of seven infants, and were restricted to the cerebellum in only two. MRI showed punctate haemorrhage in the cerebellum in six infants with normal cUS findings. Overall, the incidence of CBH varies between 1.3 % and 9%.[16,17,36,37]

Outcome data are still limited. Limperoupolos et al.[38] studied 86 premature infants (35 with isolated CBH, 16 with CBH plus supratentorial parenchymal injury, and 35 age-matched controls). Subjects underwent formal neurological examinations and a battery of standardized developmental, functional, and behavioural evaluations (mean age: 32.1 ± 11.1 months). Infants with isolated CBH injury vs controls had significantly lower mean scores on all tested measures, including motor abilities (48% vs 0%), expressive language (42% vs 0%), receptive language (37% vs 0%), and cognition (40% vs 0%), significantly associated with severe functional limitations in day-to-day activities. Significant differences were noted between cases with CBH injury vs controls on autism screening (37% vs 0%) and internalizing behavioral problems (34% vs 9%). Global developmental, functional, and social-behavioral deficits were more common and profound in infants with injury to the vermis. A more recent study emphasized the difference in outcome for those with CBH detected by cUS compared with smaller punctate lesions only seen with MRI.[37]

2.1.7. White matter damage

A distinction should be made between c-PVL and more diffuse white matter damage without (apparent) cystic evolution. Of 58 preterm infants with CP diagnosed at ≥2 years, 36% were able to walk independently, 41% could walk with an assistive device, and 24% were wheelchair dependent.[39] While the chance that a child with CP following PVL grade I [periventricular echogenicity (PVE) lasting beyond 1 week] or grade II (localized) c-PVL would achieve independent walking was as high as 85%, <10% of those with grade III (extensive) c-PVL were able to do so.[39] cUS will be able to visualize the extensive cysts, but localized cysts may be easily missed. PVE is subjective and very common, with 4–10% of the children developing mild bilateral spastic CP (BSCP) with more involvement of the lower than upper extremities.[40,41] The importance of the duration of PVE was stressed by Resch et al.,[40] who noted a significant increase in adverse neurodevelopmental outcome with increasing duration of PVE. The exact duration of this echogenicity (so-called flares) is not always known, as this requires sequential scans after the first postnatal week. Non-homogeneous echogenicity helps to distinguish more

significant PVE and is more often associated with punctate white matter lesions (PWML) on MRI. It has been suggested that PWML are associated with a reduced maturation score at TEA and a worse outcome.[42–44]

2.2. Magnetic resonance imaging

MRI is increasingly being used routinely in infants with a GA <28 or <30 weeks. The examination is usually performed at TEA or at the time the infant is being discharged. Only a few units are performing sequential scans and are therefore able to visualize the more acute changes as well.[45,46] Mirmiran et al.[47] found a better sensitivity for predicting CP using MRI near or at TEA than cUS (71% vs 29% at 20 months and 86% vs 43% at 31 months) as opposed to specificity (91% vs 86% at 20 months and 89% vs 82% at 31 months).

2.2.1. White matter damage

The major gain of conventional MRI at TEA is more reliable assessment of the diffuse and more subtle white matter abnormalities and the level of myelin seen in the posterior limb of the internal capsule (PLIC). A large cohort of preterm infants was studied at TEA by Woodward et al.[48] They used a white matter grading score, ranging from normal to moderate–severe. They found a positive predictive value (PPV) of moderate–severe white matter abnormalities for abnormal motor outcome of 31% (95% confidence interval: 17–49). Miller et al.[43] found the presence of PWML on early MRI (i.e. 31–33 weeks' PMA) to be equally predictive of motor outcome, compared with TEA MRI. Using more sophisticated MRI techniques, white matter damage is associated with loss of volume of the central gray nuclei.[49] Similar observations were done with cUS.[50]

2.2.2. Unilateral parenchymal injury

MRI at TEA improves the predictive accuracy of subsequent development of USCP in infants with HPI or middle cerebral artery (MCA) stroke recognized with sequential cUS.[51] Asymmetry of myelination of the PLIC can be reliably assessed at 40–42 weeks' PMA. In children with bilateral c-PVL, myelination in the PLIC is often sparse or absent, predictive of subsequent development of BSCP.

2.2.3. Neuroimaging as a predictor of cerebral palsy in our own population

2.2.3.1. Subjects / methods

During the years 2000–2008, 1859 preterm infants with a GA <32 weeks were admitted to our NICU; 168 (9%) died and 43 had severe parenchymal injury but died before MRI could be performed. TEA MRI was performed in 83 infants with a GA <32 weeks, when parenchymal injury was seen on sequential cUS or because of a large IVH and PHVD requiring neurosurgical intervention.

A 1.5 T or 3.0 T Philips system was used. MRI consisted of sagittal T1-weighted images, axial T2-weighted and axial inversion recovery images (1.5 T) or axial T1-weighted (3.0 T) images. Six infants had MRI but subsequently died. All survivors were seen in the follow-up clinic at a minimum of 24 months' corrected age whether they had MRI or not.

2.2.3.2. Results

Overall, 46 of 1691 survivors (2.7%) developed CP. Twenty-six of the 77 infants (34%) with neonatal MRI went on to develop CP. Six infants had MRI and would probably have developed CP but died following redirection of care (Table I). Thus, 26/46 (57%) surviving children who developed CP had cUS findings that warranted MRI. Of these 26, 15 had unilateral HPI, four had c-PVL grades I–II, and seven had c-PVL grade III.

Of the 20 who had milder cUS changes not thought to predict CP or warrant a neonatal MRI, 16 had PVL grade I, one had a small HPI, one had a MCA infarction not recognised before discharge and two had an IVH grade 2. The severity of CP in all but two of these 20 children was classified as level I according to the Gross Motor Function Classification System (GMFCS), and these 18 were independently ambulatory.[51,52] Eleven of these 20 infants had MRI in infancy. Evidence of injury to the white matter on cUS was present in 10 infants with PVL-I and HPI, and a cortical MCA infarct was seen in one child. The other nine did not have MRI.

Of the 37 infants with HPI who had neonatal MRI, the 15 who developed USCP were predicted to do so on the basis of an asymmetrical PLIC on their MRI at TEA. Poor bilateral signal intensity in the PLIC was seen in those with bilateral c-PVL who developed CP.

Table I Relationship between different ultrasound-diagnosed abnormalities in the preterm infant and subsequent motor outcome

Cranial ultrasonography	Neonatal MRI		Later MRI	No MRI	Total	
	CP	No CP	CP	CP	No CP	CP
PVL-I	2	6	9	7	6	18
c-PVL-II	2	4	–	–	4	2
c-PVL-III	7	1	–	–	1	7
PHVD following IVH grades II–III	–	12	–	2	12	2
Haemorrhagic parenchymal infarction	15	22[a]	1	–	22[a]	16
Middle cerebral artery	–	6[a]	1[b]	–	6[a]	1
Cerebellar haemorrhage	3[c]	–	–	–	–	3[c]
Hypoxic-ischaemic encephalopathy	3[c]	–	–	–	–	3[c]
Total	32	51	11	9	51	52

MRI, magnetic resonance imaging; CP, cerebral palsy; c-PVL, cystic periventricular leukomalacia; PHVD, post-haemorrhagic ventricular dilatation; IVH, intraventricular haemorrhage.
a Symmetrical posterior limb of the internal capsule in all but two infants.
b Missed term-equivalent age appointment.
c Died in the neonatal period, CP expected.

Fifty-one infants with neonatal MRI did not develop CP (Table I); 33 (65%) had neonatal MRI because of moderate-to-severe parenchymal lesions seen on cUS, and 18 because of PHVD following an IVH grade II or III (n = 12) or marked and/or non-homogeneous echogenicity in the white matter (n = 6). In only three of the 33 with parenchymal cysts, CP was expected on the basis of an asymmetry of the PLIC in two infants with HPI or the presence of extensive c-PVL in one. In two infants, the PLIC could not be assessed because the MRI was performed too early and not repeated at TEA. In the remaining infants, CP was not expected.

Eleven infants had MRI in infancy once they were diagnosed with CP. In these infants, CP had not been predicted by cUS: nine had had PVL-I, one a small HPI, and one a MCA infarction not recognised before discharge. The latter missed her TEA appointment and was later diagnosed once she presented with a USCP (Fig. 2).

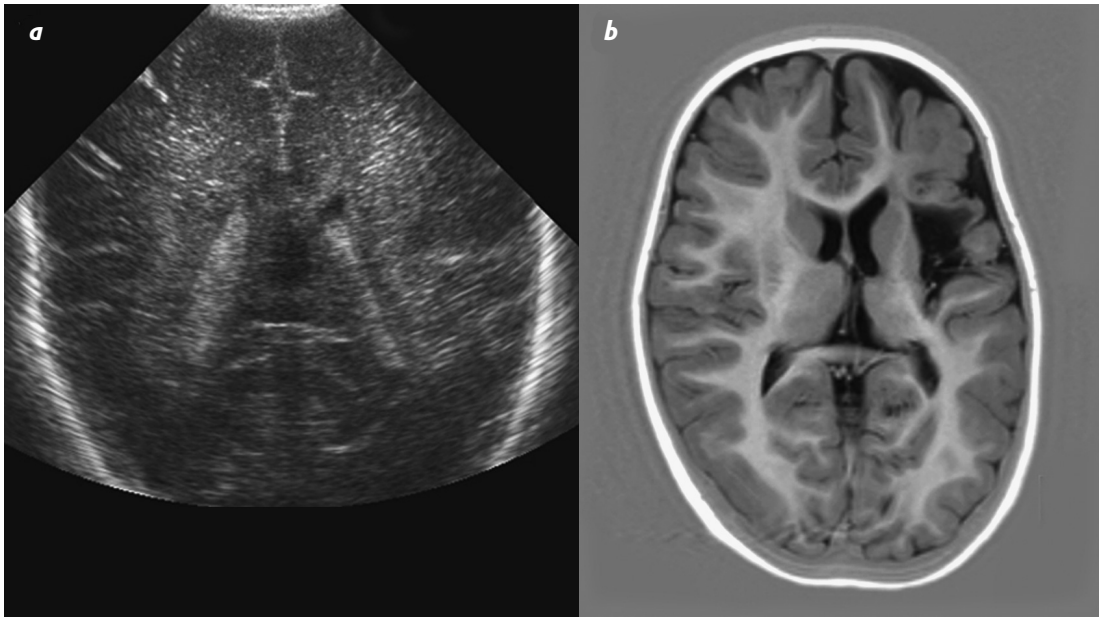

Fig. 2 GA 31 weeks, discharged on day 10.
cUS (***a***) before discharge and inversion recovery MRI (***b***) at 18 months corrected age.
The asymmetrical PVE was not recognised on cUS.
The MCA infarct is clearly seen on later MRI when the child presented with USCP.

When MRI was performed in these children in infancy/childhood, evidence of injury to the white matter was present in those with PVL-I and the child with the small HPI on cUS, and a cortical MCA infarct was seen in the other child. All had CP and were classified as GMFCS level I. A further nine infants, who had never had MRI, developed mild CP (GMFCS level I in all). Seven had had PVL-I on cUS and two grade II IVH.

The PPV for death or CP using combined sequential cUS showing c-PVL, HPI and MCA and subsequent TEA MRI with assessment of the PLIC was 0.96 (74/77), whereas the negative predictive value (NPV) was 0.69 (44/64) (Table II). The relatively low NPV resulted from 16 infants with PVL-I without a neonatal MRI, who subsequently developed mild BSCP. All were classified as level I on the GMFCS. Only 2/20 infants who developed CP in the absence of a neonatal MRI were classified as GMFCS level III.

Table II Predictive value of major cranial imaging abnormalities for cerebral palsy (CP) in preterm and term infants

Abnormal ultrasound and MRI	Preterm infant[a]	Term infant with HIE[b]	Term infant with stroke[c]
Sensitivity (%)	79	71	88
Specificity (%)	94	94	93
PPV (%)	96	88	78
NPV (%)	69	86	96

MRI, magnetic resonance imaging; HIE, hypoxic-ischaemic encephalopathy; PPV, positive predictive value; NPV, negative predictive value.
a Imaging data taken as predictive for abnormal outcome: severe parenchymal injury on cranial ultrasound (including infants who died); haemorrhagic parenchymal infarction and middle cerebral artery with an asymmetrical posterior limb of the internal capsule (PLIC); periventricular leukomalacia (PVL)-II and PVL-III with abnormal PLIC.
b 'White brain' abnormalities, basal ganglia and thalamus as a predictor of death or CP.
c Diffusion-weighted imaging abnormalities involving the cerebral peduncle.

2.3. Conclusions for the preterm infant

Sequential cUS until discharge followed by a repeat cUS at TEA should identify infants with c-PVL, HPI, and MCA who are most at risk for developing moderate-to-severe CP. Infants with PVL-I who subsequently develop mild BSCP (GMFCS level I) will not be reliably predicted by cUS, and it is still uncertain whether the outcome of these infants will be better predicted by TEA MRI. A combination of sequential cUS until discharge and cUS and MRI at TEA will improve predictive accuracy for motor outcome. Normal myelination of the PLIC, which should be seen on MRI by TEA, is highly predictive of normal gross motor outcome, and asymmetrical or bilaterally abnormal PLIC myelination is highly predictive of subsequent USCP and BSCP, respectively. In the majority of infants with either HPI or MCA, asymmetry of the PLIC will correctly predict USCP. In infants with extensive c-PVL, there is a bilateral lack or delay in myelination of the PLIC at TEA. Performing MRI at discharge (e.g. 35–38 weeks' PMA) is a problem, as this is too early to reliably assess PLIC myelination.

Infants with PVL-I are the most difficult group to evaluate; a minority (<10%) will develop mild CP (GMFCS level I with independent ambulation). Although these infants do not have a normal cUS, they are not reliably distinguished from others with PVL-I without subsequent motor problems. Not all infants with PVL-I will undergo a neonatal MRI and available data do not give evidence that MRI is more helpful than cUS. However, infants with non-homogeneous PVE are more likely to show changes in the white matter, and this could be a targeted group (Fig. 3). Since 2007, all infants with a GA <28 weeks in our NICU have had a routine MRI at TEA: so far, only two have developed mild CP following PVL-I, and one had symmetrical myelination of the PLIC despite extensive periventricular white matter lesions found on an early and TEA MRI. The number of such infants is still very small, and we do not have sufficient data to say how often mild BSCP occurs following PVL-I and whether this outcome will be more reliably predicted by TEA MRI than by cUS.

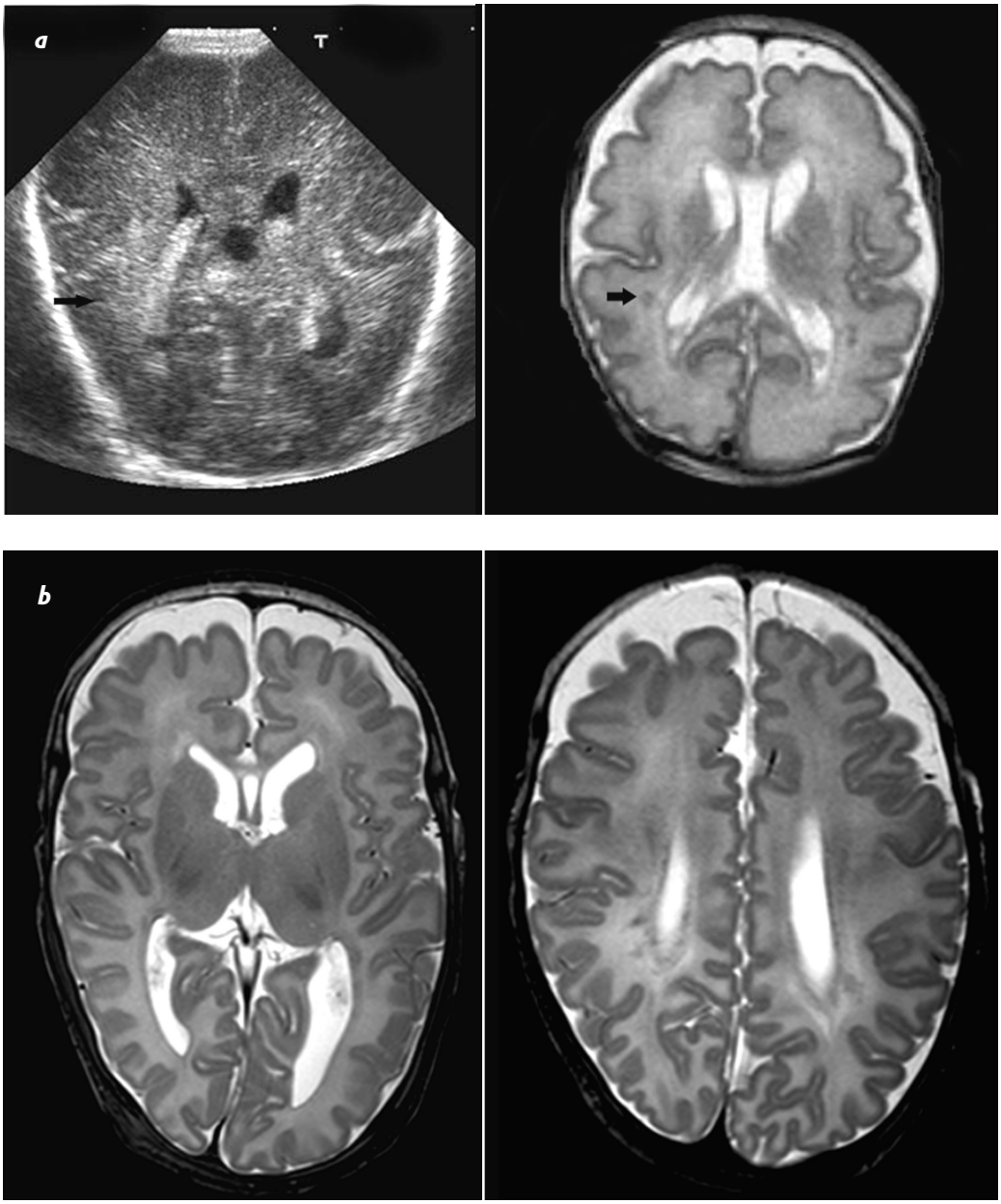

Fig. 3. (***a***) cUS and early MRI, T2 SE. The cUS shows patchy echogenicity (arrow). These areas are seen as low signal intensity on MRI (arrow). (***b***) TEA MRI, T2 SE sequence, showing mild VM, widening of the subarachnoid space, bilateral punctate white matter lesions, but normally appearing symmetrical low signal intensity of the PLIC. The child developed BSCP (GMFCS level I).

3. THE TERM INFANT

Newer techniques, such as evoked potentials, amplitude-integrated electroencephalography (aEEG), and neuroimaging have been used to predict outcome, in particular the development of CP, in term neonates with hypoxic-ischaemic encephalopathy (HIE). These techniques were used to assess the severity of the hypoxic-ischaemic insult, to evaluate the effects of neonatal intensive care, and to identify patients who might benefit from interventions such as physical therapy.[53,54]

Although electrophysiology has previously been shown to be useful, the predictive value is less clear in the era of therapeutic hypothermia.[55]

Imaging techniques were developed and used to detect cerebral injury, and may therefore be the most effective tools to predict CP in asphyxiated or encephalopathic term neonates.

Two main patterns of injury can be detected, which are comparable to patterns described previously in post-mortem studies and animal experiments.[56,57] Following acute, near-total asphyxia, injury to the basal ganglia and thalamus (BG/T) will appear 24–48 h later, and may become more obvious thereafter. In cases of chronic, subacute asphyxia, changes of the white matter can be seen.

3.1. Cranial ultrasonography

cUS has been used extensively to evaluate asphyxiated term neonates, sometimes combined with Doppler studies. cUS has a more limited role in the term neonate with HIE than in the preterm infant. However, increased echogenicity can be seen in the BG/T after a few days and when present is useful in the prediction of CP.[58] The predictive value of cUS for the development of CP has not been established in prospective studies (Table II). Ischaemic (focal) infarcts will become obvious with cUS a few days after the insult.[59] cUS has not been used in full-term neonates to predict USCP.

3.2. Magnetic resonance imaging

Using T1- and T2-weighted imaging, changes in the BG/T preceded the development of dyskinetic CP.[60–69] Changes in the myelination of the PLIC were noted to be a strong predictor of adverse motor outcome.[70] Unfortunately, these changes cannot be detected until the second half of the first week of life. Since the mid 1990s, diffusion-weighted MRI has been used.[64,71,72] Diffusion-weighted changes occur early after the hypoxic-ischaemic insult, and become more obvious during secondary energy failure.[73]

Perinatal arterial ischaemic stroke is another well-recognized cause of CP in term neonates. Prediction of USCP is facilitated by observing the presence of pre-Wallerian degeneration on diffusion-weighted MRI.[74–76]

A recent meta-analysis by Thayyil et al. showed that proton magnetic resonance spectroscopy (MRS) had the highest predictive value for neurodevelopmental outcome.[77] Since proton MRS is not available in all hospitals, the following section will focus on the more widely available MRI findings as predictors of CP.

3.2.1. Neuroimaging as a predictor of cerebral palsy in our own population

To study the predictive value of MRI during the first week of life, we analysed MRI data obtained from 2000 to 2008 in 167 term infants with HIE and in 37 term infants with neonatal stroke without asphyxia. MRI was performed as soon as was clinically feasible in cases with seizures of unknown etiology, and in neonates with evidence of asphyxia, preferably 72 h after the insult, but before the end of the first week.

MRI was based on pattern recognition. Injury to the BG/T, watershed predominant pattern of injury, and extensive injury ('white brain') was recorded, as described previously.[68] DWI and apparent diffusion coefficient (ADC) maps were used to identify areas of ischaemic lesions, which improved the detection of abnormalities using early MRI (Fig. 4).

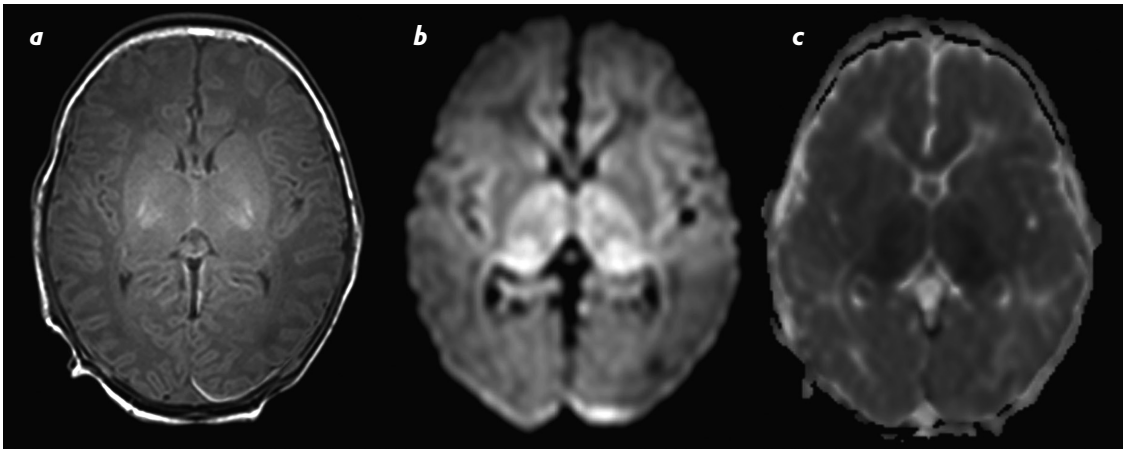

Fig. 4 MRI on the third day of life in a full-term neonate with severe, acute perinatal asphyxia. T1 weighted image (***a***) shows subtle changes to the thalami, whereas DWI (***b***) and ADC (***c***) show extensive changes in thalami, and less severe decrease in ADC values of basal ganglia and subcortical white matter. Also note a small subdural haemorrhage, best seen on the T1 weighted image. Care was withdrawn.

3.2.1.1. Imaging in hypoxic-ischaemic encephalopathy

Of the 167 neonates with HIE who underwent MRI, 36 died (21.6%). Severe abnormalities were demonstrated in all of them. Eleven had a 'white brain' pattern of injury, and 16 had a BG/T predominant pattern of injury. Watershed lesions were less common, and when present were extensive and often associated with milder lesions in the BG/T.

Twenty-three neonates (17.6% of the 131 survivors) developed CP including one girl who also developed symptomatic hypoglycemia, but no abnormalities on MRI performed within 24 h of birth. The MRI performed at 2 years of age showed abnormalities of the periventricular white matter. Interestingly, the neonatal proton MRS of this infant showed a high lactate peak in the BG/T and periventricular white matter. In more than half of the other neonates with CP, abnormalities were noted in the BG/T. Thus, in 95.6% (22 of 23) of the infants with HIE who developed CP, abnormalities could be demonstrated on early MRI (Table III).

In the 108 neonates who did not develop CP, the main MRI abnormalities were watershed lesions or PWML.[78] Six of these neonates (5.6%) had small, localized areas of abnormal signal intensity in the BG/T.

Table III Magnetic resonance imaging (MRI) and outcome following hypoxic-ischaemic encephalopathy

MRI	No cerebral palsy	Cerebral palsy	Died
Normal	50	1	–
Watershed lesions	42	6	9
Basal ganglia/thalamus	6	15	16
White brain	–	–	11
Other	10	1	–
Total	108	23	36

The PPV of MRI with BG/T lesions or the 'white brain' pattern of injury for death or CP was 0.88 (42 of 48), whereas the NPV was 0.86 (102 of 119) (Table II).

Although the majority did not develop CP, 16/108 (14.8%) had abnormalities seen during follow-up visits, consisting of epilepsy (3), learning disabilities (5), visual impairment (1) and behavioral difficulties (7).

3.2.1.2. Imaging in neonatal stroke

Of the 37 patients with neonatal stroke, one patient with bilateral posterior cerebral artery infarcts died from intractable seizures following severe hypoglycemia. Seven of the 36 survivors (19.4%) developed USCP. In all of them, pre-Wallerian degeneration was demonstrated. In all but two of the 29 patients who did not develop USCP, the internal capsule and peduncles were not affected. In these two infants, the DWI changes in the peduncles were small and at 2 years of age one child did develop a hand preference (Table IV).

3.2.1.3. Can neonatal imaging predict abnormal motor development in the term neonate with cerebral hypoxia-ischaemia?

Our findings demonstrate that abnormalities of the BG/T in term neonates with severe HIE have a high predictive value for subsequent CP as reported by others.[60–68,70] Abnormalities in the PLIC on MRI were previously regarded as an important predictive marker.[70] Since the use of DWI and ADC, hypoxic-ischaemic brain lesions are visible

Table IV Magnetic resonance imaging (MRI) and outcome following stroke

MRI	No cerebral palsy	Cerebral palsy	Died
Middle cerebral artery	14	7	–
Posterior cerebral artery	10	–	–
Watershed lesions	5	–	1
Total	29	7	1

much earlier, i.e. even from the first day of life onwards, compared with T1- or T2-weighted images, which tend to become positive by the end of the first week.[73,79,80] In our institute, DWI has been used routinely since the mid 1990s. DWI abnormalities in the BG/T may evolve and progress to more extensive abnormalities during and after the first week of life.[66] During the second week of life, DWI abnormalities become less obvious from pseudo-normalization, whereas abnormalities seen on conventional T1- and T2-weighted images become more obvious.[64,79,80] Timing of imaging should therefore be taken into account when MRI is interpreted.

Use of therapeutic hypothermia has an effect on previously recognized predictive tools, such as clinical examination or aEEG.[55] In our study, 15 of the neonates underwent hypothermia. However, MRI remained predictive of outcome, as has been described recently in a randomized controlled trial of hypothermia.[81]

Studies in CP cohorts have shown adverse perinatal events in most of the children who developed dyskinetic CP.[82]

In our cohort, watershed lesions were followed by CP in the minority of cases. Only severe white matter lesions resulted in CP.

In neonates with stroke of the middle cerebral artery, pre-Wallerian degeneration predicted the development of USCP, as shown previously.[74–76]

Another MR technique with excellent predictive properties is proton magnetic resonance spectroscopy (MRS). In particular, abnormal metabolism of the BG/T is followed by an adverse neuromotor developmental outcome.[77,83] This technique is, however, unavailable in many centres. We speculate that prediction of CP can be improved further when MRI and proton MRS are combined.

In conclusion, MRI, including DWI, during the first week of life is a valuable tool to predict the development of CP in term neonates with HIE or stroke. Lesions of the basal ganglia or thalamus, the presence of the 'white brain' or pre-Wallerian degeneration all reliably predict CP.
The myth that CP cannot be predicted by brain imaging in neonates is therefore not true for those with non-ambulatory CP, or preterm and full-term infants with USCP, but does hold true for the preterm infant who develops ambulant CP (GMFCS level I) following non-cystic c-PVL.

Practice points

- Non-ambulatory CP can be predicted in most newborn infants using a combination of sequential cUS and TEA MRI.
- Myelination of the PLIC is useful in prediction of CP. In the preterm infant this can first be reliably assessed at TEA.
- DWI is of additional value in assessment of the term infant with HIE and stroke, predicting bilateral and unilateral CP, respectively.

Research directions

- Better methods are needed to assess the severity of PVL-I on cUS and PWML on MRI.
- Quantitative MRI techniques will be required to better predict cognitive outcome.
- Development of MRS as a predictive tool.

Acknowledgements

The authors would like to thank Frances Cowan for her helpful comments when reading the manuscript and the enthusiasm and patience of magnetic resonance technicians.

REFERENCES

1 Hamilton BE, Miniño AM, Martin JA, et al. Annual summary of vital statistics. Pediatrics 2007;119:345–60.

2 Hintz SR, Kendrick DE, Wilson-Costello DE, et al, for the NICHD Neonatal Research Network. Early-childhood neurodevelopmental outcomes are not improving for infants born at <25 weeks' gestational age. Pediatrics 2011;127:62–70.

3 Vohr BR, Wright LL, Dusick AM, et al. Center differences and outcomes of extremely low birth weight infants. Pediatrics 2004;113:781–9.

4 Wilson-Costello D, Friedman H, Minich N, et al. Improved neurodevelopmental outcomes for extremely low birth weight infants in 2000-2002. Pediatrics 2007;119:37–45.

5 van Haastert IC, Groenendaal F, Uiterwaal CSPM, et al. Decreasing incidence and severity of cerebral palsy in prematurely born children. J Pediatr, 2011 Feb 24 [Epub ahead of print].

6 Hack M, Wilson-Costello D. Trends in the rates of cerebral palsy associated with neonatal intensive care of preterm children. Clin Obstet Gynecol 2008;51:763–74.

7 O'Shea TM, Klinepeter KL, Dillard RG. Prenatal events and the risk of cerebral palsy in very low birth weight infants. Am J Epidemiol 1998;147:362–9.

8 Wheater M, Rennie MA. Perinatal infection is an important risk factor for cerebral palsy in very low birthweight infants. Dev Med Child Neurol 2000;42:364–7.

9 Ment LR, Hirtz D, Hüppi PS. Imaging biomarkers of outcome in the developing preterm brain. Lancet Neurol 2009;8:1042–55.

10 Koldewijn K, van Wassenaer A, Wolf MJ, et al. A neurobehavioral intervention and assessment program in very low birth weight infants: outcome at 24 months. J Pediatr 2010;156:359–65.

11 Spittle AJ, Anderson PJ, Lee KJ, et al. Preventive care at home for very preterm infants improves infant and caregiver outcomes at 2 years. Pediatrics 2010;126:e171–8.

12 Neubauer AP, Voss W, Wachtendorf M, Jungmann T. Erythropoietin improves neurodevelopmental outcome of extremely preterm infants. Ann Neurol 2010;67:657–66.

13 Pape KE, Blackwell RJ, Cusick G, et al. Ultrasound detection of brain damage in preterm infants. Lancet 1979;16(8129):1261–4.

14 Correa F, Enríquez G, Rosselló J, et al. A. Posterior fontanelle sonography: an acoustic window into the neonatal brain. Am J Neuroradiol 2004;25:1274–82.

15 Miall LS, Cornette LG, Tanner SF, Arthur RJ, Levene MI. Posterior fossa abnormalities seen on magnetic resonance brain imaging in a cohort of newborn infants. J Perinatol 2003;23:396–403.

16 Limperopoulos C, Benson CB, Bassan H, et al. Cerebellar hemorrhage in the preterm infant: ultrasonographic findings and risk factors. Pediatrics 2005;116:717–24.

17 Steggerda SJ, Leijser LM, Wiggers-de Bruïne FT, van der Grond J, Walther FJ, van Wezel-Meijler G. Cerebellar injury in preterm infants: incidence and findings on US and MR images. Radiology 2009;252:190–9.

18 Pierrat V, Duquennoy C, van Haastert IC, Ernst M, Guilley N, de Vries LS. Ultrasound diagnosis and neurodevelopmental outcome of localised and extensive cystic periventricular leucomalacia. Arch Dis Child Fetal Neonatal Ed 2001;84:F151–6.

19 de Vries LS, van Haastert IL, Rademaker KJ, Koopman C, Groenendaal F. Ultrasound abnormalities preceding

cerebral palsy in high-risk preterm infants. J Pediatr 2004;144:815–20.
20 Ment LR, Bada HS, Barnes P, et al. Practice parameter: neuroimaging of the neonate: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2002;58:1726–38.
21 Shah DK, Doyle LW, Anderson PJ, et al. Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term. J Pediatr 2008;153:170–5.
22 Verboon-Maciolek MA, Groenendaal F, Cowan F, et al. White matter damage in neonatal enterovirus meningoencephalitis. Neurology 2006;66:1267–9.
23 Verboon-Maciolek MA, Groenendaal F, Hahn CD, et al. Human parechovirus causes encephalitis with white matter injury in neonates. Ann Neurol 2008;64:266–73.
24 Hintz SR, Slovis T, Bulas D, et al, NICHD Neonatal Research Network. Interobserver reliability and accuracy of cranial ultrasound scanning interpretation in premature infants. J Pediatr 2007;150:592–6.
25 Harris DL, Bloomfield FH, Teele RL, Harding JE, Australian and New Zealand Neonatal Network. Variable interpretation of ultrasonograms may contribute to variation in the reported incidence of white matter damage between newborn intensive care units in New Zealand. Arch Dis Child Fetal Neonatal Ed 2006;91:F11–6.
26 Stewart AL, Thorburn RJ, Hope PL, Goldsmith M, Lipscomb AP, Reynolds EO. Ultrasound appearance of the brain in very preterm infants and neurodevelopmental outcome at 18 months of age. Arch Dis Child 1983;58:598–604.
27 Vollmer B, Roth S, Baudin J, Stewart AL, Neville BG, Wyatt JS. Predictors of long-term outcome in very preterm infants: gestational age versus neonatal cranial ultrasound. Pediatrics 2003;112:1108–14.
28 Ancel PY, Livinec F, Larroque B, et al, EPIPAGE Study Group. Cerebral palsy among very preterm children in relation to gestational age and neonatal ultrasound abnormalities: the EPIPAGE cohort study. Pediatrics 2006;117:828–35.
29 Kuban K, Sanocka U, Leviton A, et al. White matter disorders of prematurity: association with intraventricular hemorrhage and ventriculomegaly. The Developmental Epidemiology Network. J Pediatr 1999;134:539–46.
30 Sherlock RL, Anderson PJ, Doyle LW, Victorian Infant Collaborative Study Group. Neurodevelopmental sequelae of intraventricular haemorrhage at 8 years of age in a regional cohort of ELBW/very preterm infants. Early Hum Dev 2005;81:909–16.
31 de Vries LS, Roelants-van Rijn AM, Rademaker KJ, Van Haastert IC, Beek FJ, Groenendaal F. Unilateral parenchymal haemorrhagic infarction in the preterm infant. Eur J Paediatr Neurol 2001;5:139–49.
32 Rademaker KJ, Groenendaal F, Jansen GH, Eken P, de Vries LS. Unilateral haemorrhagic parenchymal lesions in the preterm infant: shape, site and prognosis. Acta Paediatr 1994;83:602–8.
33 Bassan H, Limperopoulos C, Visconti K, et al. Neurodevelopmental outcome in survivors of periventricular hemorrhagic infarction. Pediatrics 2007;120:785–92.
34 Roze E, Kerstjens JM, Maathuis CG, ter Horst HJ, Bos AF. Risk factors for adverse outcome in preterm infants with

periventricular hemorrhagic infarction. Pediatrics 2008;122:e46–52.
35 McCarthy LK, Donoghue V, Murphy JFA. Ultrasound detectable cerebellar haemorrhage in preterm infants. Arch Dis Child Fetal Neon Ed; 2011 Jan 19 [Epub ahead of print].
36 Muller H, Beedgen B, Schenk JP, Troger J, Linderkamp O. Intracerebellar hemorrhage in premature infants: sonographic detection and outcome. J Perinat Med 2007;35:67–70.
37 Tam EWY, Rosenbluth G, Rogers EE, et al. Cerebellar hemorrhage on magnetic resonance imaging in preterm newborns associated with abnormal neurologic outcome. J Pediatr 2011;158:245–50 [Epub 2010 Sep 15].
38 Limperopoulos C, Bassan H, Gauvreau K, et al. Does cerebellar injury in premature infants contribute to the high prevalence of long-term cognitive, learning, and behavioral disability in survivors? Pediatrics 2007;120:584–93.
39 van Haastert IC, de Vries LS, Eijsermans MJ, Jongmans MJ, Helders PJ, Gorter JW. Gross motor functional abilities in preterm-born children with cerebral palsy due to periventricular leukomalacia. Dev Med Child Neurol 2008;50:684–9.
40 Resch B, Jammernegg A, Perl E, Riccabona M, Maurer U, Muller WD. Correlation of grading and duration of periventricular echodensities with neurodevelopmental outcome in preterm infants. Pediatr Radiol 2006;36:810–5.
41 Pisani F, Leali L, Moretti S, Turco E, Volante E, Bevilacqua G. Transient periventricular echodensities in preterms and neurodevelopmental outcome. J Child Neurol 2006;21:230–5.
42 Ramenghi LA, Fumagalli M, Righini A, et al. Magnetic resonance imaging assessment of brain maturation in preterm neonates with punctate white matter lesions. Neuroradiology 2007;49:161–7.
43 Miller SP, Ferriero DM, Leonard C, et al. Early brain injury in premature newborns detected with magnetic resonance imaging is associated with adverse early neurodevelopmental outcome. J Pediatr 2005;147:609–16.
44 Bassi L, Chew A, Merchant N, Ball G, et al. Diffusion tensor imaging in preterm infants with punctate white matter lesions. Pediatr Res 2011;69:561–6.
45 Miller SP, Mayer EE, Clyman RI, Glidden DV, Hamrick SE, Barkovich AJ. Prolonged indomethacin exposure is associated with decreased white matter injury detected with magnetic resonance imaging in premature newborns at 24 to 28 weeks' gestation at birth. Pediatrics 2006;117:1626–31.
46 Dyet LE, Kennea N, Counsell SJ, et al. Natural history of brain lesions in extremely preterm infants studied with serial magnetic resonance imaging from birth and neurodevelopmental assessment. Pediatrics 2006;118:536–48.
47 Mirmiran M, Barnes PD, Keller K, et al. Neonatal brain magnetic resonance imaging before discharge is better than serial cranial ultrasound in predicting cerebral palsy in very low birth weight preterm infants. Pediatrics 2004;114:992–8.
48 Woodward LJ, Anderson PJ, Austin NC, et al. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. N Engl J Med 2006;355:685–94.
49 Srinivasan L, Dutta R, Counsell SJ, et al. Quantification of deep gray matter in preterm infants at term-equivalent age using manual volumetry of 3-tesla magnetic resonance images. Pediatrics 2007;119:759–65.

50 Fukuda S, Yokoi K, Suzuki S, Goto H. Serial ultrasonographic observation of bilateral thalami in low birth weight infants with periventricular leukomalacia. Brain Dev 2011;33:394–9.

51 Rosenbaum PL, Palisano RJ, Bartlett DJ, Galuppi BE, Russell DJ. Development of the gross motor function classification system for cerebral palsy. Dev Med Child Neurol 2008;50:249–53.

52 de Vries LS, Groenendaal F, Eken P, Rademaker KJ, Meiners LC. Asymmetrical myelination of the posterior limb of the internal capsule: an early predictor of hemiplegia. Neuropediatrics 1999;30:314–9.

53 Eken P, de Vries LS, van der Graaf Y, Meiners LC, van Nieuwenhuizen O. Haemorrhagic-ischaemic lesions of the neonatal brain: correlation between cerebral visual impairment, neurodevelopmental outcome and MRI in infancy. Dev Med Child Neurol 1995;37:41–55.

54 Groenendaal F, de Vries LS. Selection of babies for intervention after birth asphyxia. Semin Neonatol 2000;5:17–32.

55 Thoresen M, Hellstrom-Westas L, Liu X, de Vries LS. Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. Pediatrics 2010;126:e131–9.

56 Myers RE. Fetal asphyxia due to umbilical cord compression. Metabolic and brain pathologic consequences. Biol Neonate 1975;26:21–43.

57 Volpe JJ. Neurology of the newborn. 5 ed. Philadelphia: WB Saunders; 2008.

58 Daneman A, Epelman M, Blaser S, Jarrin JR. Imaging of the brain in full-term neonates: does sonography still play a role? Pediatr Radiol 2006;36:636–46.

59 Cowan F, Mercuri E, Groenendaal F, et al. Does cranial ultrasound imaging identify arterial cerebral infarction in term neonates? Arch Dis Child Fetal Neonatal Ed 2005;90:F252–6.

60 Rutherford MA, Pennock JM, Murdoch-Eaton DM, Cowan FM, Dubowitz LM. Athetoid cerebral palsy with cysts in the putamen after hypoxic-ischaemic encephalopathy. Arch Dis Child 1992;67(7, Special No.):846–50.

61 Rutherford M, Pennock J, Schwieso J, Cowan F, Dubowitz L. Hypoxic-ischaemic encephalopathy: early and late magnetic resonance imaging findings in relation to outcome. Arch Dis Child Fetal Neonatal Ed 1996;75:F145–51.

62 Krägeloh-Mann I, Helber A, Mader I, et al. Bilateral lesions of thalamus and basal ganglia: origin and outcome. Dev Med Child Neurol 2002;44:477–84.

63 Cowan F, Rutherford M, Groenendaal F, et al. Origin and timing of brain lesions in term infants with neonatal encephalopathy. Lancet 2003;361:736–42.

64 Rutherford M, Counsell S, Allsop J, et al. Diffusion-weighted magnetic resonance imaging in term perinatal brain injury: a comparison with site of lesion and time from birth. Pediatrics 2004;114:1004–14.

65 Boichot C, Walker PM, Durand C, et al. Term neonate prognoses after perinatal asphyxia: contributions of MR imaging, MR spectroscopy, relaxation times, and apparent diffusion coefficients. Radiology 2006;239:839–48.

66 Barkovich AJ, Miller SP, Bartha A, et al. MR imaging, MR spectroscopy, and diffusion tensor imaging of sequential studies in neonates with encephalopathy. Am J Neuroradiol 2006;27:533–47.

67 Rutherford M, Srinivasan L, Dyet L, et al. Magnetic resonance imaging in perinatal brain injury: clinical presentation, lesions and outcome. Pediatr Radiol 2006;36:582–92.

68 de Vries LS, Groenendaal F. Patterns of neonatal hypoxic-ischaemic brain injury. Neuroradiology 2010;52:555–66.
69 Martinez-Biarge M, Diez-Sebastian J, Rutherford MA, Cowan FM. Outcomes after central grey matter injury in term perinatal hypoxic-ischaemic encephalopathy. Early Hum Dev 2010;86:675–82.
70 Rutherford MA, Pennock JM, Counsell SJ, et al. Abnormal magnetic resonance signal in the internal capsule predicts poor neurodevelopmental outcome in infants with hypoxic-ischemic encephalopathy. Pediatrics 1998;102(2 Pt 1):323–8.
71 Hunt RW, Neil JJ, Coleman LT, Kean MJ, Inder TE. Apparent diffusion coefficient in the posterior limb of the internal capsule predicts outcome after perinatal asphyxia. Pediatrics 2004;114:999-1003.
72 Liauw L, van Wezel-Meijler G, Veen S, van Buchem MA, van der Grond J. Do apparent diffusion coefficient measurements predict outcome in children with neonatal hypoxic-ischemic encephalopathy? Am J Neuroradiol 2009;30:264–70.
73 L'Abee C, de Vries LS, van der Grond J, Groenendaal F. Early diffusion-weighted MRI and ^{1}H-magnetic resonance spectroscopy in asphyxiated fullterm neonates. Biol Neonate 2005;88:306–12.
74 de Vries LS, van der Grond J, van Haastert IC, Groenendaal F. Prediction of outcome in new-born infants with arterial ischaemic stroke using diffusion-weighted magnetic resonance imaging. Neuropediatrics 2005;36:12–20.
75 Kirton A, Shroff M, Visvanathan T, deVeber G. Quantified corticospinal tract diffusion restriction predicts neonatal stroke outcome. Stroke 2007;38:974–80.
76 Husson B, Hertz-Pannier L, Renaud C, et al. Motor outcomes after neonatal arterial ischemic stroke related to early MRI data in a prospective study. Pediatrics 2010;126:912–8.
77 Thayyil S, Chandrasekaran M, Taylor A, et al. Cerebral magnetic resonance biomarkers in neonatal encephalopathy: a meta-analysis. Pediatrics 2010;125:e382–95.
78 Li AM, Chau V, Poskitt KJ, et al. White matter injury in term newborns with neonatal encephalopathy. Pediatr Res 2009;65:85–9.
79 Wolf RL, Zimmerman RA, Clancy R, Haselgrove JH. Quantitative apparent diffusion coefficient measurements in term neonates for early detection of hypoxic-ischemic brain injury: initial experience. Radiology 2001;218:825–33.
80 Winter JD, Lee DS, Hung RM, et al. Apparent diffusion coefficient pseudo-normalization time in neonatal hypoxic-ischemic encephalopathy. Pediatr Neurol 2007;37:255–62.
81 Rutherford M, Ramenghi LA, Edwards AD, et al. Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic-ischaemic encephalopathy: a nested substudy of a randomised controlled trial. Lancet Neurol 2010;9:39–45.
82 Himmelmann K, Hagberg G, Wiklund LM, Eek MN, Uvebrant P. Dyskinetic cerebral palsy: a population-based study of children born between 1991 and 1998. Dev Med Child Neurol 2007;49:246–51.
83 Groenendaal F, Veenhoven RH, van der Grond J, Jansen GH, Witkamp TD, de Vries LS. Cerebral lactate and N-acetyl-aspartate/choline ratios in asphyxiated full-term neonates demonstrated in vivo using proton magnetic resonance spectroscopy. Pediatr Res 1994;35:148–51.

Specific neuromotor developmental pathways

Part 3

Chapter 5

GROSS MOTOR FUNCTIONAL ABILITIES IN PRETERM-BORN CHILDREN WITH CEREBRAL PALSY DUE TO PERIVENTRICULAR LEUKOMALACIA

Ingrid C. van Haastert
Linda S. de Vries
Maria J.C. Eijsermans
Marian J. Jongmans
Paul J.M. Helders
Jan Willem Gorter

Dev Med Child Neurol. 2008 Sep; 50(9): 684-9.

ABSTRACT

To describe the impact of periventricular leukomalacia (PVL) on gross motor function, data on 59 children (37 males, 22 females) with a gestational age (GA) of 34 weeks or less with cerebral palsy (CP) due to PVL grade I (*n*=20), II (*n*=13), III (*n*=25), and IV (*n*=1) were studied; (mean GA 29wk 4d [SD 4wk 6d]; mean birthweight 1318g [SD 342]).

Two independent raters used the Gross Motor Function Classification System (GMFCS) at four time points: T1, mean corrected age (CA) 9 months 15 days (SD 2mo 6d); T2, mean CA 16 months (SD 1mo 27d); T3, mean CA 24 months 27 days (SD 2mo 3d); and T4, median age 7 years 6 months (range 2y 2mo–16y 8mo). Interrater reliability and stability across time with respect to the total cohort were κ ≥0.86 and ρ ≥0.74 respectively.

The association between PVL and gross motor outcome at T4 was strong (positive and negative predictive values 0.92 and 0.85 respectively). The proportion of children who remained in the same GMFCS level increased from 27% (T1–T4) to 53% (T2–T4) and 72% (T3–T4). PVL grade I to II, as diagnosed in the neonatal period, has a better functional mobility prognosis than PVL grade III–IV. These findings have implications for habilitation counselling and intervention strategies.

INTRODUCTION

The main determinant for cerebral palsy (CP) in children born preterm is periventricular leukomalacia (PVL).[1–6] PVL mainly occurs in infants born preterm with a birthweight of less than 1500g and between 24 and 34 weeks gestational age (GA).[3,7,8] The pathogenesis of PVL is multifactorial.[3,9]

The prognosis of neuromotor development in children with PVL depends on the extent and localization of the white matter damage.[2,4,8] PVL has a predilection for the transition of the corona radiata to the internal capsule where the corticospinal tracts are localized. Damage in this area may result in a typical clinical picture, often recognized and classified as 'spastic diplegia'.[2,4,9] As soon as the lesions extend laterally, quadriplegia may occur.[2,8] Extensive lesions affecting the basal ganglia and/or the occipital area may also lead to cortical visual impairment [2,5,8,10,11] and/or epilepsy.[11]

Several studies have shown a relationship between PVL in general and subsequent development of CP.[1–9,11] However, different PVL grades can result in different CP subtypes and outcomes. This phenomenon was reported earlier by our group[1] and by Serdaroglu et al.[11] Previous studies have reported other outcome classification systems at an early age,[5,12] or have not focused exclusively on infants born preterm.[11]

To the best of our knowledge, there has not been a longitudinal study describing the relationship between the different PVL grades in infants born preterm and subsequent gross motor functional abilities classified with the Gross Motor Function Classification System (GMFCS). We, therefore, performed a cohort study of children born preterm with CP, to determine the association between the severity of PVL and the course and stability of gross motor abilities measured with the GMFCS at four time points between early infancy and childhood/adolescence.

METHOD

Patients

The children who were eligible for this hospital-based follow-up study were born between 1990 and 2004 and discharged from a level three

neonatal intensive care unit in the Wilhelmina Children's Hospital, University Medical Center Utrecht (UMCU), the Netherlands, which serves a population of approximately 2 million inhabitants. Children were included who met the following criteria: a GA of 34 weeks or less, PVL identified by sequential neonatal cranial ultrasound, and a definite CP syndrome defined at 2 years of age.[13] Children with the following conditions were excluded: a diagnosed genetic syndrome, a neuromuscular disorder, congenital anomalies, and less than 2 years of age at the time of the study. The parents were offered the opportunity to let their infants participate in a standardized follow-up programme from term age onwards until a rehabilitation programme was established. All parents were informed about data collection and consented to the study and ethical permission was obtained by the UMCU. Data were collected from January 1991 to May 2007.

Neuroimaging

Cranial ultrasound was performed soon after admission to the neonatal intensive care unit and thereafter at least once a week until discharge, and again during the first visit to the neonatal follow-up clinic around term age. Infants were scanned with an ATL UM-4 mechanical sector scanner with a multifrequency transducer (5, 7.5, and 10MHz crystals). For preference the 7.5MHz transducer was used for the best possible resolution. Cranial ultrasound abnormality was classified after its full evolution, which was either at discharge or at term age.[1] Because there is no generally accepted classification system for PVL, we used the classification described by de Vries et al.[8]: PVL grade I, periventricular areas of increased echogenicity present for 7 days or more; grade II, periventricular areas of increased echogenicity evolving into small localized fronto-parietal cysts; grade III, periventricular areas of increased echogenicity evolving into extensive periventricular cystic lesions involving the occipital and fronto-parietal white matter; and grade IV, areas of increased echogenicity in the deep white matter evolving into extensive subcortical cysts. PVL grade IV is usually seen in more mature infants born preterm and in term infants after perinatal asphyxia.[8]

All scans were interpreted by a neonatal neurologist (LSdeV).

The diagnosis of PVL was confirmed by magnetic resonance imaging (MRI): 52 / 59 (88.1%) children had at least one MRI, whereas 7 / 59 (11.9%) children had no MRI. Of the 36 children who had only one MRI, 10 / 59 children (16.9%) had the scan in the neonatal period and 26 / 59 (44.1%) in childhood. In 16 / 59 (27.1%) children MRI was performed in the neonatal period as well as in childhood.

Gross motor function

To classify the gross motor function according to the descriptions of the GMFCS,[3,14–22] clinical notes in medical records were used with respect to the gross motor abilities of the children. The GMFCS describes the major functional characteristics of children with CP. It is a five-level pattern-recognition system. Children that are classified in GMFCS Levels I and II have the potential to walk independently both indoors and outdoors, and in the community as well. In contrast, children classified in GMFCS Levels III to V are limited in their self mobility. They walk with a mobility device and are potential wheelchair users.

Use of the GMFCS requires no formal training.[20] There are four age bands: before the second birthday, and at 2 to 4, 4 to 6, and 6 to 12 years of age. The GMFCS discriminates between children with CP syndromes according to their age-specific gross motor activity and is based on self-initiated movements.[23] The GMFCS for children >2 years of age is reliable. The predictive value between the ages of 2 and 12 years is relatively stable over time (r=0.79).[14,23] However, the reported interrater reliability for infants with CP who are less than 2 years old is moderate (κ=0.55).[20] All children in the present study were, therefore, classified independently by two experienced paediatric physical therapists (ICvH and MJCE) at four age ranges, of which two were under the age of 2 years. In the event of discrepancies, consensus was reached by consulting a third person (JWG, a physician in paediatric rehabilitation medicine).

Data analysis

Data were analyzed with SPSS software (version 13.0). Because there was only one participant with PVL grade IV, we had to exclude this case from data analysis with regard to GA, birthweight, stability, proportion, and

distribution of GMFCS levels across time. To determine whether the mean GA and the mean birthweight of the PVL grade I to III subgroups were comparable, one-way analysis of variance between groups was performed. Interrater reliability with respect to GMFCS levels was calculated as κ and its 95% confidence intervals (CI) with quadratic weighting for each period before correlations were calculated. Kappa statistics were categorized as poor agreement when lower than 0.20, as fair between 0.21 and 0.40, as moderate agreement between 0.41 and 0.60, as good agreement between 0.61 and 0.80, and as very good agreement above 0.80.[24] The stability of GMFCS levels across time of the total cohort and of the PVL subgroups was determined by Spearman's rank-order correlations and was expressed as both numbers and percentages. For clinical purposes we examined the prognostic value of PVL for gross motor outcome in childhood/adolescence by calculating the sensitivity, specificity, positive and negative predictive values, and odds ratio with 95% CI. Data for children with PVL were, therefore, dichotomized into grades I and II (mild) and III and IV (severe) and GMFCS Levels I and II and Levels III to V. A p value of less than 0.05 was considered to be statistically significant.

RESULTS

Participant characteristics

In all, 59 children born preterm (37 males, 22 females) met the inclusion criteria; complete GMFCS data were available for 57 children. Twenty children were diagnosed with PVL grade I, 13 with PVL grade II, 25 with PVL grade III, and one child with PVL grade IV. Their GA ranged from 26 weeks to 33 weeks 3 days (mean 29wk 4d [SD 4wk 6d]) and birthweight from 730 to 2140g (mean 1318g [SD 342]). There was no statistically significant difference between the PVL grade I to III subgroups with respect to GA and birthweight (p=0.70 and p=0.91 respectively). All children of our study cohort received paediatric physical therapy at some point in their life, and 49/59 (83%) of them were subsequently treated at a rehabilitation centre.

Gross motor function classification

The four periods were as follows: T1, mean corrected age (CA) 9 months 15 days (SD 2mo 6d), range 5 months 8 days to 12 months 23 days; T2, mean CA 16 months (SD 1mo 27d), range 12 months 23 days to 19 months 27 days; T3, mean CA 24 months 27 days (SD 2mo 3d), range 20 to 31 months; and T4, median age 7 years 6 months, range 2 years 2 months to 16 years 8 months. (The wide age range at T4 was due to the fact that the study period was up to May 2007; for some children we had a long follow-up period and for others the follow-up period was shorter).

Interrater agreement, correlation of GMFCS levels across time, and stability

For 3/236 (1.3%) possible classifications we had missing data at T2 for one male with PVL grade I and at T2 and T3 for one male with PVL grade III.

Interrater reliability with respect to the GMFCS levels of the total cohort was very good: 0.86 (95% CI 0.75–0.97) at T1, 0.89 at T2, 0.94 at T3 and 0.96 at T4. Because of a substantial proportion of zeros in the data entries, the 95% CI could not be calculated for T2 to T4. The two raters disagreed in 53/233 (23%) of all ratings: at T1 in 15/59 (25%) ratings, at T2 in 16/57 (28%), at T3 in 13/58 (22%), and at T4 in 9/59 (15%). The difference between the raters was one level in 52/53 disagreements and two levels in one case. Correlations ranged between ρ=0.74 and ρ=0.90 (p<0.001) from T1 onwards with respect to the total cohort (the only participant with PVL IV was excluded). Within the PVL subgroups, correlations ranged from ρ=0.17 (p=0.48) to 0.88 (p<0.001; Table I). Table I also presents the number and percentage of children who remained in the same GMFCS level (stability) between T1 and T4, between T2 and T4 and between T3 and T4. Proportions increased from T1 onwards, with respect to both the total cohort and the PVL subgroups. In this part of Table I, the male with PVL grade IV is included in the total cohort (n=59).

Table I Correlations of Gross Motor Function Classification System (GMFCS) levels in children born preterm with cerebral palsy due to periventricular leukomalacia (PVL), from T1 to T4, and stability

PVL grades	*Correlation (ρ) of GMFCS levels*			*Stability[a] relative to T4*	
	T2	*T3*	*T4*	*n*	*%*
I to III (*n=58*)					
T1 (9.5mo)	0.76 (*p*<0.001)	0.74 (*p*<0.001)	0.74 (*p*<0.001)	16/59[b]	27.1
T2 (16mo)		0.90 (*p*<0.001)	0.88 (*p*<0.001)	30/57[b]	52.6
T3 (24.9mo)			0.89 (*p*<0.001)	42/58[b]	72.4
I (*n=20*)					
T1 (9.5mo)	0.53 (*p*=0.019)	0.17 (*ns*)	0.32 (*ns*)	2/20	10
T2 (16mo)		0.64 (*p*=0.003)	0.64 (*p*=0.003)	10/19	52.6
T3 (24.9mo)			0.36 (*ns*)	14/20	70
II (*n=13*)					
T1 (9.5mo)	0.33 (*ns*)	0.42 (*ns*)	0.35 (*ns*)	2/13	15.4
T2 (16mo)		0.83 (*p*<0.001)	0.88 (*p*<0.001)	6/13	46.2
T3 (24.9mo)			0.84 (*p*<0.001)	9/13	69.2
III (*n=25*)					
T1 (9.5mo)	0.54 (*p*=0.006)	0.56 (*p*=0.004)	0.51 (*p*=0.009)	11/25	44
T2 (16mo)		0.87 (*p*<0.001)	0.81 (*p*<0.001)	13/24	54.2
T3 (24.9mo)			0.84 (*p*<0.001)	18/24	75

[a] Number and percentage of children who remained in the same GMFCS level from T1, T2, and T3 (mean corrected ages) versus T4 (median age 7y 6mo); [b] case with PVL grade IV included. *ns*, not significant.

GMFCS levels across time

For the total study group better gross motor function, as expressed by GMFCS levels, was observed in 42 / 59 (71.2%) children at T4, in comparison with T1: 6/7 (86%) children with an initial GMFCS Level II, 18/23 (78%) with Level III, 12/19 (63%) with Level IV, and 6/10 (60%) with Level V; 16/59 (27.1%) showed a stable level and one child (1.7%) had to be classified from Level I to Level II.

Figure 1 presents the changing panorama of the GMFCS levels (median and 5–95% range) of the three PVL subgroups (grades I–III) from early infancy (T1) through to childhood/adolescence (T4).

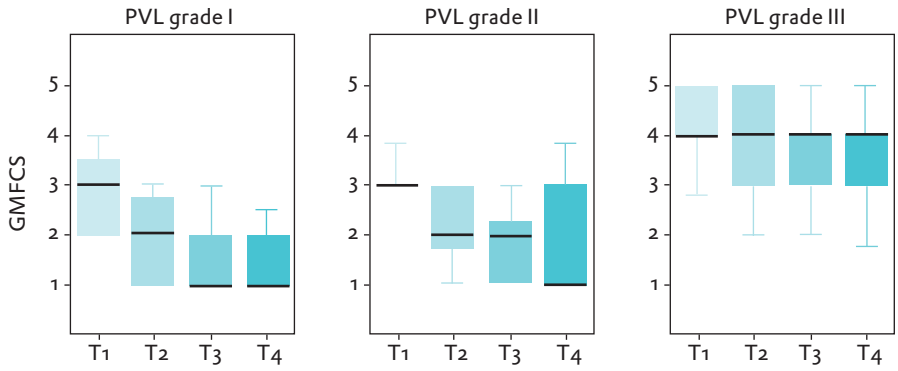

Figure 1 Gross Motor Function Classification System (GMFCS) levels from T1 to T4 in children born preterm with cerebral palsy due to periventricular leukomalacia (PVL). Box and whisker plots of the GMFCS levels according to PVL group (grade I, n=20; grade II, n=13; grade III, n=25) at T1, mean corrected age (CA) 9 months 15 days; at T2, mean CA 16months; at T3, mean CA 24 months 27 days; at T4, median 7 years 6 months. The solid box shows 25th to 75th centiles; whisker bars extend to lowest and highest observed levels within 5 to 95% range. The bold horizontal line shows the median.

Table II Association between periventricular leukomalacia (PVL) grade and gross motor function at T4 in children born preterm with cerebral palsy

PVL grades	*GMFCS levels*		*Total*
	III–V	*I–II*	
III and IV	24	2	26
I and II	5	28	33
Total	29	30	59

GMFCS, Gross Motor Function Classification System. T4, median age 7y 6mo. Sensitivity, 0.83; specificity, 0.93; negative predictive value, 0.85; positive predictive value, 0.92; odds ratio for PVL grades III and IV, 67.2 (95% confidence interval 11.9–378.3).

GMFCS levels in relation to severity of PVL

PVL grade I

All children with PVL grade I and CP (*n*=20) were classified in GMFCS Levels I and II at T4, with one exception who was classified in GMFCS Level III at T4. In more detail, the results show that 2/20 (10%) children remained within the same GMFCS level at all time points, whereas 18/20 (90%) children were classified in levels describing better gross motor abilities at T2 or T3 (Fig. 1).

PVL grade II

With regard to children with PVL grade II (*n*=13), none were classified in GMFCS Level V at T4: 9/13 (69.2%) were classified in GMFCS levels I and II, and 4/13 (30.8%) in Levels III and IV. In more detail, the results show that 1/13 (7.7%) children remained within the same GMFCS level at all time points, 10/13 (76.9%) children were classified in levels describing better gross motor abilities at T2 or T4. Two children (15.4%) were classified from Level II (T3) to Level III (T4) and from Level III (T3) to Level IV (T4) respectively.

The chance that a child with PVL grade I or II would subsequently be classified in GMFCS Levels III to V at T4 was 15% (negative predictive value 0.85; Table II).

PVL grade III

At T4, 2/25 (8%) children with PVL grade III were classified in GMFCS Levels I and II and 23/25 (92%) in GMFCS Levels III–V. In more detail, the results show that 8/25 (32%) children remained within the same level at all time points, whereas 3/25 (12%) were classified in GMFCS Level IV at all time points except one. A change to GMFCS levels describing better gross motor abilities was observed in 14/25 (56%) children: 11 children shifted one level from T1 to T4 and three children shifted two levels. One female was initially classified in GMFCS Level III but from T2 onwards in Level II, and one male, who had PVL more localized in the frontal area of the brain, shifted from GMFCS Level II at T1 and T2 to Level I from T3 onwards.

PVL grade IV

The male with PVL grade IV was classified in GMFCS Level V from the beginning and throughout the study period. The chance that a child with PVL grade III or IV was subsequently classified in GMFCS Levels III to V at T4 was 92% (positive predictive value 0.92), with an odds ratio of 67.2 (95% CI 11.9–378.3; Table II).

Distribution of PVL severity related to CP subtype

At 2 years of age, a minority of the study cohort was diagnosed with a spastic unilateral CP and the majority with a spastic bilateral CP with more involvement of the lower extremities than the upper extremities (Table III). It is noteworthy that, at T4, three children with a PVL grade I and one female with a PVL grade II no longer met the criteria of CP,[13,25] although they still showed other (motor) problems.

Table III Distribution of periventricular leukomalacia (PVL) severity related to cerebral palsy (CP) subtypes diagnosed at 2 years of age in children born preterm

PVL grades	*CP subtype*			*Total*
	SU	*SBD*	*SBQ*	
I and II	3	30	–	33
III and IV	–	12	14	26
Total (%)	3 (5.1)	42 (71.2)	14 (23.7)	59 (100)

SU, spastic unilateral; SBD, spastic bilateral diplegia; SBQ, spastic bilateral quadriplegia.

Ambulation

With regard to the total cohort, 35.6% of the children were able to walk independently, 40.7% could walk with an assistive device, and 23.7% could not walk at all and were wheelchair users at T4 (Table IV).

Table IV Periventricular leukomalacia (PVL) severity related to ambulation of children born preterm with cerebral palsy

PVL grades	*1–2y*	*2–4y*	*4–6y*	*Assisted*	*Not walking*	*Total*
I and II	11	8	–	13	1	33
III and IV	1	–	1	11	13	26
Total (%)	12 (20.3)	8 (13.6)	1 (1.7)	24 (40.7)	14 (23.7)	59 (100)

The children between the ages of 1 and 6 years walked totally independently. Assisted, walking with device; Not walking, totally dependent on wheelchair (and adapted bicycle).

Ambulation in relation to PVL grade

The chance that a child with PVL grade I or II would walk independently was 93% (specificity; Table II). Of the children with PVL grades I and II, 19/33 (57.6%) were able to walk unassisted before preschool age, 13/33 (39.4%) could walk with an assistive device and one child (3%) was not yet able to walk at the age of 3 years 8 months (Table IV).

The chance that a child with PVL grade III or IV would not be able to walk in childhood/adolescence was 83% (sensitivity; Table II). One male (4%) with a PVL grade III was able to walk unassisted at 19 months CA and one female (4%) at 5 years 6 months. Eleven out of 25 (44%) children could walk with a device. Three of them could walk indoors but were dependent on assistive mobility aids in the community or needed a wheelchair for longer distances. Twelve out of 25 (48%) children were totally dependent on a wheelchair, of whom two used an adapted bicycle in addition to their wheelchair. The male with PVL grade IV was totally dependent on a wheelchair (Table IV).

DISCUSSION

The gross motor abilities of children born preterm who developed CP as a result of PVL vary depending on the severity of the PVL. Most infants with PVL grade III and IV were never classified in GMFCS Levels II or I and, therefore, did not achieve the potential to walk independently. This is in contrast with children with PVL grade I, and to a lesser extent PVL grade II, in which most of the children were able to walk. These findings are supported by the studies of Rogers et al.[2] and Serdaroglu et al.[11]

The present study emphasizes the importance not only of studying children with a specific type of brain lesion, but also of studying them in more detail by subdividing them into different grades of PVL, to obtain a better clinical picture than by considering them as one undifferentiated group.

The interrater reliability in the present study was very good and in agreement with previous studies,[14,19] even with regard to infants younger than 2 years of age.[20] This applies to the total cohort and the subgroups with PVL grades II and III in particular. The use of the GMFCS in children with PVL grade I yielded less consistent results before 2 years of age. Rating of their gross motor function can, therefore, best be determined by a consensus of at least two examiners.

Stability of gross motor function, as expressed by GMFCS levels, became more robust after the first year of age. However, the results suggest that it is possible to predict gross motor outcome in children with PVL before this age. Our findings are consistent with the observation that children's gross motor function changes with age and experience[13,14] when it comes to children with PVL grades I and II. Palisano et al.[19] demonstrated that, across time, 72% of the children remained at the same GMFCS level. With regard to our study group this applies to T3. As with Palisano et al. we showed that children initially classified in the extreme levels (I and V) were least likely to be reclassified.[19] Our findings are also comparable to those of Gorter et al.[18] and Romeo et al.,[26] showing that children with a spastic unilateral type of CP do have better gross motor abilities than children with a spastic bilateral type in which all extremities are involved.

Children with a spastic bilateral type, with more involvement of the lower extremities than the upper extremities, showed the most diverse gross motor clinical picture.

By comparing GMFCS levels across time with the severity of PVL and type of CP in children born preterm, the present study adds to the construct- and criterion-related validity of the GMFCS.

Several explanations for interobserver differences can be identified: (1) the quantity and quality of information available in the clinical notes,[23] more specifically a lack of functional descriptions in the clinical records; (2) overlap in descriptions between GMFCS levels without clear distinctions; (3) different weighting by the raters of various aspects within the descriptions of the GMFCS[23]; and (4) a lack of clear definitions such as 'running' and 'jumping'. We noticed that, over time, some children had to be reclassified in a level describing more limited gross motor abilities, although there was no deterioration of their functional capacities. This applied in particular to the transition from age category 0 to 2 years to age category 2 to 4 years.

One of the limitations of this study concerns the subgroup of infants with PVL grade I. Only infants with PVL and subsequent development of CP were eligible for the study. However, it is known from several studies that only 4 to 10% of infants with a cranial ultrasound diagnosis of PVL grade I will go on to develop CP. It is also well known that this form of white matter injury is more reliably diagnosed with MRI than with cranial ultrasound.[27–29] A further possible limitation of the study is that we did not take into account the existing comorbidities (visual and / or hearing problems, epilepsy, learning difficulties) and interventions (type of therapy and spasticity treatment) of the children as predictors of GMFCS level, although most of them were seen in the regional rehabilitation centres on a regular basis. Another limitation might be that 13 participants were older than 12 years of age and 11 of these could have been considered adolescents at T4. The GMFCS for the adolescent population has not yet been published. However, the predictive values in our study support the observations of McCormick et al.,[23] who stated that 'the GMFCS level observed around 12 years of age is highly predictive of adult motor function'.

It is also true to say that we do not know whether the gross motor function of the nine participants who were rated in GMFCS Levels II to V and who were between 2 and 4 years of age at T4 will improve; neither do we yet know whether the gross motor function of some of the children in our cohort will deteriorate with age.

In infants born preterm with PVL it is important to know the severity of the brain damage. Children with PVL grades I and II have the potential to walk independently and thus may find it easier to participate in their community. Children with PVL grades III and IV are more dependent on environmental modifications for daily activities, on mobility devices, and on support from others. The choice for specific indoor and / or outdoor mobility devices is dependent on the personal preferences of the caregivers and the child, and on environmental circumstances.[22,30]

CONCLUSION

This study contributes to a better understanding of the impact of PVL on gross motor functional abilities in children born preterm by demonstrating that a 'composite diagnosis' (neuroimaging and GMFCS) is worthwhile to obtain a clear clinical picture. The present study also offers opportunities to inform parents of the early and future functional possibilities of their child, and to choose the most appropriate intervention strategy.

Acknowledgements

We are grateful to our secretaries Mrs I G Borger-Gerritse and Mrs L Brouwer-Prins for their support, and to Dr E J H Mulder for his help in creating Figure 1.

REFERENCES

1 De Vries LS, van Haastert IC, Rademaker KJ, Koopman C, Groenendaal F. Ultrasound abnormalities preceding cerebral palsy in high-risk preterm infants. J Pediatr 2004;144:815–20.

2 Rogers B, Msall M, Owens T, Guernsey K, Brody A, Buck G, et al. Cystic periventricular leukomalacia and type of cerebral palsy in preterm infants. J Pediatr 1994;125:S1–8.

3 Back SA. Perinatal white matter injury: the changing spectrum of pathology and emerging insights into pathogenetic mechanisms. Ment Retard Dev Disabil Res Rev 2006;12:129–40.

4 Nanba Y, Matsui K, Aida N, Sato Y, Toyoshima K, Kawataki M, et al. Magnetic resonance imaging regional T1 abnormalities at term accurately predict motor outcome in preterm infants. Pediatrics 2007;120:e10–19.

5 Ohgi S, Akiyama T, Fukuda M. Neurobehavioural profile of low-birthweight infants with cystic periventricular leukomalacia. Dev Med Child Neurol 2005;47:221–28.

6 Banker B, Larroche J. Periventricular leukomalacia of infancy. A form of neonatal anoxic encephalopathy. Arch Neurol 1962;7:386–410.

7 Platt MJ, Cans C, Johnson A, Surman G, Topp M, Torrioli MG, et al. Trends in cerebral palsy among infants of very low birthweight (<1500 g) or born prematurely (<32 weeks) in 16 European centres: a database study. Lancet 2007;369:43–50.

8 De Vries LS, Eken P, Dubowitz LMS. The spectrum of leukomalacia using cranial ultrasound. Behav Brain Res 1992;49:1–6.

9 Bracewell M, Marlow N. Patterns of motor disability in very preterm children. Ment Retard Dev Disabil Res Rev 2002;8:241–48.

10 Eken P, van Nieuwenhuizen O, van der Graaf Y, Schalij-Delfos NE, De Vries LS. Relation between neonatal cranial ultrasound abnormalities and cerebral visual impairment in infancy. Dev Med Child Neurol 1994;36:3–15.

11 Serdaroglu G, Tekgul H, Kitis O, Serdaroglu E, Gökben S. Correlative value of magnetic resonance imaging for neurodevelopmental outcome in periventricular leukomalacia. Dev Med Child Neurol 2004;46:733–39.

12 Ricci D, Cowan F, Pane M, Gallini F, Haataja L, Luciano R, et al. Neurological examination at 6 to 9 months in infants with cystic periventricular leukomalacia. Neuropediatrics 2006;37:247–52.

13 Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol 2007;49(Suppl.109):8–14.

14 Wood E, Rosenbaum P. The gross motor function classification system for cerebral palsy: a study of reliability and stability over time. Dev Med Child Neurol 2000;42:292–96.

15 Rosenbaum PL, Walter SD, Hanna SE, Palisano RJ, Russell DJ, Raina P, et al. Prognosis for gross motor function in cerebral palsy: creation of motor development curves. JAMA 2002;288:1357–63.

16 Vohr BR, Msall ME, Wilson D, Wright LL, McDonald S, Poole WK. Spectrum of gross motor function in extremely low birth weight children with cerebral palsy at 18 months of age. Pediatrics 2005;116:123–29.

17 Bodkin AW, Robinson C, Perales FP. Reliability and validity of the Gross Motor Function Classification System for Cerebral Palsy. Pediatr Phys Ther 2003;15:247–52.
18 Gorter JW, Rosenbaum PL, Hanna SE, Palisano RJ, Bartlett DJ, Russell DJ, et al. Limb distribution, motor impairment, and functional classification of cerebral palsy. Dev Med Child Neurol 2004;46:461–67.
19 Palisano RJ, Cameron D, Rosenbaum PL, Walter SD, Russell D. Stability of the gross motor function classification system. Dev Med Child Neurol 2006;48:424–28.
20 Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39:214–23.
21 Østensjø S, Carlberg EB, Vøllestad NK. Motor impairments in young children with cerebral palsy: relationship to gross motor function and everyday activities. Dev Med Child Neurol 2004;46:580–89.
22 Østensjø S, Carlberg EB, Vøllestad NK. The use and impact of assistive devices and other environmental modifications on everyday activities and care in young children with cerebral palsy. Disabil Rehabil 2005;27:849–61.
23 McCormick A, Brien M, Plourde J, Wood E, Rosenbaum P, McLean J. Stability of the Gross Motor Function Classification System in adults with cerebral palsy. Dev Med Child Neurol 2007;49:265–69.
24 Altman DG. Practical statistics for medical research. London: Chapman & Hall, 1997.
25 Nelson KB, Ellenberg JH. Children who 'outgrew' cerebral palsy. Pediatrics 1982;69:529–36.
26 Romeo DMM, Cioni M, Scoto M, Mazzone L, Palermo F, Romeo MG. Neuromotor development in infants with cerebral palsy investigated by the Hammersmith Infant Neurological Examination during the first year of age. Eur J Paediatr Neurol 2008;12:24–31.
27 Inder TE, Anderson NJ, Spencer C, Wells S, Volpe JJ, et al. White matter injury in the premature infant: a comparison between serial cranial sonographic and MR findings at term. AJNR Am J Neuroradiol 2003;24:805–09.
28 Maalouf EF, Duggan PJ, Counsell SJ, Rutherford MA, Cowan F, Azzopardi D, et al. Comparison of findings on cranial ultrasound and magnetic resonance imaging in preterm infants. Pediatrics 2001;107:719–27.
29 Miller SP, Cozzio CC, Goldstein RB, Ferriero D, Partridge JC, Vigneron DB, et al. Comparing the diagnosis of white matter injury in premature newborns with serial MR imaging and transfontanel ultrasonography findings. AJNR Am J Neuroradiol 2003;24:1661–69.
30 Graham HK, Harvey A, Rodda J, Nattrass GR, Pirpiris M. The Functional Mobility Scale (FMS). J Pediatr Orthop 2004;24:514–20.

Chapter 6

DECREASING INCIDENCE AND SEVERITY OF CEREBRAL PALSY IN PREMATURELY BORN CHILDREN

Ingrid C. van Haastert
Floris Groenendaal
Cuno S.P.M. Uiterwaal
Jacqueline U.M. Termote
Marja van der Heide-Jalving
Maria J.C. Eijsermans
Jan Willem Gorter
Paul J.M. Helders
Marian J. Jongmans
Linda S. de Vries

J Pediatr. 2011 Jul;159 (1): 86-91. e1. Epub 2011 Mar 2.

ABSTRACT

Objective: To examine incidence and severity of cerebral palsy (CP), and associated factors among preterm survivors (gestational age <34 weeks), admitted to a neonatal intensive care unit from 1990–2005.

Study design: Eighteen antenatal, perinatal and postnatal factors were analyzed. The cohort was divided in four birth periods: 1990–1993 (n = 661), 1994–1997 (n = 726), 1998–2001 (n = 723), and 2002–2005 (n = 850). The Gross Motor Function Classification System was used as primary outcome measure (mean age: 32.9 ± 5.3 months). Logistic regression analyses were used.

Results: CP incidence decreased from 6.5% in period I, to 2.6%, 2.9% and 2.2% (p <.001) in period II-IV, respectively. Simultaneously, cystic periventricular leukomalacia (c-PVL) decreased from 3.3% in period I to 1.3% in period IV (p = .004). Within the total cohort (n = 3287), c-PVL grade III decreased from 2.3% in period I to 0.2% in period IV (p = .003). The number of children with Gross Motor Function Classification System levels III-V decreased from period I to IV (p = .035). Independent risk factors for CP were c-PVL and severe intraventricular hemorrhage, whereas antenatal antibiotics, presence of an arterial line, Caesarean section, and gestational age were independent protective factors.

Conclusion: CP incidence and severity decreased from 1990–1993 onward, which could be attributed to a reduction of 93% in severe c-PVL.

INTRODUCTION

Cerebral palsy (CP) is a neurodevelopmental condition that can be recognized from early childhood onward and is the result of antenatal or neonatal brain injury.[1] CP rates in preterm infants, across a period of time, are considered to be a good indicator to monitor effects of perinatal and neonatal care.[2] Although there is an increasing interest in monitoring CP prevalence rates, published results are often inconsistent.[3-5] Outcomes can vary depending on whether CP rates were assessed by birth weight (BW), gestational age (GA), birth years studied, sample size, or age at assessment.[4-7] Rates of CP during the last two decades have been described as being quite stable or decreasing in children born preterm.[2,3,5,7-9] The CP rate in very low–birth weight children is considered by some as unchanged, by others as increasing with lower BW and more immaturity.[2-4,8]

The rates of different types of CP were reported in some studies, and in other studies, the severity of CP was taken into account. [8,10] The most detrimental brain injuries that put infants born preterm at high risk for CP are severe intraventricular hemorrhage (IVH) and cystic periventricular leukomalacia (c-PVL).[2,6,11] The incidence of c-PVL has declined for children with a GA <30 weeks in several parts of the world, including our center.[12,13] The prognosis for neurodevelopmental outcome of infants after a severe hemorrhage or c-PVL depends on localization and extent of the lesion.[11] The aim of this study was to analyze changes in CP incidence and the degree of severity of gross motor function in early childhood and to identify associated factors related to the development of CP in children born preterm.

METHODS

Data for a hospital-based cohort of infants born preterm were prospectively collected. Eighteen potentially relevant factors were analyzed: antenatal administration of corticosteroids (bethamethasone) and antibiotics; place of birth, Cesarean section, GA, BW, sex, multiple birth, Apgar score at 5 minutes, need for and duration of mechanical

ventilation, placement of an arterial line for blood pressure monitoring and arterial blood-gas sampling, postnatal administration of corticosteroids (hydrocortisone), surfactant, bronchopulmonary dysplasia (BPD), sepsis, IVH grade III, hemorrhagic parenchymal infarction (grade IV), and c-PVL. A medical ethics committee approved the study without informed consent.

Children with a GA <34 weeks who were admitted within 4 days of birth were included. The second criterion was chosen to avoid the impact of differences in treatment and care practices in referral centers, and consequently on outcome.[14]

From January 1, 1990, to December 31, 2005, 3816 preterm infants were admitted to our level-three neonatal intensive care unit (NICU). Infants with a diagnosed genetic syndrome, neuromuscular disorder, or major congenital malformation were excluded.

Neuroimaging

Routinely, cranial ultrasound scanning (cUS) through the anterior fontanel was performed as soon as possible after admission to the NICU.[15] Scanning was repeated at least once a week until discharge and again at term-equivalent age. Between 1990 and 2003 an ATL UM-4 mechanical sector scanner (Philips Medical Systems, Andover, Massachusetts) was used. Since 2003, a Toshiba-Aplio XG ultrasound machine (Toshiba, Tokyo, Japan) was used with a 5- to 8.5-MHz broadband transducer. Brain injury was classified after its full evolution, which was either at discharge or at term-equivalent age and included IVH grade III, hemorrhagic parenchymal infarction, non-cystic PVL, c-PVL, and perinatal arterial stroke (middle cerebral artery infarction).[15] When different brain injuries were diagnosed in an infant who eventually developed CP, the most important injury was used for the analysis.

Magnetic resonance imaging (MRI) was performed in 457/3287 (13.9%) cases, either during the neonatal period or later in infancy or childhood. Of 457, 10 (2.2%) died in the neonatal period, 81 (17.7%) had development of CP, for 244 (53.4%) without CP (one died at 5.5 months of age), MRI was part of a research project. For 122 (26.7%) infants, MRI served as a supplement to cUS to confirm or reconsider cUS findings.

MRI was performed in 81/102 (79.4%) of the children who subsequently had development of CP. All cUS and MRI diagnoses were retrieved from the ultrasound and MRI database after interpretation in the neonatal period (LS.dV. and F.G.).

Gross Motor Outcome

CP was diagnosed according to the definition and classification described by Rosenbaum et al.[1] Predominant type of motor impairment and limb distribution was classified according to the Surveillance of Cerebral Palsy in Europe study group.[16,17] The following terms were used: unilateral spastic CP, bilateral spastic CP-D with more involvement of the lower than the upper extremities ('Diplegia'), and bilateral spastic CP-Q with almost equal difficulties in the lower as upper extremities ('Quadriplegia').

To classify the gross motor abilities of the children following the descriptions of the Gross Motor Function Classification System (GMFCS), medical records including letters from rehabilitation centers were reviewed. The GMFCS describes the major functional characteristics of children with CP and has excellent reliability and validity for children age 2 years and older.[18,19] It is a five-level pattern recognition system with level I describing the best gross motor abilities possible and Level V the worst. GMFCS levels I-II descriptions refer to walking without and with limitations, whereas GMFCS levels III-V descriptions refer to walking with a mobility device through to being transported in a wheelchair.

In this study, two experienced pediatric physical therapists (I.vH. and M.E.) used the second age band (between the second and fourth birthday) and independently classified the children. In case of discrepancies, consensus was reached by discussion.

Statistical Methods

Data were analyzed by use of independent-sample *t* tests for continuous variables and χ^2 tests or Fisher exact tests for dichotomous variables. Because of relatively small numbers of children with CP in each birth year, the 16-year period was divided into four periods: I, 1990–1993; II, 1994–1997; III, 1998–2001; and IV, 2002–2005. To compare the four periods, χ^2 tests or one-way analysis of variance were used, followed by Bonferroni

adjustment where appropriate. To determine the best cut-off point for duration of mechanical ventilation, a receiver operating characteristic curve was constructed. Relevant factors are mentioned in the first paragraph of the Methods section. Significant factors were entered in a binary logistic regression model to determine associated factors that could be related to CP. Severe IVH was defined as IVH grade III or hemorrhagic parenchymal infarction. Furthermore, to determine the seriousness of illness at admission as a potential risk factor for CP, a composite 'disease' score was created (Apgar score <4 at 1 minute or <7 at 5 minutes or need for mechanical ventilation) with a range of 0-3, and included in the model. Also a composite 'pulmonary' score was created (need for surfactant or mechanical ventilation or mechanical ventilation >7 days) with a range of 0-3. The results of the logistic models were expressed as OR with a 95% CI. A p value <.05 was considered to indicate a significant result. Statistical analysis was performed by use of SPSS (version 15.0; SPSS, Inc, Chicago, Illinois) software. The interrater reliability between the two raters who classified every child on one of the five GMFCS Levels was examined by means of kappa and its 95% CI with quadratic weighting and determined to check for an acceptable degree of reliability, that is, weighted kappa ≥0.80.

RESULTS

After using the exclusion criteria mentioned above, 3287/3816 (86.1%) children were eligible for this study (mean GA: 30 ± 2.2 weeks; mean BW: 1332 ± 443 g). Newborns who were admitted to our NICU in the first period (1990–1993) had significantly higher 'disease' scores than those who were born thereafter (p < .001), with no differences through the years for the 'pulmonary' scores (p = .43). Non-survivors (n = 327) differed significantly from survivors (n = 2960) with respect to GA (mean 28.3 ± 2.3 weeks vs 30.2 ± 2.1, p < .001) and BW (mean 1051 ± 429 g vs 1363 ± 434 g; p < .001) and were diagnosed significantly more often with an intracranial lesion (c-PVL and severe IVH, both p < .001). Regarding survivors, BW, sex, multiple birth, and IVH grade III did not show significant differences over the years (Table I).

Table I Main characteristics of study population of infants born preterm 1990-2005

Total cohort	Total (N=3287)	1990–1993 Period I (n =755)	1994–1997 Period II (n =812)	1998–2001 Period III (n = 807)	2002–2005 Period IV (n = 913)	*P* value
Born in UMCU	2426 (73.8)	484 (64.1)	590 (72.7)*	613 (76.0)*	739(80.9)*†	<.001
Mortality	327 (9.9)	94 (12.5)	86 (10.6)	84 (10.4)	63 (6.9)*	.002
Survivors	2960 (90.1)	661 (87.5)	726 (89.4)	723 (89.6)	850 (93.1)*	.001
GA (mean ± SD)	30.2 ± 2.1	29.9 ± 2.2	30.3 ± 2.1‡	30.3 ± 2.0‡	30.3 ± 2.0‡	.002
Antenatal steroids	1580 (53.4)	247 (37.4)	397 (54.7)*	426 (58.9)*	510 (60.0)*	<.001
Antenatal antibiotics	943 (31.9)	138 (20.9)	197 (27.1)	261 (36.1)*†	347 (40.8)*†	<.001
Cesarean section	1701 (57.5)	359 (54.3)	428 (59.0)	443 (61.3)	471 (55.4)	.028
Apgar score/5 minutes <7	330 (11.1)	98 (14.8)	77 (10.6)	80 (11.1)	75 (8.8)*	.003
Arterial line	2509 (84.8)	476 (72.0)	563 (77.5)§	673 (93.1)*†	797 (93.8)*†	<.001
Surfactant	952 (32.2)	139 (21.0)	234 (32.2)*	258 (35.7)*	321 (37.8)*	<.001
Mechanical ventilator >7	883 (29.8)	239 (36.2)	225 (31.0)	216 (29.9)	203 (23.9)*¶	<.001
Postnatal steroids	597 (20.2)	149 (22.5)	180 (24.8)	164 (22.7)	104 (12.2)*†‖	<.001
BPD	588 (19.9)	171 (25.9)	150 (20.7)	133 (18.4)‡	134 (15.8)*	<.001
Sepsis	919 (31.0)	178 (26.9)	223 (30.7)	265 (36.7)*	253 (29.8)**	<.001
Hemorrhagic parenchymal infarction	65 (2.2)	21 (3.2)	9 (1.2)	21 (2.9)	14 (1.6)	0.30
c-PVL	52 (1.8)	22 (3.3)	12 (1.7)	7 (1.0)‡	11 (1.3)§	.004
CP	102 (3.4)	43 (6.5)	19 (2.6)*	21 (2.9)*	19 (2.2)*	<.001

UMCU, University Medical Centre Utrecht. Numbers between brackets are percentages.
* $p < .001$, period differs from period I.
† $p < .001$, period differs from period II.
‡ $p < .01$.
§ $p < .05$.
¶ $p < .05$.
|| $p < .001$, period differs from period III.
** $p < .05$.

The 102 (3.4%) children who had development of CP differed in several antenatal and postnatal factors from the 2858 survivors who did not have development of CP. Fewer antenatal steroids and antibiotics were administered to mothers of children with development of CP (44.1% vs 53.7%, p = .036, and 23.5% vs 32.2%, p = .039, respectively). Their children had a lower GA (mean 29.2 ± 2.1 weeks vs 30.3 ± 2.0, p < .001), a lower BW (mean 1261 ± 373 g vs 1366 ± 435, p = .007), were born less often by Cesarean section (43% vs 58%; p = .004), and an arterial line was less often inserted (73.5% vs 85.2%, p = .003).

However, children with development of CP more often had a 'disease' score of 2 and 3 (30.0% vs 16.9%; p <.001), as was the case with respect to a 'pulmonary' score (64.7% vs 43.0%; p < .001). They also needed more often postnatal steroids (42.2% vs 19.4%; p < .001) and developed more often BPD (30.4% vs 19.5%; p = .011). Finally, more children with development of CP were diagnosed with IVH grade III (14.7% vs 2.3%), hemorrhagic parenchymal infarction (27.5% vs 1.3%), and c-PVL (31.4% vs 0.7%; all three p < .001).

CP Categorization

Overall, 38/102 (37.25%) children have development of unilateral spastic CP, 51/102 (50%) bilateral spastic CP-D and 13/102 (12.75%) bilateral spastic CP-Q. Bilateral spastic CP declined significantly (p < .001) when period I is compared with period IV: 31/661 (4.7%) and 9/850 (1.1%), respectively, whereas unilateral spastic CP did not decline significantly: 12/661 (1.8%) and 10/850 (1.2%), respectively (Figure 1).

GMFCS

At the time of classification, the mean chronological age of the children was 32.9 ± 5.3 months. The interrater reliability with respect to the GMFCS levels was high (quadratic kappa 0.95). The two raters disagreed in 15/102 (14.7%) of the classifications, but the differences never exceeded one level. The distribution of the different brain injuries associated with CP and gross motor function for each birth period from 1990–2005 are shown in Table II.

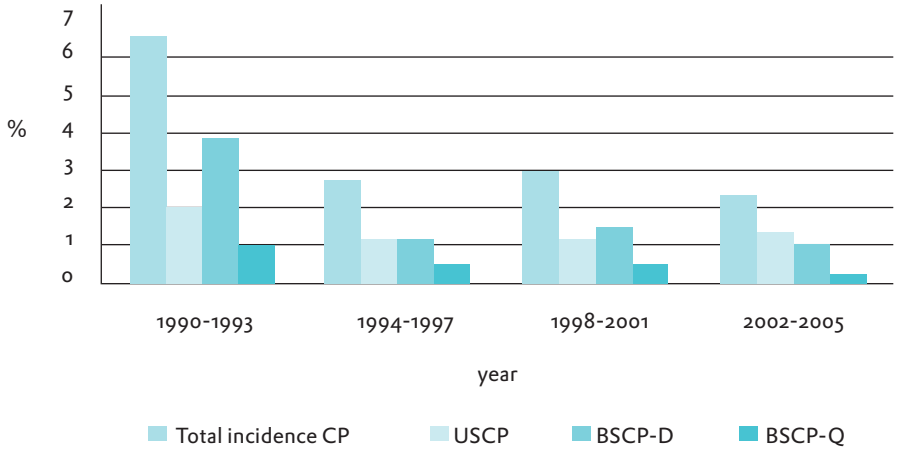

Figure 1 CP incidence and type from 1990 to 2005.

Table II Brain injuries in 102 children born preterm from 1990-2005 with CP related to GMFCS Level

US/day	1990-1993	1994-1997	1998-2001	2002-2005	GMFCS Level					Total
					I	II	III	IV	V	
PVL grade I	12	2	11	7	25	4	3	0	0	32 (31.4)
cPVL grade II	4	6	0	2	9	1	1	1	0	12 (11.8)
cPVL grade III	12	3	4	1	1	2	4	10	3	20 (19.6)
IVH grade III	2	3	0	1	5	0	1	0	0	6 (5.9)
HPI	12	3	4	7	20	3	2	1	0	26 (25.5)
MCA infarction	1	2	2	1	6	0	0	0	0	6 (5.9)
Total	43 (42.2)	19 (18.6)	21 (20.6)	19 (18.6)	66 (64.7)	10 (9.8)	11 (10.8)	12 (11.8)	3 (2.9)	102 (100)

HPI, hemorrhagic parenchymal infarction; *MCA*, middle cerebral artery.
Numbers between brackets are percentages.

Significantly more children with CP in period I experienced severe functional limitations, as expressed by GMFCS level III-V, compared with period IV (p = .035; Figure 2). Twenty of 21 infants with CP where no MRI was available were functioning in GMFCS level I.

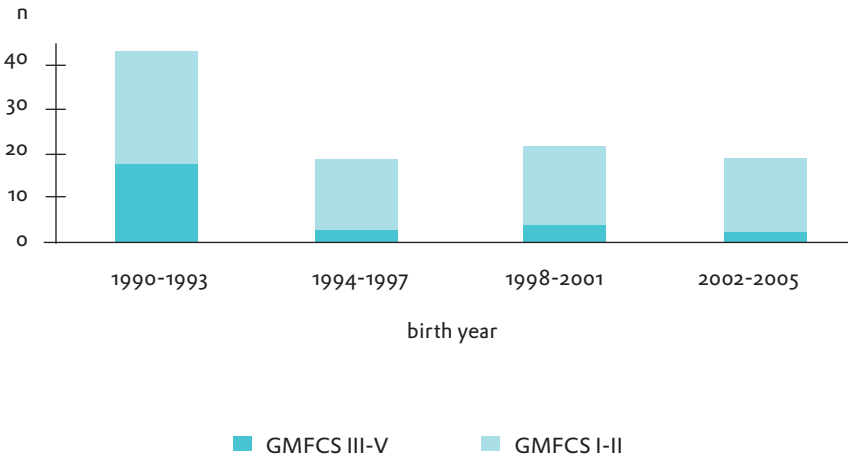

Figure 2 GMFCS level I-II and III-IV from 1990 to 2005.

We focused in more detail on the 51 children with c-PVL who survived infancy (one child, born in 1990, died at the age of 4.5 months because of BPD). The proportion of children who did not have development of CP increased from period I to IV: 5/21 (23.8%), 3/12 (25%), 3/7 (42.9%) and 8/11 (72.7%), respectively, and was significant for period I versus IV after correction for multiple comparisons (p < .05; Table I and Figure 3).

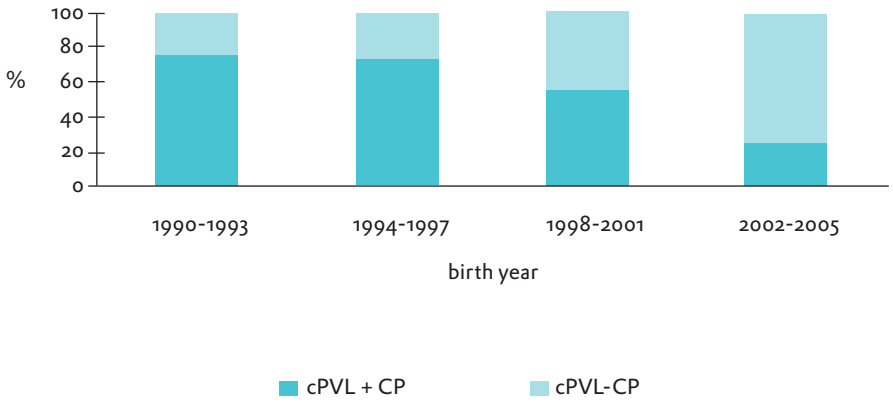

Figure 3 C-PVL in relation to CP.

Next, we studied the severity of the lesions to understand why 19/51 (37.3%) children did not have development of CP: 17/29 (58.6%) children who were diagnosed with c-PVL grade II were free of CP compared with 2/22 (9.1%) with c-PVL grade III. One of the two children with c-PVL grade III but without CP had cysts restricted to the frontal periventricular white matter, and the other had cysts restricted to the parietal periventricular white matter.

In addition, for each birth period we assessed how many children were diagnosed with either c-PVL grade II or III. For this part of the analysis, infants who died in the neonatal period were also included. There was a significant decline in the occurrence of c-PVL when comparing period I with period III and IV (p = .011 and p = .001, respectively), but especially in the occurrence of c-PVL grade III from period I onward (2.3%, 1%, 1.1% and 0.2% respectively; p = .003; Figure 4).

The contribution of c-PVL grade III to severe CP (GMFCS III-V) was 58.8% (10/17 children) in period I and 77.8% (7/9 children) in periods II to IV combined.

Severe CP declined from 17/661 survivors (2.6%) in period I to 2/850 survivors (0.2%) in period IV, which is a decrease of 92%. Simultaneously, c-PVL grade III declined from 10/661 survivors (1.5%) to 1/850 survivors (0.1%), which is a decrease of 93%.

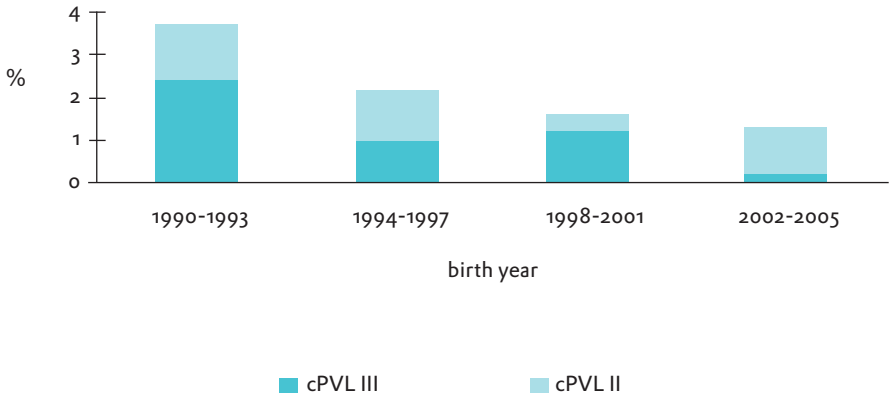

Figure 4 C-PVL grade II and III within total cohort.

Associated Factors Related to CP

Two independent risk factors for CP were identified: c-PVL (OR 71.5; 95% CI: 37.3-137.2; $p < .001$) and severe IVH (OR 5.5; CI: 3.1-10.0; $p < .001$), and four independent protective factors: antenatally administered antibiotics (OR 0.46; CI 0.27-0.79; $p = .005$), Cesarean section (OR: 0.57; CI: 0.35-0.92; $p = .022$), GA as a continuous variable in weeks (OR: 0.84; CI: 0.75-0.94; $p = .002$), and placement of an arterial line after admission (OR 0.47; CI: 0.28-0.80; $p = .005$). Additional analyses to asses the independent association of c-PVL with CP revealed a significant interaction with the 'pulmonary' score of neonates (OR: 5.6; 95% CI: 2.8-11.1; $p < .001$).

DISCUSSION

Coinciding with increasing rates of survival from 1990–2005 in our hospital-based cohort of infants born preterm, CP incidence decreased significantly since 1990–1993 and was stable thereafter. Simultaneously, a reduction in the number of children with severe gross motor functional limitations, as expressed by GMFCS levels III-V, was seen over time. The reduction in the incidence of severe CP could almost completely be explained by a reduction of c-PVL grade III. In periods II to IV, c-PVL grade III explained severe CP in 77.8% of the cases, whereas it explained severe CP in 58.8% in period I. Thus c-PVL appeared to be the most important risk factor for CP, similar to the findings of the EPIPAGE study.[4] Hamrick et al[12] also found a significant decrease in the incidence of c-PVL but no change in the incidence of CP, suggesting that lesions not identified by cUS would be associated with the development of CP. This difference in observation could be due to a greater number of sequential cUS examinations in our unit, performed on a weekly basis during the admission, at discharge and again at term-equivalent age, also allowing us to diagnose small cystic lesions.[15] In this study, we did not have any infants with development of CP and a completely normal cUS. Almost a third of our children who had development of CP had a cUS diagnosis of PVL grade I. Assessment of increased echogenicity is subjective with low sensitivity, when taking MRI as the gold standard.[20] On the other hand, more than half of these children had an MRI once the clinical diagnosis of CP was made, and sequelae of mild white matter injury with periventricular gliosis were present in all. Overall, 79% of the children with CP had at least one MRI, confirming previously diagnosed cUS abnormalities.

Our finding that 37.3% of the children who were diagnosed with c-PVL did not have development of CP is in agreement with data by Ancel et al[4] and can be explained by the localization and extent of the cystic lesions in the white matter. Most of our children with CP are functioning in GMFCS level I and II and are thus able to walk independently. This is in accordance with the results described by Vohr et al,[10] who studied a very similar cohort of infants.

Through the years, fewer children had development of severe bilateral spastic CP, whereas the number of children with unilateral spastic CP did not change significantly. This is consistent with the findings of Platt et al[8] from the Surveillance of Cerebral Palsy in Europe study group. Himmelmann et al[21] also reported that bilateral spastic CP is decreasing in children born preterm.

The decrease of CP in this study was predominantly due to a significant decrease in c-PVL and to a lesser degree to severe IVH. Wilson-Costello et al[9] found a decrease in the overall rate of severe cUS abnormalities in the early years of this century, but reported an increase in PVL in infants with a BW <1000 g when comparing the 1980s with the 1990s with no change in the beginning of this millennium. The rate of severe IVH in their study decreased from the 1990s to the early years of 2000.

The condition of preterm infants immediately after birth, as expressed by a 'disease' score, was found to be most severe in the first period (1990–1993) and was strongly associated with the development of severe brain injury and subsequent development of CP. We were also able to identify a strong association between the severity of pulmonary problems, as expressed by a 'pulmonary' score, and c-PVL. However, not one specific risk factor could be causally related to c-PVL. Therefore we can only speculate about the underlying causes of this condition and assume that there is more than one factor involved.[2] Other studies also showed detrimental effects of prolonged exposure to mechanical ventilation on neurodevelopmental outcome (eg, CP).[6,14,22] Although sepsis may contribute to diffuse changes in the white matter,[23,24] development of c-PVL after late-onset sepsis, which is mostly caused by coagulase-negative staphylococci, has been a rare finding in our unit where repeated cUS is performed after any deterioration to enable detection of late onset c-PVL.[25] Analysis of our data revealed that sepsis did not play a role in the change in CP because the proportion of infants who suffered from sepsis increased from period I through to period III, whereas the number of children with CP decreased simultaneously.

In this study, antenatal exposure to antibiotics but not corticosteroids was significantly associated with a lower CP rate, although mothers of children with CP received corticosteroids less often. We speculate that a reduction

of cytokine production in the preterm brain may reduce injury to the white matter. In contrast, Kenyon et al[26] discovered from structured parental questionnaires assessing the health status of 7-year-old children, that more children who were antenatally exposed to erythromycin or co-amoxiclav had development of CP than those who did not receive any of these antibiotics. In our study it was not possible to analyze an obstetric variable such as chorioamnionitis in detail because this was not part of the database.

Although we hypothesized that an increase in intrauterine transportation to our tertiary center would decrease the risk of brain injury and the proportion of neonates born in our center increased significantly through the years, we were unable to confirm this.

In the early 1990s, arterial lines providing more accurate blood-pressure and blood-gas measurements were inserted in 72% of the newborns who were admitted to our NICU, whereas in the second half of the study period this applied to almost 94%. Monitoring blood pressure and CO_2 values was therefore less accurate in the early 1990s and possibly related to undetected hypotension and hypocarbia associated with brain injury and subsequent CP.[27]

In contrast with what others reported,[2,5,22] our results showed an association between Cesarean section and CP in favour of delivery by Cesarean section. Wilson-Costello et al[9] found that Cesarean section delivery was associated with improved outcomes in a cohort of ELBW infants and Deulofeut et al[28] showed that vaginal delivery is associated with a higher risk for PVL. Whether Cesarean section is the mode of delivery of first choice in case of an expected preterm birth, to prevent the neonate from a brain injury, needs to be studied further.

Some limitations should be considered when interpreting our study results. This is a study that is examining associations. Certain positive predictor variables may also be outcomes that are caused by unidentified factors that may also cause CP.

Next, we are aware that this is a single-center study and not a population-based study.[2,7] However, all infants requiring intensive care in our unit come from a region serving a population of 2 million inhabitants.

It is likely that CP incidence in this study would have been slightly higher when intensive care would not have been withdrawn in infants with extensive brain injury, at high risk for development of CP. Besides, infants with a GA <25 weeks were not eligible for intensive care in the Netherlands during the study period. The mortality rate did, however, significantly decrease with time and is comparable with other studies.[5,9,10] Because clinical features related to CP in early infancy and childhood can resolve or become more clear over the years, it is recommended to establish a confirmed diagnosis beyond 4 years of age.[16,29] The mean age at classifying the gross motor function of the 102 children with CP in our study was 32.9 months. In 2/66 (3%) children functioning in GMFCS level I, the diagnosis of CP could no longer be confirmed according to the definition by Rosenbaum et al[1] (ie, presence of activity limitations in middle childhood), whereas this was still possible in 62 (94%) children. We do not have any information about later gross motor functioning of two (3%) children.

Acknowledgements

We are grateful to Mrs. S. J. M. van Hemert-Glaubitz for her contribution to improve the accessibility of the dataset, and to Dr. I. van Ertbruggen for her contribution to the database in 1990 to 1999.

REFERENCES

1 Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl 2007;109:8-14.

2 Hack M, Wilson-Costello D. Trends in the rates of cerebral palsy associated with neonatal intensive care of preterm children. Clin Obstet Gynecol 2008;51:763-74.

3 Krägeloh-Mann I, Cans C. Cerebral palsy update. Brain Dev 2009;31:537-44.

4 Ancel PY, Livinec F, Larroque B, Marret S, Arnaud C, Pierrat V, et al. Cerebral palsy among very preterm children in relation to gestational age and neonatal ultrasound abnormalities: The EPIPAGE Cohort Study. Pediatrics 2006;117:828-35.

5 Robertson CM, Watt MJ, Yasui Y. Changes in the prevalence of cerebral palsy for children born very prematurely within a population-based program over 30 years. JAMA 2007;297:2733-40.

6 Walsh MC, Morris BH, Wrage LA, Vohr BR, Poole WK, Tyson JE, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. J Pediatr 2005;146:798-804.

7 Surman G, Hemming K, Platt MJ, Parkes J, Green A, Hutton J, et al. Children with cerebral palsy: severity and trends over time. Paediatr Perinat Epidemiol 2009;23:513-21.

8 Platt MJ, Cans C, Johnson A, Surman G, Topp M, Torrioli MG, et al. Trends in cerebral palsy among infants of very low birthweight (<1500g) or born prematurely (<32 weeks) in 16 European centres: a database study. Lancet 2007;369:43-50.

9 Wilson-Costello D, Friedman H, Minich N, Siner B, Taylor G, Schluchter M, et al. Improved neurodevelopmental outcomes for

extremely low birth weight infants in 2000-2002. Pediatrics 2007;119:37-45.
10 Vohr BR, Msall ME, Wilson D, Wright LL, McDonald S, Poole WK. Spectrum of gross motor function in extremely low birth weight children with cerebral palsy at 18 months of age. Pediatrics 2005;116:123-9.
11 Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol 2009;8:110-24.
12 Hamrick SE, Miller SP, Leonard C, Glidden DV, Goldstein R, Ramaswamy V, et al. Trends in severe brain injury and neurodevelopmental outcome in premature newborn infants: the role of cystic periventricular leukomalacia. J Pediatr 2004;145:593-9.
13 Groenendaal F, Termote JU, van der Heide-Jalving M, van Haastert IC, De Vries LS. Complications affecting preterm neonates from 1991 to 2006: what have we gained? Acta Paediatr 2010;99:354-8.
14 Vohr BR, Wright LL, Dusick AM, Perritt R, Poole WK, Tyson JE, et al. Center differences and outcomes of extremely low birth weight infants. Pediatrics 2004;113:781-9.
15 De Vries LS, Van Haastert IL, Rademaker KJ, Koopman C, Groenendaal F. Ultrasound abnormalities preceding cerebral palsy in high-risk preterm infants. J Pediatr 2004;144:815-20.
16 Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Surveillance of Cerebral Palsy in Europe (SCPE). Dev Med Child Neurol 2000;42:816-24.
17 Gorter JW, Rosenbaum PL, Hanna SE, Palisano RJ, Bartlett DJ, Russell DJ, et al. Limb distribution, motor impairment, and functional classification of cerebral palsy. Dev Med Child Neurol 2004;46:461-7.
18 Gorter JW, Ketelaar M, Rosenbaum P, Helders PJ, Palisano R. Use of the GMFCS in infants with CP: the need for reclassification at age 2 years or older. Dev Med Child Neurol 2009;51:46-52.
19 Rosenbaum PL, Palisano RJ, Bartlett DJ, Galuppi BE, Russell DJ. Development of the Gross Motor Function Classification System for cerebral palsy. Dev Med Child Neurol 2008;50:249-53.
20 Miller SP, Cozzio CC, Goldstein RB, Ferriero DM, Partridge JC, Vigneron DB, et al. Comparing the diagnosis of white matter injury in premature newborns with serial MR imaging and transfontanel ultrasonography findings. Am J Neuroradiol 2003;24:1661-9.
21 Himmelmann K, Hagberg G, Uvebrant P. The changing panorama of cerebral palsy in Sweden. X. Prevalence and origin in the birth-year period 1999-2002. Acta Paediatr 2010;99:1337-43.
22 Miller SP, Ferriero DM, Leonard C, Piecuch R, Glidden DV, Partridge JC, et al. Early brain injury in premature newborns detected with magnetic resonance imaging is associated with adverse early neurodevelopmental outcome. J Pediatr 2005;147:609-16.
23 Glass HC, Bonifacio SL, Chau V, Glidden D, Poskitt K, Barkovich AJ, et al. Recurrent postnatal infections are associated with progressive white matter injury in premature infants. Pediatrics 2008;122:299-305.
24 Shah DK, Doyle LW, Anderson PJ, Bear M, Daley AJ, Hunt RW, et al. Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term. J Pediatr 2008;153:170-5.
25 Andre P, Thebaud B, Delavaucoupet J, Zupan V, Blanc N, d'Allest AM, et al. Late-onset cystic periventricular leukomalacia in premature infants: a threat until term. Am J Perinatol 2001;18:79-86.
26 Kenyon S, Pike K, Jones DR, Brocklehurst P, Marlow N, Salt A, et al. Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial. Lancet 2008;372:1319-27.
27 Shankaran S, Langer JC, Kazzi SN, Laptook AR, Walsh M. Cumulative index of exposure to hypocarbia and hyperoxia as risk factors for periventricular leukomalacia in low birth weight infants. Pediatrics 2006;118:1654-9.
28 Deulofeut R, Sola A, Lee B, Buchter S, Rahman M, Rogido M. The impact of vaginal delivery in premature infants weighing less than 1251 grams. Obstet Gynecol 2005;105:525-31.
29 Nelson KB, Ellenberg JH. Children who "outgrew" cerebral palsy. Pediatrics 1982;69:529-36.

Chapter 7

ACTIVE HEAD LIFTING IN SUPINE IN EARLY INFANCY: AN INDICATOR FOR NON-OPTIMAL COGNITIVE OUTCOME IN LATE INFANCY

Ingrid C. van Haastert
Floris Groenendaal
Maria K. van de Waarsenburg
Maria J.C. Eijsermans
Corine Koopman-Esseboom
Marian J. Jongmans
Paul J.M. Helders
Linda S. de Vries

Submitted

ABSTRACT

Aim: To explore whether active head lifting in supine (AHLS) in early infancy is associated with cognitive outcome in late infancy.

Method: Data for this case-control study was collected by reviewing hospital charts. Random sampling was used to pair cases with two controls whose gender, gestational age, birth year (1993-2009), time of assessment and developmental test were comparable. Neonatal cranial ultrasound (cUS) scans were classified as no-mild or moderate-severe brain injury. Z-scores of cognitive test outcomes were calculated for multivariable analysis.

Results: 87 preterm and 40 full-term born cases were identified. AHLS was associated with cognition in preterm and full-term infants (p .002 and p .004 respectively). This association remained after excluding infants with cerebral palsy (CP) with matching controls (p .001 and p .000 respectively). Preterm and full-term cases with moderate-severe brain injury on cUS scored lower compared to controls only when CP infants were included (p .002 and p .001 respectively).

Interpretation: AHLS is associated with an adverse cognitive outcome in the second year of life in preterm as well as in full-term born cases compared with controls.

INTRODUCTION

One of the objectives of neonatal follow-up (FU) is assessment of the development of high-risk preterm and full-term born infants and children, who are discharged from the neonatal intensive care unit (NICU). Observation of spontaneous motor behaviour is an important part of such an out-patient assessment.

One example of spontaneous motor behaviour of an infant that can be easily observed during the first year of life, particularly between 3-9 months of (corrected) age, is active head lifting in supine (AHLS). Throughout the years, we recognized this behaviour and wondered whether there could be a relationship between AHLS in early infancy and cognitive outcome.

The possible association with cognitive outcome was suggested by a suboptimal behavioural performance at the time of AHLS and became apparent during the FU into late infancy. While AHLS may occasionally be seen in healthy infants, AHLS observed in our cases occurred immediately when the infant was put in a supine position and tended to be sustained for long periods of time. Although postural reactions to hands-on manoeuvres like traction and vertical and horizontal suspension have been described as diagnostically relevant[1], AHLS as an example of spontaneous generated activity has, to the best of our knowledge, never been described.

When AHLS is seen as part of the spontaneous motor repertoire of an infant, this behaviour can offer information which may alert clinicians (e.g. paediatricians, child health clinicians, paediatric neurologists and paediatric physical therapists) to follow the child more carefully.

The aim of this study is to explore whether AHLS in early infancy is associated with adverse cognitive development in late infancy.

METHODS

Design

In this retrospective case-control study, random sampling was used to pair infants with AHLS with two infants without AHLS whose gender, gestational age (GA), birth year, time of assessment and developmental

test used were comparable to the cases. For this type of study, no informed consent or permission from the Internal Review Board is required in our hospital.

Participants

Infants were born between April 1993 and December 2009 and recruited from the neonatal FU program. In this program, the (neuromotor) development of preterm and full-term born infants, discharged from our level three NICU is assessed by experienced developmental specialists usually until 5.5 years of age. The presence of AHLS was always separately recorded in the notes.

Measurements

Small for GA (SGA) is defined as a birth weight (BW) percentile <10. BW percentiles were determined according to the data of the Perinatal Registry of the Netherlands.[2]

Sequential cranial ultrasound (cUS) examinations were performed in all infants during their stay in the NICU and a repeat cUS during the first visit at our neonatal FU clinic (i.e. at term-equivalent age in infants born preterm and at three months of age in infants born full-term). CUS examinations were classified into two categories: 0=no or mild brain injury (*preterm*: germinal layer haemorrhage, intraventricular haemorrhage grade II, periventricular leukomalacia grade I; *full-term*: punctate white matter lesions) and 1=moderate (*preterm*: intraventricular haemorrhage grade III or cystic periventricular leukomalacia grade II; *full-term*: watershed injury or focal infarct) or severe brain injury (*preterm*: unilateral parenchymal haemorrhage, cystic periventricular leukomalacia grade III or cerebral artery infarction; *full-term*: basal ganglia/thalamic injury or large stroke).

Motor development in the first year of life was assessed by observation and assessment of the spontaneous general movement repertoire, postures and postural reactions by use of the motor assessment of the developing infant, according to Alberta Infant Motor Scale, and passive and active muscle tone and responses to deliberately elicited primitive reflexes according to Amiel-Tison.[3-5]

AHLS is characterized by spontaneous and sustained head lifting in supine position while mostly simultaneously extending and adducting the lower extremities free from the surface, often with plantar flexion in the ankles and grasping of the toes. The upper extremities may show variable postures or movements. (Figure 1) When present, AHLS is usually seen immediately once the infant is put in a supine position.

Figure 1 Active head lifting in supine with simultaneous lifting of the lower extremities in extension, adduction, plantar flexion of the ankles and grasping of the toes.

To determine cognitive outcome in the second year of life, either the Griffiths Mental Development Scales (GMDS), the Mental Scale of the Bayley Scales of Infant Development-second edition, Dutch version (BSID-II-NL) or the Cognitive subtest of the Bayley Scales of Infant and Toddler Development-third edition (BSITD-III) were administered.[6-8] Prior to 2003, all children up to two years of age were assessed by use of the GMDS, consisting of five subscales: the locomotor, personal-social, hearing and speech, eye-hand coordination, and performance scale. Information can be obtained by testing or direct observation of the performance of the child. In addition to quotients derived from the subscales, an overall developmental quotient (DQ) and a Z-score can be calculated.

The mean DQ and standard deviation (SD) for the general population is 100 (±12).[6] From 2003 onwards, the BSID-II-NL was used for children with a GA <30 weeks or a BW <1000 grams at 24 months corrected age (CA) and from March 2008 onwards the BSITD-III. All others were assessed by use of the GMDS. Items within the Mental Scale of the BSID-II-NL are related to memory and object permanence, problem solving, perceptual organization, number concepts, language and sociability.[7] The Cognitive subtest of the BSITD-III 'includes items that assess sensorimotor development, exploration and manipulation, object relatedness, concept formation, memory, and other aspects of cognitive processing'.[8] Raw scores of the BSID-II-NL were converted into a mental development index (MDI) and of the BSITD-III into a composite score (CS). Z-scores were also calculated. The mean (SD) in the normal population for the Mental Scale and for the Cognitive subtest is 100 (±15). Normative values for the Dutch population are not yet available for the BSITD-III.

Statistical analysis

Data were analyzed by use of SPSS software (Predictive Analytics SoftWare Statistics 17.0). T-tests were performed for continuous variables, and chi-square tests for categorical variables. A *p*-value <.05 was considered significant. Multivariable analysis using general linear modelling was performed of Z-scores of cognitive test outcomes as the dependent variable and AHLS, GA, BW (SGA or AGA) and cUS abnormalities as co-variants.

RESULTS

In total, 127 cases were identified: 87 preterm and 40 full-term born infants, and for each case two control subjects were selected. Characteristics of the preterm and full-term born sample are presented in Table I.

Table I Characteristics of **preterm** (*n*=261) and **full-term** (*n*=120) infants with and without AHLS

	Male			Female			Total sample		
	case	control	*p*	case	control	*p*	case	control	*p*
Preterm (***n***)	34	68		53	106		87	174	
GA in weeks mean (SD)	31.0 (2.6)	30.9 (2.6)	ns	30.2 (2.3)	30.3 (2.2)	ns	30.5 (2.4)	30.6 (2.4)	ns
BW in grams mean (SD)	1595 (594)	1670 (560)	ns	1310 (429)	1381 (469)	ns	1423 (514)	1494 (524)	ns
CA (mo) AHLS mean (SD)	7.4 (1.8)	6.8 (1.1)	.046	7.2 (2.0)	6.9 (1.7)	ns	7.3 (2.0)	6.9 (1.5)	ns
CHR age (mo) AHLS mean (SD)	9.5 (2.0)	8.8 (1.1)	ns	9.4 (2.1)	9.2 (1.8)	ns	9.5 (2.1)	9.0 (1.6)	ns
SGA, n (%)	5 (14.7)	0 (0)	.005	5 (9.4)	0 (0)	.005	10 (11.5)	0 (0)	.000
cUS, n (%)	5 (14.7)	1 (1.5)	.015	10 (18.9)	4 (3.8)	.003	15 (17.2)	5 (2.9)	.000
CP, n (%)	3 (8.8)	0 (0)	.035	3 (5.7)	0 (0)	.036	6 (6.9)	0 (0)	.001
Full-term (***n***)	17	34		23	46		40	80	
GA in weeks mean (SD)	40.1 (1.6)	40.2 (1.6)	ns	40.1 (1.7)	40.2 (1.6)	ns	40.1 (1.7)	40.2 (1.6)	ns
BW in grams mean (SD)	3298 (831)	3557 (421)	ns	3442 (680)	3525 (484)	ns	3468 (742)	3539 (456)	ns
Age (mo) AHLS mean (SD)	8.5 (2.3)	8.8 (1.8)	ns	7.2 (2.2)	8.2 (2.3)	ns	7.5 (2.2)	8.4 (2.1)	.03
SGA, n (%)	6 (35.3)	0 (0)	.001	4 (17.4)	1 (2.2)	.039	10 (25)	1 (1.3)	.000
cUS, n (%)	10 (58.8)	1 (3)*	.000	7 (30.4)	1 (2.2)	.001	17 (42.5)	2 (2.6)	.000
CP, n (%)	3 (17.6)	0 (0)	.033	5 (21.7)	0 (0)	.003	8 (20)	0 (0)	.000

AHLS, active head lifting in supine; GA, gestational age; SD, standard deviation; ns, not significant; BW, birth weight; CA, corrected age on which AHLS was observed or not; CHR age, chronological age on which AHLS was observed or not; mo, months; SGA, small for GA; cUS, cranial ultrasound, moderate or severe abnormalities; *, cUS of one control is missing; CP, cerebral palsy.

Preterm born infants

Slightly more female (60.9%) than male cases were identified. The mean (SD) GA of cases and controls combined (n=261) was 30.6 (±2.4) weeks and the mean BW 1470 (±521) gram. About half of all infants were delivered by Caesarean section (49.4%) and 85.1% was singleton. There were no statistical differences between proportion of *cases* and *controls* for the total sample and sub samples regarding these variables. AHLS was most often observed during the second FU visit at a mean (SD) CA of 7 months (±1.7) and at a mean (SD) chronological age of 9.2 months (±1.7).

At T1 (mean 15.7mo CA, SD 1.7, *n*=261), all but one infant were assessed by use of the GMDS, and at T2 (mean 23.9mo CA, SD 1.6, *n*=207), children were assessed by use of the GMDS (*n*=151), the BSID-II-NL (*n*=37) and the BSITD-III (*n*=19).

Z-scores of *cases* differed significantly from *controls* for the total sample with regard to neurodevelopmental outcome (mean difference .40 SD, *p* .004) at T1, as well as at T2 (mean difference .58 SD, *p* .000, see Table II). Male *cases* differed significantly from male *controls* (mean difference .58 SD, *p* .023) at T1, as well as at T2 (mean difference .94 SD, *p* .000, see Table II and Figure 2). Female *cases* differed significantly from female *controls* (mean difference .35 SD, *p* .031) only at T2.

For 242/261 (93%) infants, data regarding feet playing during the second FU visit was available: more infants *without* AHLS played with their feet compared to those *with* AHLS (68% versus 61%), but this did not reach statistical significance. The opposite applied for rolling from supine to prone. For 260/261 (99.6%) infants, data was available: more infants *with* than *without* AHLS rolled over (66% versus 62%), but there was no significant difference between *cases* and *controls*. Data regarding independent walking was available for 237/261 (90.8%). Infants *without* AHLS (*n*=160) walked one month earlier on average than infants *with* AHLS (*n*=77): mean (SD) 15 months (±3) and 16 months (±4) CA respectively, but the difference did not reach statistical significance.

Table II Outcome of **preterm** (*n*=261) and **full-term** (*n*=120) born infants with and without AHLS

	Male			Female			Total sample		
	case	control	*p*	case	control	*p*	case	control	*p*
Preterm									
T1 (*n*)	34	68		52*	106		86*	174	
CA in months mean (SD)	15.3 (1.9)	15.4 (1.6)	ns	16.1 (1.9)	15.7 (1.5)	ns	15.8 (1.9)	15.6 (1.6)	ns
DQ mean (SD)	100 (16)	107 (8)	.023	103 (12)	106 (9)	ns	102 (14)	106 (9)	.004
Z-score mean (SD)	-.03 (1.36)	.55 (.66)	.023	.25 (1.0)	.53 (.76)	ns	.14 (1.15)	.54 (.72)	.004
T2 (*n*)	28	56		41	82		69	138	
CA in months mean (SD)	23.5 (2.4)	23.8 (1.7)	ns	24.1 (1.8)	24.1 (0.9)	ns	23.8 (2.1)	24.0 (1.3)	ns
Z-score mean (SD)	-.54 (1.14)	.40 (.81)	.000	-.09 (.92)	.26 (.76)	.031	-.27 (1.03)	.31 (.78)	.000
Full-term (*n*)	17	34		23	46		40	80	
Age in months mean (SD)	20.1 (2.6)	19.4 (2.4)	ns	18.9 (2.3)	18.6 (1.8)	ns	19.5 (2.5)	19.0 (2.2)	ns
DQ mean (SD)	91 (15)	107 (8)	.001	98 (16)	110 (9)	.000	95 (16)	109 (8)	.000
Z-score mean (SD)	-.77 (1.3)	.58 (.63)	.001	-.19 (1.3)	.82 (.73)	.000	-.44 (1.3)	.72 (.69)	.000

AHLS, active head lifting in supine; *, one female case was too ill to be tested during the FU visit; CA, corrected age; SD, standard deviation; DQ, developmental quotient.

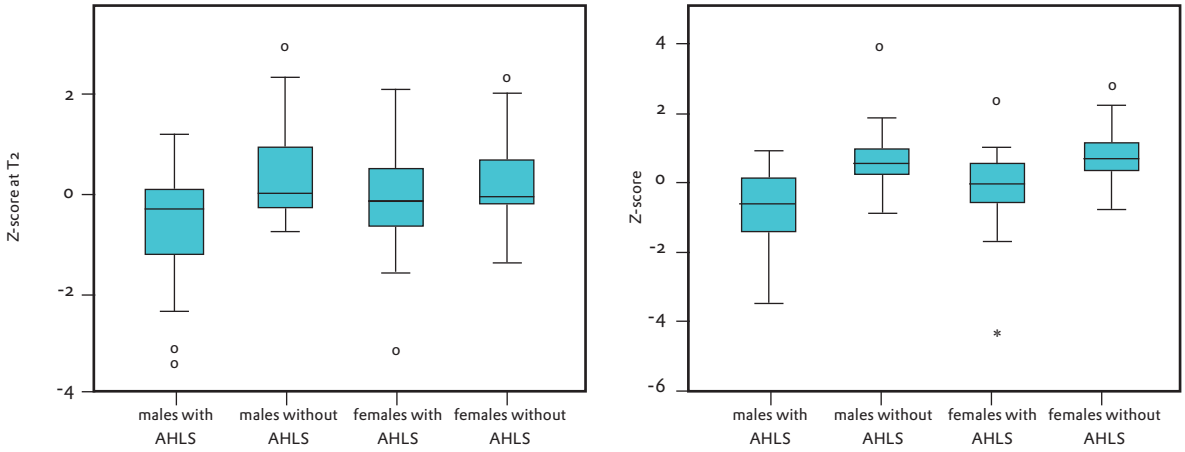

Figure 2 Z-scores of 207 preterm infants at 24 months CA (left) and 120 full-term infants at 19 months (right) with and without AHLS.

Z-scores are based on scores of the Griffiths Mental Development Scales, the Bayley Scales of Infant Development second (Dutch) version and the Bayley Scales of Infant and Toddler Development third version; AHLS, active head lifting in supine; CA, corrected age for degree of prematurity. The circles (cases) represent outliers (1.5-3 inter quartile distance from the box), the asterisk an extreme (IQR >3). Preterm male *cases* differ significantly from male *controls (p .000)*; full-term male *cases* differ significantly from male controls (*p* .000) and full-term female *cases* differ significantly from female controls (*p* .000).

Full-term born infants

Again, slightly more female (57.5%) than male cases were identified. The mean (SD) GA of cases and controls combined (*n*=120) was 40.1 (±1.6) weeks and the mean BW 3468 (±574) gram. Almost one third of the infants was born by Caesarean section (31.7%) and 98.3% was singleton. AHLS was most often observed during the second FU visit at a mean (SD) age of 8.1 (±2.2) months. For the total full-term sample, the mean age at FU of infants in whom AHLS was observed was significantly lower than of controls (mean difference 0.9 months). (Table I) However, this did not apply to the sub samples of full-term males and females. Data regarding feet playing during the second FU visit was available for 78/120 (65%) infants: more infants *without* AHLS played with their feet compared to those *with* AHLS (80% versus 71%), but this did not reach statistical significance. There was however a significant difference in rolling from supine to prone: for 105/120 (87.5%) data was available. Almost all infants *without* AHLS rolled over compared to infants *with* AHLS (97% versus 69%, *p* .000). Data regarding independent walking was available for 105/120 (87.5%) infants. Infants *without* AHLS (*n*=70) walked three months earlier on average than infants *with* AHLS (*n*=30): mean (SD) 14 months (±2) and 17 months (±5) respectively, *p* .002.

The GMDS was administered at a mean age of 19.1 months (SD 2.3). Z-scores of *cases* differed significantly from *controls* for the total sample with regard to neurodevelopmental outcome (mean difference 1.15 SD, *p* .000). See Table II. The mean difference between male *cases* and male *controls* is 1.34 SD (*p* .000) and between female *cases* and female *controls* 1.02 SD (*p* .000). See Table II, and Figure 2.

Multivariable analysis

Multivariable analysis showed that AHLS and cUS were independently associated with cognitive test outcomes at a mean age of 24 months CA in infants born preterm, and at a mean age of 19 months in infants born full-term. (Table III)

Table III Predictors of cognitive outcome (based on Z-scores) for **preterm** infants (n=207) at 2 years CA and full-term **infants** (n=120) at 19 months using multivariable analysis

	B	SE	Sign.	95% C.I.	
Preterm					
Constant	.34	.07	.000	.20	.48
AHLS	-.42	.13	.002	-.68	-.16
cUS-2	-.70	.22	.002	-1.14	-.26
Full-term					
Constant	.75	.10	.000	.55	.95
AHLS	-.65	.22	.004	-1.09	-.22
cUS-2	-.92	.27	.001	-1.44	-.40

CA, corrected age; B, coefficient; SE, standard error; CI, confidence interval; AHLS, active head lifting in supine (0 = no; 1 = yes); cUS-2, cranial ultra sound scans in 2 categories (0 = no or mild, 1 = moderate or severe brain injury).

Because 6 preterm born *cases* were later diagnosed to have cerebral palsy (CP), the same analysis was performed excluding CP *cases* with matching *controls*. AHLS remained associated with cognitive outcome (p .001), whereas cUS did not reach statistical significance anymore (p .051). Likewise, we repeated the analysis with the full-term born sample where 8 *cases* were later diagnosed to have CP. Again, AHLS remained associated with cognitive outcome (p .000) but cUS did not reach statistical significance anymore (p .12).

DISCUSSION

AHLS in early infancy appears to be associated with an adverse cognitive outcome in the second year of life compared to infants who do not show this phenomenon. This applies to preterm as well as to full-term born infants and supports our hypothesis. The action seems not goal-directed and is stereotype. In addition, the full-term infant with AHLS is less inclined to roll over from supine to prone, and starts to walk independently at a later age. Moreover, AHLS is often sustained and repeated time and time again by the infant when lying in supine. The infant seems unable to use other movement strategies during supine lying or to move out of this position. It is our experience that parents interpret AHLS as the intention of their child to come to a sitting position, tend to be proud of the strong abdominal muscles of their child or interpret AHLS as being an expression of curiosity.

We do not know of any explanation for the underlying mechanism or neural substrate for this behaviour. Transitions from variable, non-adaptive behaviour to adaptive selection strategies occur at specific ages for different motor functions.[9] Interestingly, AHLS is most often observed during the second to third trimester of the first year of life, the same period in which 'selection of the most efficient postural adjustment in which all direction-specific neck, trunk, and proximal leg muscles are activated' occurs according to Hadders-Algra.[10] One can speculate about the potential influences of factors associated with the environment, parent-infant interactions and the neuronal development related to AHLS. It is possible that an infant is curious to see what is happening in his environment and in the absence of other motor strategies uses AHLS in supine to interact socially. De Groot postulated that the influence of the environment and spontaneous motility both play an important role in the fine-tuning of postural control.[11] As such, stereotypic postural control in early infancy may interfere with further motor development, social interactions and later cognitive development. Although there is not much evidence about the influence of positioning while awake on motor development, AHLS may result from too much time spent in supine position or in a device like an infant seat, with fewer possibilities to

experience a variety of play positions and motor strategies.[12-14] Besides, parents may have the habit during daily activities and care giving practices, to pull the infant from supine to a sitting position by taking the infant by both hands. Until now, we have no exact information about these aspects.

Another assumption is that AHLS is based on reduced cerebral connectivity due to diffuse or overt brain injury and that this stereotypic behaviour is 'the motor correlate of impaired cognitive function'.[15, 16] The present study shows that not only AHLS made a unique contribution to the prediction of a poorer cognitive outcome in the second year of life in preterm and full-term born cases with controls, but also moderate or severe cUS abnormalities when infants with CP were included. No interaction between these and the other aforementioned variables could be detected in the analyses.

Mc Phillips showed 'how the educational functioning of children may be linked to interference from an early neurodevelopmental system (the primary-reflex system)'. The symmetrical tonic neck reflex is one of the more than 70 reflexes known within the primary-reflex system which can be normally observed between 4-6 months of age.[17, 18] AHLS partly mirrors the symmetrical tonic neck reflex at which infants not only show flexion of the head but also extension of the legs, often combined with plantar flexion in the ankles and a tendency to adduct the feet or crossing them as we show in Figure 1. However, the position of the upper extremities may be variable.

A limitation of this study is that it is retrospective and that we only used information that was available to us. As the infants were seen at either 6 months CA (preterm) or at 9 months (full-term), we cannot exclude the possibility that AHLS was more common than noted by us. It would be interesting to follow infants with AHLS longitudinally in a prospective study. Another limitation is that the GMDS and BSITD-III are not yet standardized for Dutch children.[6, 8] Judging the results of the preterm born *control subjects* on the GMDS, BSID-II-NL and BSITD-III, it is noteworthy that although the start of life of these infants was not optimal, the mean values corrected for the degree of prematurity were higher than expected at T1 as well as at T2, with the mean DQs and Z-scores well above the normative mean and the SD lower than the norm values (Table II and III).

This applied also to the full-term born *control* subjects. The question whether normative values for cognitive development in the general Dutch population are different from other populations has not been answered yet.[6, 8] However, our findings are in accordance with Anderson *et al.*, who compared the results on the BSITD-III of extremely preterm, low BW infants with term born infants with a normal BW and detected higher mean values than expected for the control group.[19]

It is challenging to unravel the underlying mechanism or neural substrate of AHLS. In the meantime, parents should be provided with information on how to handle and position their child. Children who show AHLS, especially those with moderate to severe cUS abnormalities, need a long-lasting FU to detect possible special needs in time. Whether or not an intervention program may be beneficial to improve the cognitive development of a child who showed AHLS in early infancy remains to be seen. A systematic review and meta-analysis by Orton *et al*., could not detect long-term benefits in cognitive outcome of developmental intervention programs for preterm born infants.[20] Koldewijn *et al*. showed in a multicenter, randomized, controlled trial in which parents of 83 very low BW infants received a post-discharge intervention program, that groups did not differ on the MDI and other variables at 24 months CA. However, subgroup analyses revealed that motor and mental outcomes of intervention infants with bronchopulmonary dysplasia and with combined biological and social risk factors, improved.[21]

In future studies, healthy full-term control subjects can be recruited from an obstetric or well-baby clinic and, in case of more mature preterm infants with AHLS, from a level two or community hospital.

In conclusion, this study provides provisional evidence of a relation between AHLS in early infancy and subsequent consequences for cognitive outcome in late infancy, an interference that may result from an underlying developmental deficit. Within the present study, AHLS in early infancy was significantly associated with an adverse cognitive outcome in the second year of life, in preterm as well as full-term born infants.

Acknowledgments

We are grateful to Lidian F. Sinnecker, bachelor of medicine, who performed some of the data collection and Mrs. I. Janssen, technical draughtswoman, who created the drawing of an infant who actively lifts his head in supine.

REFERENCES

1 Zafeiriou DI. Primitive reflexes and postural reactions in the neurodevelopmental examination. *Pediatr Neurol*. 2004;31:1-8

2 The Netherlands Perinatal Registry. Birth weight centiles and SD. www.perinatreg.nl 2001.

3 Einspieler C, Prechtl HF. Prechtl's assessment of general movements: a diagnostic tool for the functional assessment of the young nervous system. *Ment Retard Dev Disabil Res Rev*. 2005;11:61-67.

4 Piper MC, Darrah J. *Motor assessment of the developing infant.* Philadelphia, USA: W.B.Saunders; 1994.

5 Amiel-Tison A, Grenier A. *Neurological assessment during the first year of life.* New York, USA: Oxford University Press; 1986.

6 Griffiths R. *The Abilities of Young Children. A Comprehensive System of mental Measurement for the First Eight Years of Life.* London, UK: The test agency Ltd; 1984.

7 Van der Meulen BF, Ruiter SAJ, Lutje Spelberg HC, Smrkovsky M. *BSID-II-NL, Dutch Manual*. Lisse, The Netherlands: Swets Test Publishers; 2002.

8 Bayley N. *Bayley Scales of Infant and Toddler Development*. San Antonio,TX, USA: Harcourt Assessment, Inc; 2006.

9 Heineman KR, Middelburg KJ, Hadders-Algra M. Development of adaptive motor behaviour in typically developing infants. *Acta Paediatr*. 2010;99:618-624.

10 Hadders-Algra M. The neuronal group selection theory: promising principles for understanding and treating developmental motor disorders. *Dev Med Child Neurol*. 2000;42:707-715.

11 De Groot L. Posture and motility in preterm infants. *Dev Med Child Neurol*. 2000;42:65-68.

12 Bartlett DJ, Kneale Fanning JE. Relationships of equipment use and play positions to motor development at eight months corrected age of infants born preterm. *Pediatr Phys Ther*. 2003;15:8-15.

13 Fetters L, Huang HH. Motor development and sleep, play, and feeding positions in very-low-birthweight infants with and without white matter disease. *Dev Med Child Neurol*. 2007;49:807-813.

14 Majnemer A, Barr RG. Influence of supine sleep positioning on early motor milestone acquisition. *Dev Med Child Neurol*. 2005;47:370-376.

15 Hadders-Algra M. Reduced variability in motor behaviour: an indicator of impaired cerebral connectivity? *Early Hum Dev*. 2008;84:787-789.

16 Hadders-Algra M. Variation and variability: key words in human motor development. *Phys Ther*. 2010;90:1823-1837.

17 McPhillips M, Hepper PG, Mulhern G. Effects of replicating primary-reflex movements on specific reading difficulties in children: a randomised, double-blind, controlled trial. *Lancet*. 2000;355:537-541.

18 McPhillips M, Sheehy N. Prevalence of persistent primary reflexes and motor problems in children with reading difficulties. *Dyslexia*. 2004;10:316-338.

19 Anderson PJ, De Luca CR, Hutchinson E, Roberts G, Doyle LW. Underestimation of developmental delay by the new Bayley-III Scale. *Arch Pediatr Adolesc Med*. 2010;164:352-356.

20 Orton J, Spittle A, Doyle L, Anderson P, Boyd R. Do early intervention programmes improve cognitive and motor outcomes for preterm infants after discharge? A systematic review. *Dev Med Child Neurol*. 2009;51:851-859.

21 Koldewijn K, van Wassenaer A, Wolf MJ et al. A neurobehavioral intervention and assessment program in very low birth weight infants: outcome at 24 months. J Pediatr.2010;156:359-365.

Summary, general discussion and directions for future research

Part 4

Chapter 8

SUMMARY GENERAL DISCUSSION AND CONCLUSION

SUMMARY

The studies in this thesis are the result of many years of work in the neonatal follow-up (FU) outpatient clinic in which we provide care for infants and children that had to be admitted to the neonatal intensive care unit (NICU) of the Wilhelmina Children's Hospital in Utrecht, the Netherlands because they were born too soon or at term with difficulties before, during or soon after birth.
The main aim of this thesis was to obtain answers to certain questions that arose during the FU sessions of hundreds of so-called 'NICU graduates'. This thesis describes the typical and a-typical neuromotor developmental course and outcome of these children.

Chapter 1 serves as an introduction for the thesis in which we give a global overview of 20 years of neonatal FU and the aims and outline of the study. This chapter focuses on the FU schedules in our outpatient clinic, the different neurological and neuromotor assessment tools and neuro-imaging techniques which were used and on which we built our knowledge, experience and clinical view.

In **Part I, Chapter 2**, we examined the results on the Alberta Infant Motor Scale (AIMS) in a cross-sectional study of 800 infants born preterm with a gestational age (GA) ≤32 weeks from December 1993 to November 2005. The infants were between 1–19 months of age corrected for the degree of prematurity (CA). At all age levels, the AIMS scores were significantly lower compared to the norm-referenced values of infants born full-term, a finding that has implications for decision-making whether or not developmental intervention or treatment is justified. If the norm-referenced values would be used to determine the outcome of infants born preterm, there is a real chance that the AIMS score will be in the abnormal range and the decision of the professional may be that an infant needs developmental intervention. However, to select those who may benefit from a developmental intervention, the following procedure is recommended: when the result is below the 5th percentile according to the norms of infants born full-term, one should turn to the norms of the

preterm sample presented in this study. Is the result then below the 25th percentile, the infant may need careful attention and developmental intervention like paediatric physical therapy.
This study provides evidence for the existence of specific early motor developmental trajectories of infants born preterm. They exhibit a different trajectory in their gross motor development in the first 18 months of life compared to full-term infants.
Although our results can not be generalized to all preterm born infants, it is possible that the gross motor developmental pathway shown by infants born preterm is characteristic for this population, reflecting a variant of typical gross motor development.
This implies that standard gross motor developmental scales used for full-term infants, should be adjusted to enable proper evaluation and clinical decision-making in relation to preterm infants.

In **Part II, Chapter 3**, we evaluated whether sequential high-quality cranial ultrasonography (cUS) in 2139 high-risk preterm infants born between January 1990 and January 1999 could predict cerebral palsy (CP) at the age of at least 24 months. The cohort was divided in two groups: A) 1636 children with a GA ≤32 weeks and B) 503 children with a GA 33–36 weeks.
Soon after admission to the NICU, cUS examinations were performed at least once a week until discharge and again at 40 weeks postmenstrual age. Grade III and IV haemorrhage, cystic periventricular leukomalacia (c-PVL) and focal infarction were considered major cUS abnormalities.
In group A, 76/1460 (5%) survivors developed CP. In 70/76 (92%) children with development of CP, cUS abnormalities were present: 58/70 (83%) had major and 12/70 (17%) minor cUS abnormalities. No cUS abnormalities were detected in 6/76 (8%) children with CP of which 3 developed ataxic CP. In 17/58 (29%) of the CP cases with major cUS abnormalities, cysts were first detected beyond day 28 after birth.
In group B, 29/469 (6%) survivors developed CP. In 28/29 (96%) children with CP, cUS abnormalities were present: 25/28 (89%) had major and 3/28 (11%) minor cUS abnormalities. One child with CP did not have cUS abnormalities. In this group, none of the infants presented with major cUS abnormalities beyond day 28.

Altogether, 83/105 (79%) children with a development of CP in both groups had major cUS abnormalities. To detect c-PVL, it is of utmost importance to examine infants born with a GA ≤32 weeks also beyond 4 weeks after birth and at 40 weeks postmenstrual age.

In **Part II, Chapter 4** (a review), we aimed to refute the myth that CP cannot be predicted by neonatal brain imaging in neonates when combining sequential cUS with conventional magnetic resonance imaging (MRI) at term-equivalent age (TEA) in the preterm infant, and when using first week MRI including diffusion-weighted imaging (DWI) in the term infant.

In the preterm infant, there is agreement about the predictive accuracy of persistent normal cUS for a normal outcome, whereas major intracranial lesions (haemorrhagic parenchymal infarction and c-PVL) will predict those with non-ambulatory CP. MRI at TEA will refine the prediction of CP by assessment of myelination of the posterior limb of the internal capsule in those diagnosed with haemorrhagic parenchymal infarction, middle cerebral artery stroke or extensive, bilateral c-PVL. Prediction of motor outcome in preterm infants with subtle white matter injury remains difficult, even with conventional MRI.

In the term infant with hypoxic-ischaemic encephalopathy (HIE) or perinatal arterial ischaemic stroke, MRI techniques are effective tools to predict CP. Two main patterns of injury can be detected: injury to the basal ganglia and thalamus following acute, near-total asphyxia, and changes of the white matter following chronic, subacute asphyxia. DWI, as an additional sequence, is able to visualize HIE lesions as early as the first day of life and adds to the predictive value for motor outcome.

Sequential and dedicated neuro imaging for a sufficient length of time should enable us to predict motor outcome in high-risk newborns infants, as long as timing of imaging is taken into account and experienced examiners perform interpretation of the images.

In **Part III, Chapter 5**, we examined the impact of periventricular leukomalacia (PVL) on gross motor functional abilities longitudinally, by use of the Gross Motor Function Classification System (GMFCS) in 59 children with CP (37 males, 22 females) born between 1990 and 2004 with a GA ≤34 weeks. Twenty children were diagnosed with PVL grade I, 13 with PVL grade II, 25 with PVL grade III, and one child with PVL grade IV. GMFCS levels were determined at four timepoints: at T1, mean CA 9 months 15 days (SD 2mo 6d); T2, mean CA 16 months (SD 1mo 27d); T3, mean CA 24 months 27 days (SD 2mo 3d) and at T4, median age 7 years 6 months (range 2y 2mo–16y 8mo).

The gross motor abilities vary depending on the severity of PVL. Most infants with PVL grade III and IV were never classified in GMFCS Levels II or I and therefore, did not achieve the potential to walk independently. This is in contrast with children with PVL grade I, and to a lesser extent PVL grade II, where most of the children were able to walk.

The use of the GMFCS in children with PVL grade I yielded less consistent results before 2 years of age. However, children initially classified in the extreme levels (I and V) were least likely to be reclassified. Stability of gross motor function, as expressed by GMFCS levels, became more robust after the first year of age. The proportion of children who remained in the same GMFCS level increased from 27% (T1–T4) to 53% (T2–T4) and 72% (T3–T4). The association between PVL and gross motor outcome at T4 was strong (positive and negative predictive values 0.92 and 0.85 respectively). PVL grade I to II has a better functional mobility prognosis than PVL grade III–IV.

These findings have implications for habilitation counselling and intervention strategies.

In **Part III, Chapter 6**, we examined the incidence and severity of CP and associated factors among preterm survivors (GA <34 weeks, admitted to the NICU within 4 days after birth) from 1990-2005. The cohort was divided in four birth periods: 1990–1993 (n = 661), 1994–1997 (n = 726), 1998–2001 (n = 723), and 2002–2005 (n = 850).

Eighteen antenatal, perinatal and postnatal factors were analyzed. The GMFCS was used as primary outcome measure at a mean age of 32.9 (SD 5.3) months.

Of a total of 3816 admitted newborns, 3287 (86.1%) were eligible for the study but 327 (9.9%) infants died. The 102/2960 (3.4%) children who developed CP differed in several antenatal and postnatal factors from those with no CP. Unilateral spastic CP was present in 37.25% (n = 38), bilateral spastic CP with more involvement of the lower extremities in 50% (n = 51) and bilateral spastic CP with equally distributed spasticity in the limbs in 12.75% (n = 13).

CP incidence decreased from 6.5% in period I, to 2.6%, 2.9% and 2.2% (p <.001) in period II–IV, respectively. Simultaneously, cystic periventricular leukomalacia (c-PVL grade II and III) decreased from 3.3% in period I to 1.3% in period IV (p = .004). Within the total cohort (including infants who died), c-PVL grade III decreased from 2.3% in period I to 0.2% in period IV (p = .003).

The number of children with GMFCS levels III–V decreased from period I to IV (p = .035). Overall, 19/51 children with c-PVL grade II and III did not develop CP: 5/21 (23.8%) in period I, 3/12 (25%) in period II, 3/7 (42.9%) in period III and 8/11 (72.7%) in period IV. In period I, 10/17 (58.8%) children classified in GMFCS level III–V had c-PVL grade III, whereas in period II–IV this applied to 7/9 (77.8%) children.

Severe CP declined from 17/661 (2.6%) survivors in period I to 2/850 (0.2%) in period IV which is a decrease of 92%; simultaneously, c-PVL grade III declined from 10/661 (1.5%) survivors to 1/850 (0.1%) which is a decrease of 93%.

Independent risk factors for CP were c-PVL and severe intraventricular haemorrhage, whereas antenatal antibiotics, Caesarean section, increasing GA and presence of an arterial line were independent protective factors.
Independent association of c-PVL with CP revealed a significant interaction with a composite 'pulmonary' score (need for surfactant or mechanical ventilation or mechanical ventilation >7 days) of neonates (p <.001).

In **Part III, Chapter 7**, a retrospective case-control study, we examined whether active head lifting in supine (AHLS) in early infancy is associated with cognitive development in late infancy and whether there are associated factors during the period 1993–2009.
Random sampling was used to pair infants with AHLS with two counterparts without AHLS whose gender, gestational age, birth year, time of assessment and developmental test used were comparable to the cases. Neonatal cUS scans were classified into two categories: no or mild, and moderate or severe brain injury. Z-scores of cognitive test outcomes were calculated for multivariable analysis.
In total, 127 cases were identified: 87 were preterm and 40 full-term born infants. AHLS was associated with cognitive outcome. Both infants born preterm as well as full-term with AHLS showed a lower cognitive score compared to their counterparts without AHLS (p .002 and p .004 respectively). This association remained significant after excluding infants with cerebral palsy (CP) with matching controls (p .001 and p .000 respectively). Preterm and full-term *cases* with moderate or severe brain injury on cUS scored lower compared to *controls* only when CP infants were included (p .002 and p .001 respectively).
AHLS in particular made a clear contribution to the prediction of an adverse cognitive outcome in the second year of life in preterm as well as in full-term born *cases* compared with *controls*. Therefore, AHLS can be used as an early marker for non-optimal cognitive development.

GENERAL DISCUSSION

From methodical thinking to pattern recognition

In the early seventies, there were no validated and reliable tools available to measure motor function and motor development, only methods that focused on a specific problem (neurological, muscular, bones and joints, and organs). One example of these methods is the widespread concept of Dr. Karel Bobath (psychiatrist and neurophysiologist, 1906-1991) and his spouse Bertha Bobath (physical therapist, 1907-1991) who developed their own method to assess and treat children with CP and other developmental disorders.[1,2]

From the early nineties, the number of measurement tools grew gradually, leading to more systematic and problem oriented working, and supporting the development and improvement of our pattern recognition system. One of these assessment tools, the AIMS, focuses on gross motor maturation of an infant.[3,4] Using the AIMS, the examiner is forced to observe the gross motor repertoire of an infant very carefully, keeping hands off. By doing so and noting the scores consistently, we discovered that the gross motor maturity of infants born preterm (GA ≤32 weeks) proceeds quite different and at a slower pace in the first 1.5 years of life compared to infants born full-term.[5,6] The different motor trajectory these infants show made us realize that it is not fair to judge their gross motor developmental course against the norms of infants born full-term. Therefore we are convinced that appropriate and adjusted norms should be used for proper evaluation and clinical decision-making (Part I, Chapter 2).[7,8]

Developing pattern recognition is also an important aspect when examining and interpreting brain images. Interest *in* normal brain development and knowing what is normal and abnormal must go together with looking *at* the brain, by viewing the output of it in real life (Part II, Chapter 3 and 4 and Part III, Chapter 5-7).

Many years ago, it was not unusual that a clinical diagnosis of hemiplegia or diplegia was only detected at the end of the first year of life of an infant, or even later. Parents, who were concerned about the development of

their child, were often reassured by the pediatrician or the doctor at the health clinic. Through the years we learned that the lack of early recognition of these neurological problems is possible in the absence of brain imaging, especially when the imaging of infants born with a GA ≤32 weeks is not continued until TEA. Nowadays, it is unusual for a neurological disorder to remain undetected beyond the first 6 months of life unless the symptoms are very subtle.
What we also learned is that children with a diagnosis of grade II c-PVL tend to have good locomotion possibilities. Besides, knowledge about the time of onset, site and extent of a brain lesion may provide important information about what is to be expected regarding the neurodevelopmental possibilities of an infant. As such, our body of knowledge regarding brain development and associated neuromotor outcome has clearly grown over the years.[9,10]

Advances in neonatal care and technology have given us a lot of opportunities to keep more newborns alive and provide better perspectives for their future. The other side of the coin is that more newborns with a GA <25 weeks are being admitted to and cared for at the NICUs. It remains to be seen what the future holds for these vulnerable infants. According to Allen[11], 'research should be focused on devising neuroprotective strategies and developmental supports that improve the neurodevelopmental and health outcomes of preterm survivors'. Of course, this also applies to full-term born survivors. Only by following these infants very carefully beyond childhood, even into adolescence, we will learn more about their strengths and weaknesses, and trajectories of their developmental courses.[11–22]

CONCLUSIONS

The following conclusions from this thesis can be drawn:

1. At all age levels from 1-19 months CA, the AIMS scores of infants born preterm (GA ≤32 weeks) were significantly lower compared to the norm-referenced values of infants born full-term (Part I, Chapter 2).
2. High-resolution and sequential cUS detected major abnormalities in 83/105 (79%) of preterm born survivors who developed CP. These major abnormalities often only became apparent beyond day 28 after birth (Part II, Chapter 3).
3. Major intracranial lesions can almost always be detected with cUS, provided that the examiner has sufficient experience to obtain good quality images and that the examinations are performed for a sufficient number of weeks. MRI at TEA in infants born preterm will refine the prediction of CP, but prediction of motor outcome in case of subtle white matter injury remains difficult. In the term born infant it is important to take into account the timing of imaging when interpreting the MRI (Part II, Chapter 4).
4. Gross motor abilities vary depending on the severity of PVL. PVL grade I and c-PVL grade II have a better prognosis than c-PVL grade III–IV. Most infants with c-PVL grade III and IV do not have the potential to walk independently. This is in contrast with children with PVL grade I, and to a lesser extent c-PVL grade II, as most of these children were able to walk (Part III, Chapter 5).
5. CP incidence decreased significantly from 1990–2005. Simultaneously, c-PVL decreased significantly, especially grade III. As a result, the number of children functioning in GMFCS levels III-V decreased significantly (Part III, Chapter 6).
6. AHLS in early infancy is associated with an adverse cognitive outcome in late infancy in preterm as well as in full-term born infants and can therefore be used as an early marker for non-optimal cognitive development (Part III, Chapter 7).

DIRECTIONS FOR FUTURE RESEARCH AND CLINICAL PRACTICE

Neuro-imaging

To improve early detection of CP, it is essential that newborns with a GA ≤32 weeks are scanned once a week until discharge and once again at TEA.

Clinical observation

- For neonatal FU practice, it is important that observational and/or measurement tools are simple to administer with minimal handling, not time consuming but valid and reliable. More efforts should be made to see whether adaptation of existing tools for specific groups, like infants born preterm or infants < 2 years of age with development of CP, is possible.
- Observation and appropriate interpretation of general movements of preterm infants at TEA and full-term infants at 3 months of age may be reduced to one movement: actively extension of the legs followed by a smooth actively dorsal flexion in the ankles. It has been our experience that the neurological integrity of the central nervous system in infants who show this pattern appears to be intact. To find evidence for this idea, this phenomenon as part of the movement repertoire of these infants should be registered by recording these early movements and relate these to a motor assessment in early or middle childhood.
- Since prediction of motor outcome, in particular CP remains difficult in case of subtle white matter injury, clinical observation at TEA and at 6 months CA is very important. Reviewing the clinical records in detail of all children who were once diagnosed with PVL grade I and where subtle white matter injury on TEA-MRI was confirmed, will be helpful in recognizing patterns of movements and or responses.

Assessment tools

- First, the AIMS should be validated for the Dutch population. We may profit from what is currently going on in Canada. One of the developers of the AIMS, Johanna Darrah from Edmonton, Alberta and Doreen Bartlett from London, Ontario, received national funding in January 2010 to re-evaluate the AIMS normative data. They will collect data on 675

infants across Canada representing the ethnic diversity of the Canadian population. If there are some ages where the norms are different they will recalibrate the norms. The re-visit of the norms has two reasons: one is the 'back to sleep' campaigns and the other the changing ethno-cultural diversity of Canadian infants. So far, there has been no indication that the norms are inappropriate.[23] The statistician who assisted with the AIMS norms has developed a scaling method to check the new data against the old norms and 'recalibrate' the original norms when necessary. They plan to publish the statistical methods, so if other countries or groups want to check their data against the Canadian norms, they can use the same procedure. It is a 3½ year grant and they hope to have the data analyzed in 2013 and that the AIMS norms are still appropriate. Second, the AIMS norms for infants born preterm should be up-dated to determine if adaptations are needed.

- The GMDS also need to be validated for the Dutch population. It is conceivable that the mean DQ for the general population is higher than 100 and the SD lower than 12.
- The BSITD-III normative data are currently being established and validated for the Dutch population (project coordinator Prof. Dr. A. L. van Baar, Utrecht University). The results of this project will not be available before the end of 2014.
- The GMFCS for the age band 0-2 years needs more elaboration. The descriptions of the 5 levels of functioning should be adapted. The initial way of moving forward of most infants with a development of a USCP is by use of asymmetrical bottom shuffling on the side that is not affected. Infants with a development of BSCP often sit in a W-position and move forward by non-reciprocal crawling with the insteps touching the surface. They also show creeping or hopping on the knees instead of on hands and knees.

  These are some examples of pre-walking locomotion strategies that can be observed in infants with a development of CP. The knowledge and expertise in the field of experienced pediatric physical and occupational therapists, and physicians in pediatric rehabilitation medicine should make it possible to describe the gross motor functional abilities of infants younger than 2 years of age in more detail.

REFERENCES

1 Bobath B and Bobath K. Motor development in the different types of cerebral palsy. London: William Heinemann Medical Books Lt; 1976.

2 Bobath B. Abnormal Postural Reflex Activity caused by Brain Lesions. London: William Heinemann Medical Books Ltd; 1978.

3 Piper MC, Darrah J. Motor assessment of the developing Infant. Philadelphia: WB Saunders; 1994.

4 Majnemer A, Snider L. A Comparison of Developmental Assessments of the Newborn and Young Infant. MRDD Research Reviews 2005;11:68-73.

5 Pin TW, de Valle K, Eldridge B, Galea MP. Clinimetric properties of the alberta infant motor scale in infants born preterm. Pediatr Phys Ther 2010;22:278-286.

6 Pin TW, Eldridge B, Galea MP. Motor trajectories from 4 to 18 months corrected age in infants born at less than 30 weeks of gestation. Early Hum Dev 2010;86:573-580.

7 Bartlett DJ, Lucy D. Comprehensive Approach to Outcomes Research in Rehabilitation. Physiother Can 2004;56:237-247.

8 Rosenbaum P. 'Variation and abnormality': Recognizing the differences. J of Ped 2006;149;593-594.

9 De Vries LS and Cowan FM. Evolving Understanding of Hypoxic-Ischemic Encephalopathy in the Term Infant. Semin Pediatr Neurol 2009;16:216-225.

10 Hadders-Algra M. Variation and Variability: Key Words in Human Motor Development. Physical Therapy 2010;90:1823-1837.

11 Allen MC. Neurodevelopmental assessment of the Young Child: The State of the Art. MRDD Research Reviews 2005;11:274-275.

12 Baar van AL, Wassenaer van AG, Briët JM, Dekker FW, Kok JH. Very Preterm Birth is Associated with Disabilities in Multiple Developmental Domains. J Pediatr Psychol 2005;30:247-255.

13 Marlow N, Hennessy EM, Bracewell MA, Wolke D, for the EPICure Study Group. Motor and Executive Function at 6 Years of Age After Extremely Preterm Birth. Pediatrics 2007;120:793-804.

14 Allen MC. Neurodevelopmental outcomes of preterm infants. Curr Opin Neurol 2008;21:123-128.

15 Cheong JL, Hunt RW, Anderson PJ, Howard K, Thompson DK, Wang HX, Bear MJ, Inder TE, Doyle LW. Head growth in preterm infants: correlation with magnetic resonance imaging and neurodevelopmental outcome. Pediatrics. 2008;121(6):e1534-1540.

16 Euser AM, de Wit CC, Finken MJ, Rijken M, Wit JM. Growth of preterm born children. Horm Res. 2008;70(6):319-328.

17 Latal B. Prediction of Neurodevelopmental Outcome After Preterm Birth. Pediatr Neurol 2009;40:413-419.

18 Darrah J, Senthilselvan A, Magill-Evans J. Trajectories of serial motor scores of typically developing children: Implications for clinical decision making. Infant Behav Dev. 2009;32:72-78.

19 Stephens BE, Vohr B. Neurodevelopmental Outcome of the Premature Infant. Pediatr Clin N Am 2009;56;631-646.

20 De Kievit JF, Piek JP, Aarnoudse-Moens C, Oosterlaan J. Motor Development in Very Preterm and Very Low-Birth-Weight Children From Birth to Adolescence. JAMA 2009;302:2235-2242.

21 Vederhus BJ, Markestad T, Eide GE, Graue M, Halvorson T. Health related quality of life after extremely preterm birth: a matched controlled cohort study. Health and Quality if Life Outcomes 2010;8:53-60.

22 Milligan DWA. Outcomes of children born very preterm in Europe. Arch Dis Child Fetal Neonatal Ed 2010;95:F234-F240.

23 Syrengelas D, Siahanidou T, Kourlaba G, Kleisiouni P, Bakoula C, Chrousos GP. Standardization of the Alberta infant motor scale in full-term Greek infants: Preliminary results. Early Hum Dev 2010;86;245-249.

8

NEDERLANDSE SAMENVATTING

(DUTCH SUMMARY)

INLEIDING

De studies die in dit proefschrift zijn opgenomen zijn het resultaat van vele jaren werk binnen de neonatale follow-up (FU) polikliniek. Als FU team bieden wij nazorg aan kinderen die op onze neonatale intensive care unit (NICU) van het Wilhelmina Kinderziekenhuis te Utrecht hebben gelegen omdat zij ofwel te vroeg waren geboren, ofwel op tijd maar met problemen voor, rondom of direct na de geboorte.
Het belangrijkste doel van dit proefschrift was antwoord te krijgen op bepaalde vragen die tijdens de FU sessies van honderden zogenaamde 'NICU-graduates' bij ons opkwamen.
In dit proefschrift worden de typische en afwijkende neuro-motorische ontwikkeling en uitkomsten van deze kinderen beschreven.

Hoofdstuk 1 is een introductie op het proefschrift waarin een globaal overzicht wordt gegeven van 20 jaar neonatale FU en waarin de doelen en hoofdlijnen van de studie worden beschreven. Het hoofdstuk beschrijft de verschillende FU schema's die binnen onze polikliniek worden gehanteerd, evenals de neurologische en neuro-motorische onderzoeksinstrumenten en beeldvormende technieken die werden gebruikt en waardoor onze kennis, ervaring en klinische blik zijn gevormd.

In **deel I, hoofdstuk 2** onderzochten wij in een cross-sectionele studie met 800 kinderen die werden geboren na een zwangerschapsduur (GA) van ≤32 weken in de periode december 1993 tot november 2005, de resultaten van de Alberta Infant Motor Scale (AIMS). De kinderen waren tussen de 1–19 maanden oud waarbij werd gecorrigeerd voor de mate van vroeggeboorte. Op elke leeftijd waren de gemiddelde AIMS scores significant lager vergeleken met de normwaardes van op tijd geboren kinderen.
Deze uitkomst heeft implicaties voor de beslissing of een ontwikkelingsgerichte interventie of behandeling gerechtvaardigd is. Als men uitgaat van de normen die zijn gebaseerd op de scores van op tijd geboren kinderen (zoals die in de handleiding worden gepresenteerd) dan

bestaat de kans dat de AIMS score van een prematuur geboren kind in het afwijkende gebied valt en dat op basis daarvan wordt besloten dat het kind een ontwikkelingsgerichte interventie nodig heeft. Om juist die kinderen op te sporen die daar wel van zouden kunnen profiteren, stelden wij de volgende procedure voor: als een prematuur geboren kind volgens de normwaardes voor op tijd geboren kinderen op de AIMS onder de 5e percentiel scoort, wordt geadviseerd over te stappen op de door ons ontwikkelde normwaardes voor prematuur geboren kinderen. De ontwikkeling van een kind dat dan onder de 25e percentiel scoort zou nauwlettend gevolgd moeten worden en het kind zou gebaat kunnen zijn bij bijvoorbeeld kinderfysiotherapeutische begeleiding.
Deze studie toont aan dat te vroeg geboren kinderen in de eerste 1.5 jaar van hun leven een grof motorisch ontwikkelingstraject kunnen laten zien dat verschilt van dat van op tijd geboren kinderen. Het is mogelijk dat het grof motorische ontwikkelingstraject dat prematuur geboren kinderen afleggen karakteristiek is voor deze populatie en een variant is binnen de normale grof motorische ontwikkeling. Dit betekent dat gestandaardiseerde grof motorische ontwikkelingsschalen die worden gebruikt voor op tijd geboren kinderen zouden moeten worden aangepast voor prematuur geboren kinderen om een goede evaluatie en klinische beslissing mogelijk te maken.

In **deel II, hoofdstuk 3**, onderzochten wij of hoog kwalitatieve, sequentiële schedelechografie van 2139 te vroeg geboren kinderen die werden geboren tussen januari 1990 en januari 1999, cerebrale parese (CP) kon voorspellen op een leeftijd van minstens 24 maanden. Het cohort werd in twee groepen verdeeld: A) 1636 kinderen met een GA ≤32 weken en B) 503 kinderen met een GA van 33–36 weken. Direct na hun geboorte en tijdens de NICU opname werden bij hen iedere week schedelecho's gemaakt tot aan ontslag en ook nog eens bij 40 weken post menstruele leeftijd. Een graad III en IV bloeding, cysteuze periventriculaire leucomalacie (c-PVL) en een focaal infarct werden beschouwd als grote echoafwijkingen.
In groep A ontwikkelden 76/1460 (5%) van de overlevenden CP. Bij 70/76 (92%) van de kinderen met CP kwamen schedelecho afwijkingen

voor: 58/70 (83%) had grote en 12/70 (17%) had kleine afwijkingen. Geen echoafwijkingen werden gevonden bij 6/76 (8%) kinderen met CP, van wie 3 een atactisch CP beeld ontwikkelden. Bij 17/58 (29%) kinderen met CP die grote echoafwijkingen hadden werden voor het eerst cystes ontdekt na minimaal 28 dagen vanaf de geboorte.
In groep B ontwikkelden 29/469 (6%) van de overlevenden CP. Bij 28/29 (96%) van de kinderen met CP kwamen schedelecho afwijkingen voor: 25/28 (89%) had grote en 3/28 (11%) kleine afwijkingen. Bij één kind met CP werden geen echoafwijkingen gevonden. In deze groep werden geen grote echoafwijkingen gediagnosticeerd na minimaal 28 dagen vanaf de geboorte.
In groep A en B samen had 79% (83/105) van de kinderen met CP grote schedelecho afwijkingen.
Om c-PVL op te sporen is het dus van groot belang dat er bij kinderen die worden geboren met een GA ≤32 weken ook langer dan 4 weken na de geboorte en bij 40 weken post menstruele leeftijd een schedelecho wordt gemaakt.

In **deel II, hoofdstuk 4**, (een review artikel) wilden wij de mythe uit de wereld helpen dat CP niet kan worden voorspeld op basis van neonatale beeldvorming van de hersenen van pasgeborenen.
Wat het prematuur geboren kind betreft, is er overeenstemming over het feit dat herhaaldelijk verkregen normale schedel echo's vrij nauwkeurig een normale uitkomst voorspellen, terwijl grote hersenschade (hemorrhagisch parenchym infarct en c-PVL) kan voorspellen welke kinderen CP zullen ontwikkelen zonder de mogelijkheid tot zelfstandig lopen te komen.
Een MRI op de à terme datum kan het voorspellen van CP nog verder verbeteren, omdat hiermee de myelinisatie van het achterste been van de capsula interna kan worden beoordeeld bij kinderen bij wie een hemorrhagisch parenchym infarct, een bloeding van de middelste cerebrale arterie of uitgebreide, bilaterale c-PVL is vastgesteld. Echter, het voorspellen van de motorische uitkomst bij prematuur geboren kinderen met subtiele witte stof afwijkingen blijft moeilijk, zelfs met conventionele MRI.

Bij het op tijd geboren kind met een ischemisch infarct of een hypoxisch-ischemische encefalopathie (HIE) rondom de geboorte, zijn MRI technieken effectieve middelen om CP te voorspellen. Bij kinderen met HIE kunnen twee belangrijke vormen van hersenschade worden onderscheiden: 1) beschadiging van de basale ganglia en van de thalamus volgend op acute, bijna totale asfyxie en 2) veranderingen van de witte stof volgend op chronische, subacute asfyxie. Diffusie gewogen opnames, een aanvullende sequentie op de conventionele opnames om ischemie aan te tonen, kunnen al op de eerste levensdag HIE schade visualiseren en dragen bij aan de voorspellende waarde met betrekking tot de motorische uitkomst.
Sequentiële en goed uitgevoerde beeldvorming van de hersenen (bij prematuur geboren kinderen gedurende een voldoende lange periode gecombineerd met conventionele MRI op de à terme datum, en bij op tijd geboren kinderen met een MRI met diffusie gewogen opnames in de eerste levensweek) moet het mogelijk maken de motorische uitkomst van pasgeboren kinderen met een hoog risico op problemen te voorspellen. Voorwaarde daarbij is dat ervaren onderzoekers de beelden interpreteren.

In **deel III, hoofdstuk 5**, onderzochten wij de invloed van periventriculaire leucomalacie (PVL) op het grof motorisch functioneren in de tijd. Hierbij maakten wij gebruik van het *Gross Motor Function Classification System* (GMFCS) bij 59 kinderen met CP (37 jongens, 22 meisjes), geboren bij een GA ≤34 weken in de periode 1990–2004.
Twintig kinderen werden gediagnosticeerd met PVL graad I, 13 met PVL graad II, 25 met PVL graad III, en één kind met PVL graad IV. Het niveau van functioneren volgens de GMFCS werd op vier tijdstippen (T1-T4) bepaald. Bij een gemiddelde gecorrigeerde leeftijd op T1 van 9 maanden en 15 dagen (SD 2m 6d); op T2 van 16 maanden (SD 1m 27d); op T3 van 24 maanden en 27 dagen (SD 2m 3d) en op T4 bij een mediane leeftijd van 7 jaar en 6 maanden (range 2jr 2m–16jr 8m).
De grof motorische mogelijkheden van de kinderen variëren, afhankelijk van de ernst van de PVL. De meeste kinderen met PVL graad III en IV kregen op geen enkele van de 4 meetmomenten een GMFCS niveau I of II classificatie, omdat zij niet in staat waren zelfstandig te lopen.

Hiertegenover staat dat de meeste kinderen met PVL graad I, en in mindere mate PVL graad II, wel in staat waren te lopen. Anders dan bij kinderen met c-PVL II-IV, leverde het gebruik van de GMFCS bij kinderen met PVL graad I minder consistente resultaten op voor kinderen die jonger waren dan 2 jaar. Het kwam bijna niet voor dat kinderen die aanvankelijk in de uiterste niveaus van functioneren werden ingedeeld (GMFCS niveau I en V) later heringedeeld moesten worden. De stabiliteit van het grof motorisch functioneren, uitgedrukt in GMFCS niveaus, werd robuuster na het 1e levensjaar. Het percentage kinderen dat binnen hetzelfde GMFCS niveau bleef nam bij het ouder worden toe van 27% (T1–T4) tot 53% (T2–T4) en 72% (T3–T4). De associatie tussen PVL en de grof motorische uitkomst op T4 was sterk (positieve en negatieve voorspellende waarde respectievelijk 0.92 en 0.85). Kinderen met een PVL graad I-II hebben een betere prognose betreffende hun functionele mobiliteit dan kinderen met PVL graad III–IV. Deze resultaten hebben implicaties voor revalidatie, voorlichting en strategieën voor interventie.

In **deel III, hoofdstuk 6**, onderzochten wij de incidentie en ernst van CP, als ook geassocieerde factoren bij prematuur geboren overlevenden (GA <34 weken, binnen 4 dagen na de geboorte opgenomen op de NICU) in de periode 1990–2005.
Het cohort werd in vier geboorteperiodes ingedeeld: 1990–1993 (n = 661), 1994–1997 (n = 726), 1998–2001 (n = 723), en 2002–2005 (n = 850). In totaal werden achttien antenatale, perinatale en postnatale factoren geanalyseerd. De GMFCS werd als primaire uitkomstmaat gebruikt bij een gemiddelde leeftijd van 32.9 (SD 5.3) maanden.
Van een totaal van 3816 opgenomen pasgeborenen kwamen 3287 (86.1%) in aanmerking voor de studie van wie 327 (9.9%) kinderen overleden. De 102/2960 (3.4%) kinderen die een CP ontwikkelden verschilden in diverse antenatale en postnatale factoren van hen die geen CP ontwikkelden. Eenzijdige spastische CP kwam bij 37.25% (n = 38) voor, 2-zijdige spastische CP waarbij vooral de onderste extremiteiten betrokken waren bij 50% (n = 51) en 2-zijdige spastische CP waarbij alle extremiteiten betrokken waren bij 12.75% (n = 13).
De incidentie van CP nam af van 6.5% in periode I tot 2.6%, 2.9% en 2.2%

(p <.001) in periode II–IV. Tegelijkertijd nam c-PVL graad II en III af van 3.3% in periode I tot 1.3% in periode IV (p = .004). Binnen het totale cohort (inclusief de overleden kinderen) nam c-PVL graad III af van 2.3% in periode I tot 0.2% in periode IV (p = .003).
Het aantal kinderen met GMFCS niveau III–V nam af van periode I tot IV (p =.035). Geen CP ontwikkelden 19/51 kinderen met c-PVL graad II en III: 5/21 (23.8%) in periode I, 3/12 (25%) in periode II, 3/7 (42.9%) in periode III en 8/11 (72.7%) in periode IV.
In periode I hadden 10/17 (58.8%) kinderen die in GMFCS niveau III–V functioneerden c-PVL graad III, terwijl dit in periode II–IV gold voor 7/9 (77.8%) kinderen.
Het aantal kinderen met een ernstige vorm van CP (GMFCS III–V) nam af van 17/661 (2.6%) overlevenden in periode I tot 2/850 (0.2%) in periode IV, wat een afname is van 92%; tegelijkertijd nam c-PVL graad III af van 10/661 (1.5%) overlevenden tot 1/850 (0.1%), wat een afname is van 93%.
Onafhankelijke *risico*factoren voor CP waren c-PVL en ernstige intraventriculaire bloedingen, terwijl antenataal toegediende antibiotica aan de moeder, sectio Caesarea, een langere zwangerschapsduur en het aanwezig zijn van een arterielijn bij de pasgeborene ieder op zich onafhankelijke *beschermende* factoren waren. Daarnaast bleek er bij kinderen met c-PVL die CP ontwikkelden, een significante interactie te bestaan met hun 'pulmonary' score (een samengestelde score bestaande uit het nodig hebben van Surfactant en/of van kunstmatige ventilatie en/of kunstmatige ventilatie >7 dagen; [p <.001]).

In **deel III, hoofdstuk 7**, (een case-control studie) onderzochten wij retrospectief of *active head lifting in supine* (AHLS) in het 1e levensjaar is geassocieerd met de cognitieve ontwikkeling in het 2e levensjaar, en of er andere factoren waren die van invloed waren op de cognitieve uitkomst. De kinderen die in deze studie zijn geïncludeerd, zijn geboren in de periode 1993–2009. Er werd gebruik gemaakt van gerandomiseerde sampling om elk kind dat AHLS vertoonde te koppelen aan 2 kinderen zonder AHLS van een vergelijkbaar geslacht, met een vergelijkbare zwangerschapsduur, geboortejaar, tijdstip van onderzoek en gebruikte

ontwikkelingstest (GMDS, BSID-II-NL of BSITD-III). Neonatale schedel echo's werden in 2 categorieën onderverdeeld: geen of milde, en matige of ernstige hersenschade. Op basis van de cognitieve testresultaten werden Z-scores berekend en werden multivariate analyses uitgevoerd.
In totaal werden 127 cases geïdentificeerd: 87 prematuur geboren en 40 op tijd geboren kinderen. AHLS was sterk geassocieerd met de cognitieve uitkomst. Zowel prematuur als op tijd geboren kinderen met AHLS hadden een lagere cognitieve score vergeleken met kinderen zonder AHLS (respectievelijk p .002 en p .004). Deze associatie bleef bestaan ook nadat kinderen met CP en hun controles waren geëxcludeerd (respectievelijk p .001 en p .000). Naast AHLS bleek matige of ernstige cUS afwijkingen geassocieerd te zijn met cognitie (respectievelijk p .002 en p .001) bij zowel prematuur als op tijd geboren kinderen, maar na exclusie van de kinderen met CP en hun controles niet meer.
AHLS kan dus worden gebruikt als een vroege aanwijzing voor een niet-optimaal verlopende cognitieve ontwikkeling in het 2e levensjaar, zowel bij prematuur als op tijd geboren kinderen.

CONCLUSIES

Op basis van de onderzoeksresultaten kunnen de volgende conclusies worden getrokken:

1. Op alle leeftijdsniveaus tussen de gecorrigeerde leeftijd van 1–19 maanden scoren prematuur geboren kinderen (GA ≤32 weken) op de AIMS significant lager vergeleken met de normwaardes van op tijd geboren kinderen (deel I, hoofdstuk 2).
2. Hoge resolutie, sequentiële schedelecho's toonden grote hersenafwijkingen aan bij 83/105 (79%) prematuur geboren overlevenden die CP ontwikkelden. Die afwijkingen kwamen niet zelden pas aan het licht na de 28e dag vanaf de geboorte (deel II, hoofdstuk 3).

3 Grote hersenbeschadigingen kunnen bijna altijd worden ontdekt met schedelecho's, vooropgesteld dat de onderzoeker voldoende ervaring heeft om kwalitatief goede scans te maken en dat de periode waarin opeenvolgende echo's worden gemaakt lang genoeg is. Bij prematuur geboren kinderen kan een betere voorspelling van het ontwikkelen van CP worden gemaakt, als op de à terme datum een MRI van de hersenen wordt gemaakt. Het blijft echter moeilijk om de motorische uitkomst te voorspellen als er sprake is van subtiele witte stof afwijkingen. Bij op tijd geboren kinderen is het bij het interpreteren van de MRI beelden belangrijk rekening te houden met het tijdstip waarop de MRI is gemaakt (deel II, hoofdstuk 4).

4 Bij kinderen met PVL hangen hun grof motorische mogelijkheden samen met de ernst van de PVL. PVL graad I en c-PVL graad II hebben een betere prognose dan c-PVL graad III–IV. De meeste kinderen met c-PVL graad III en IV kunnen niet zelfstandig lopen, terwijl kinderen met PVL graad I en in mindere mate c-PVL graad II dit vaak wel kunnen (deel III, hoofdstuk 5).

5 De incidentie van CP nam significant af tussen 1990–2005, een periode van 16 jaar. Tegelijkertijd nam de incidentie van c-PVL significant af, vooral c-PVL graad III. Het gevolg daarvan was dat het aantal kinderen dat in GMFCS niveau III–V functioneerde significant afnam (deel III, hoofdstuk 6).

6 AHLS in het 1e levensjaar is geassocieerd met een ongunstige cognitieve uitkomst in het 2e levensjaar, zowel bij prematuur geboren als op tijd geboren kinderen en kan daarom worden gebruikt als een vroege aanwijzing voor een niet optimaal verlopende cognitieve ontwikkeling (deel III, hoofdstuk 7).

AANBEVELINGEN VOOR TOEKOMSTIG ONDERZOEK EN DE KLINISCHE PRAKIJK

Beeldvorming

Om CP beter te kunnen voorspellen is het essentieel dat bij pasgeborenen met een zwangerschapsduur ≤32 weken een keer per week een schedelecho van de hersenen wordt gemaakt tot aan het ontslag en nog een keer op de à terme datum.

Klinische observatie

- Voor de neonatale FU praktijk is het belangrijk dat observationele en/ of meetinstrumenten eenvoudig toe te passen zijn met minimale hantering van een kind, en niet tijdrovend, maar wel valide en betrouwbaar zijn. Er zouden meer inspanningen moeten worden verricht om te zien of aanpassingen van bestaande instrumenten mogelijk zijn voor specifieke groepen, zoals te vroeg geboren kinderen en kinderen jonger dan 2 jaar die CP aan het ontwikkelen zijn.
- Observatie en goede interpretatie van *'general movements'* van prematuur geboren kinderen op de à terme datum en van op tijd geboren kinderen op de leeftijd van 3 maanden, kunnen misschien tot één beweging worden teruggebracht: actieve extensie van de benen gevolgd door een vloeiende actieve dorsale flexie in de enkels. Volgens onze ervaring is de neurologische integriteit van het centrale zenuwstelsel bij kinderen die dit patroon laten zien intact. Om bewijs voor dit idee te vinden, zou dit bewegingspatroon als onderdeel van het bewegingsrepertoire van deze kinderen, moeten worden vastgelegd op video en gerelateerd worden aan een motorisch onderzoek en/ of motorische test op de vroege of latere basisschoolleeftijd.
- Aangezien het voorspellen van de motorische uitkomst, vooral van CP, van kinderen bij wie in de neonatale periode subtiele witte stof afwijkingen werden gezien moeilijk is, is de klinische observatie van deze kinderen op de à terme datum en op de gecorrigeerde leeftijd van 6 maanden heel belangrijk. Het kritisch bekijken van de FU gegevens van alle kinderen bij wie in de neonatale periode PVL graad I is

vastgesteld en bij wie op een MRI op de à terme datum subtiele witte stof afwijkingen zijn bevestigd, zou kunnen helpen in het herkennen van bepaalde spontane bewegingspatronen en/of specifieke reacties op passief uitgevoerde manoeuvres.

Meetinstrumenten

- In de 1e plaats zou de AIMS moeten worden genormeerd en gevalideerd voor de Nederlandse populatie. Wij kunnen misschien profiteren van een onderzoek dat momenteel in Canada loopt. Eén van de ontwikkelaars van de AIMS, Johanna Darrah uit Edmonton, Alberta heeft in samenwerking met Doreen Bartlett uit London, Ontario, in januari 2010 uit een nationaal fonds geld gekregen om de normatieve data van de AIMS te re-evalueren. Zij zullen data verzamelen van 675 kinderen verspreid over Canada die representatief zijn voor de etnische diversiteit van de Canadese populatie. Als er leeftijden zijn waarvoor de normen anders zijn, zullen deze worden aangepast. Het herzien van de normen heeft 2 redenen: de ene is de zogenaamde '*back to sleep*' campagne en de andere is de veranderende etnisch-culturele verscheidenheid van Canadese kinderen. Tot dusverre zijn er geen aanwijzingen dat de normen ongeschikt zijn (Syrengelas, 2010). De statisticus die met de AIMS hernormering helpt, heeft een methode ontwikkeld om de nieuwe data te checken ten opzichte van de oude normen en zo nodig de originele normen bij te stellen. Men is van plan deze statistische methode te publiceren, zodat wanneer andere landen of groepen hun data ten opzichte van de Canadese normen willen checken, zij dezelfde procedure kunnen volgen. Het betreft een subsidie voor 3½ jaar en men hoopt a) de data in 2013 te kunnen analyseren en b) dat de AIMS normen nog steeds bruikbaar zijn. In de 2e plaats zouden de AIMS normen voor prematuur geboren kinderen ook opnieuw genormeerd moeten worden om te bepalen of er aanpassingen nodig zijn.
- Ook de GMDS zou voor de Nederlandse populatie moeten worden genormeerd en gevalideerd. Het is mogelijk dat het gemiddelde ontwikkelingsquotiënt voor de algemene populatie hoger uitkomt dan 100 en de SD lager dan 12.

- De normatieve data voor de BSITD-III worden momenteel voor de Nederlandse populatie uitgevoerd en gevalideerd (projectleider Prof. Dr. A. L. van Baar, Universiteit Utrecht). De resultaten van dit project zullen niet eerder dan eind 2014 beschikbaar zijn.
- De beschrijvingen van de vijf GMFCS niveaus voor de leeftijdscategorie 0-2 jaar zijn te globaal en weinig specifiek, waardoor het niveau van grof motorisch functioneren van jonge kinderen moeilijk te bepalen is. Die beschrijvingen moeten hoognodig worden aangepast. Zo verloopt de eerste manier van voorwaarts bewegen van de meeste kinderen met een zich ontwikkelende USCP door asymmetrisch op de billen te schuiven op de kant die niet is aangedaan. Kinderen die een BSCP ontwikkelen, zitten vaak in een W-houding (ook wel TV-zit genoemd) en bewegen voorwaarts door niet alternerend te kruipen, met de wreven contact makend met de vloer. Zij laten ook vaak kruipen of hoppen op de knieën zien in plaats van op handen en knieën.

Dit zijn een paar voorbeelden van bewegingsstrategieën die aan het lopen vooraf gaan en bij kinderen die een CP ontwikkelen kunnen worden geobserveerd.
De kennis en expertise die aanwezig wordt geacht bij ervaren kinderfysiotherapeuten, ergotherapeuten en revalidatieartsen, zou het mogelijk moeten maken de grof motorische functionele mogelijkheden van kinderen jonger dan 2 jaar meer in detail te beschrijven dan nu het geval is.

LIST OF CO-AUTHORS AND THEIR AFFILIATION

Manon J.N.L. Benders, MD, PhD. Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands

Maria J.C. Eijsermans, BSc. Child Development and Exercise Center, Division of Pediatrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands

Jan Willem Gorter, MD, PhD. CanChild Centre for Childhood Disability Research, Mc Master University, Hamilton, Canada

Floris Groenendaal, MD, PhD. Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands

Marja van der Heide-Jalving, MD. Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands

Paul J.M. Helders, MSc, PhD. Child Development and Exercise Center, Division of Pediatrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands

Marian J. Jongmans, MSc, PhD. Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands and Faculty of Social Sciences, Utrecht University, The Netherlands

Corine Koopman-Esseboom, MD, PhD. Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands

Karin J. Rademaker, MD, PhD. Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands

Jacqueline U.M. Termote, MD, PhD. Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands

Cuno S.P.M. Uiterwaal, MD, PhD. The Julius Centre for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands

Linda S. de Vries, MD, PhD. Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands

Maria K. van de Waarsenburg, BSc, University Medical Center Utrecht, The Netherlands

DANKWOORD

Het verhaal gaat dat een promotie ooit de kroon was op iemands carrière. Nu moeten jongeren gepromoveerd zijn willen zij enige kans maken op een opleidingsplaats naar hun keuze. Gelukkig hoefde ik die ratrace niet te lopen. Mijn promotietraject is te vergelijken met de ontwikkeling van een kind: meer nog dan het eindproduct ging het daarbij om het proces. In mijn lange carrière hebben veel mensen op de een of andere manier hun stempel op dat proces gedrukt, waar ik een ieder zeer erkentelijk voor ben. Het kan niet anders dan dat dit dankwoord enige omvang heeft.

Te beginnen met de ouders van kinderen die bij ons op de NICU hebben gelegen en bereid waren niet zelden flinke afstanden af te leggen om naar onze follow-up te komen, voor wie ik veel waardering heb. Zonder hun inzet zouden wij niet in staat zijn geweest de afgelopen 20 jaar zoveel kennis en ervaring op te doen betreffende verschillende ontwikkelingstrajecten van prematuur geboren en op tijd geboren kinderen.

Prof. Dr. L.S. de Vries, geachte promotor, beste Linda. Als de dag van gisteren weet ik nog hoe mijn voorgangster Annie Lensen mij bij jou op de Neonatale follow-up poli in het oude WKZ introduceerde terwijl je op een mat bezig was een kind te onderzoeken. Vanaf die tijd werken wij, nu ruim 20 jaar, samen. In al die jaren mocht ik getuige zijn van je enorm brede kennis, ervaring, fenomenale geheugen en gedrevenheid de beste zorg te leveren die denkbaar is. Als je iets specifieks bij een kind vermoedt, dan is de kans bijna 100% dat jij het bij het rechte eind hebt. Jouw hersenenactiviteit bevindt zich nooit in een sluimerstand. Je zit vol creatieve ideeën. Enkele resultaten daarvan zijn in dit boekje te vinden. Jij behoorde wat snelheid van reageren op concept manuscripten betreft tot de top 3 van coauteurs. Je wist bovendien feilloos die plekken in een tekst aan te wijzen waar ik zelf twijfels over had of die niet lekker liepen. Dat het jaar 2011 begon met een persbericht en veel aandacht van diverse media naar aanleiding van onze publicatie over de sterk afgenomen incidentie en ernst van CP in ons centrum, was een leuke opsteker en voor een belangrijk deel ook jouw verdienste.

Dank voor het in mij gestelde vertrouwen en je ondersteuning, in wat voor vorm dan ook, tijdens het promotietraject. Enkele vruchten van onze jarenlange samenwerking zijn geplukt, maar als de boom gezond blijft zal hij nog meer vrucht voortbrengen. Hopelijk is er de komende jaren nog volop gelegenheid bijzondere, rijpe of juist jonge vruchten te plukken.

Prof. Dr. P.J.M. Helders, geachte promotor, beste Paul. In de lente van 1991 maakte een vriendin mij attent op een advertentie in de Volkskrant waarin een kinderfysiotherapeut werd gevraagd om het team in het WKZ te versterken, het liefst iemand met belangstelling voor de neonatologie. Een schot in de roos! Al snel kwam je met het voorstel mij naar Dr. Stephen W. Porges in Baltimore te sturen om kennis te nemen van de 'vagal tone' en naar Dr. Heidelise Als in Boston om kennis op te doen over de 'Assessment of Preterm Infants Behavior' en de 'Neonatal Individualized Developmental Care and Assessment Program'.
Jij was het die in 1993 op een congres in de USA tegen de AIMS aanliep en mij de gelegenheid gaf daar kennis van te nemen en mij de methode eigen te maken. Je bent van grote betekenis geweest voor de ontwikkeling van de (afdeling) kinderfysiotherapie en daar heb ik ook volop van kunnen profiteren. Dank voor de gelegenheid die je hebt geboden om drs. Maaike Sprong twee periodes een ochtend op de neonatale follow-up poli in te zetten zodat ik enige ruimte had aan mijn onderzoek te werken. Dank ook voor je ondersteuning tijdens mijn promotietraject. Wat het corrigeren van manuscripten aangaat ben jij nauwelijks te evenaren in snelheid en wegstrepen! Je bent iemand van de grote lijnen en dat is voor een detaillist als ik ben vaak verhelderend. Ook al ben je met emeritaat, ik stel het zeer op prijs dat je op de 13e december getuige wil zijn van de finale van mijn promotietraject.

Prof. Dr. M.J. Jongmans, geachte promotor, beste Marian. Sinds jaar en dag zijn wij lid van het neonatale follow-up team. Onze samenwerking heeft onder andere tot het 2e hoofdstuk geleid. Die publicatie heeft zijn weg gevonden onder kinderfysiotherapeuten, ook in andere delen van de wereld. Je aanstekelijke lach, gevoel voor humor en optimisme bewonder ik zeer. Jouw commentaar op mijn stukken was zonder uitzondering

relevant. Daarnaast wist jij als geen ander de vinger op zaken te leggen die anderen nog niet hadden opgemerkt, beter tot hun recht konden komen of beter verwoord konden worden. Je bent op een prettige manier zeer kritisch, een kwaliteit waar ik veel aan heb gehad. Fijn dat je in dit laatste jaar een aantal kinderen voor mij kon testen om daarmee mijn werkdruk enigszins te verlichten.

Dr. F. Groenendaal, beste Floris. Sinds onze gezamenlijke introductie in het oude WKZ medio 1991 hebben wij een 'special bond'. Jouw ondersteuning bij het ontwikkelen en tot stand brengen van het megaproject dat in hoofdstuk 6 te lezen is, maar ook bij het laatste project over de hoofdoptillers, is van onschatbare waarde geweest. Niet alleen je kennis en ervaring als neonatoloog, maar ook je kennis van statistiek en epidemiologie maakte dat je een belangrijke schakel in mijn onderzoekstraject was. Vooral je relativeringsvermogen, gevoel voor humor, enthousiasme, broederlijke plagerijtjes en interesse in mijn onderzoek heb ik enorm gewaardeerd. Ik hoop dat onze samenwerking voort mag duren en tot nog meer interessante publicaties zal leiden.

Dr. J.W. Gorter, beste Jan Willem. Als kinderrevalidatiearts heb je een bijzondere en waardevolle bijdrage geleverd aan de hoofdstukken 5 en 6. Het contact met jou heb ik altijd als zeer plezierig ervaren. Jouw specifieke kennis, ervaring en zinvolle opmerkingen hebben die twee manuscripten kwalitatief op een hoger peil gebracht. Je opgewekte karakter en optimisme werkten aanstekelijk en je bemoedigende woorden deden mij goed. Jammer dat je de oceaan bent overgestoken. Wij missen je wel hoor!

Dr. C.S.P.M. Uiterwaal, beste Cuno. Mede door jouw inbreng is de inhoud van hoofdstuk 6 geworden tot wat die is en heeft de publicatie veel aandacht van de media gekregen. Van jou heb ik geleerd dat je data niet voor de vuist weg moet analyseren maar dat je afhankelijk van je vraagstelling logisch en ook klinisch moet redeneren alvorens aan analyses te beginnen.

Dr. T. Takken, beste Tim. Het is weer even geleden, maar dank voor je hulp bij de figuren in hoofdstuk 2.

Dr. E.J.H. Mulder, beste Edu. Dank voor je hulp bij het creëren van de figuur in hoofdstuk 5. We zijn elkaar ooit tegen het lijf gelopen toen we les moesten geven aan de opleiding voor NICU verpleegkundigen aan de Israëlslaan. Om te weten wat de een (jij) over antenatale bewegingen ging vertellen en de ander (ik) over postnatale bewegingen, stelde jij voor elkaars lessen bij te wonen. Daaruit is een blijvende interesse voor elkaars werk ontstaan.

Mevrouw I. Janssen, medisch tekenaar, dank ik voor de rake tekening die u voor het artikel in hoofdstuk 7 maakte. Uw beroep schijnt met uitsterven te worden bedreigd. Men zou in actie moeten komen om dat te verhinderen. Uw werk bewijst hoe een enkele illustratie een heel verhaal kan vertellen.

Prof. Dr. F. van Bel, beste Frank. Als mijn direct leidinggevende heb ik veel aan je te danken. Om te beginnen dat je, ruim een jaar na het behalen van mijn doctoraal examen orthopedagogiek, je sterk maakte om de overstap naar de afdeling neonatologie begin 2003 mogelijk te maken. Jij hebt mij de afgelopen jaren zonder enig voorbehoud alle ruimte en het vertrouwen gegeven om mij verder te ontplooien.

Prof. Dr. A.L. van Baar, Prof. Dr. M. Hadders-Algra, Prof. Dr. F. van Bel en Prof. Dr. A. Franx ben ik erkentelijk voor het feit dat zij zitting wilden nemen in mijn beoordelingscommissie. Dr. F. Cowan, dear Francis, it is a great pleasure and honour that you were willing to participate in the assessment committee, and that you are so kind to travel all the way from the UK to Utrecht to be 'part of your great day' as you wrote to me.

Een woord van waardering is op zijn plaats voor de pioniers van de neonatologie van ons WKZ, o.a. Dr. B. P. Cats†, Dr. I. van Ertbruggen en Dr. L.J. Gerards; de huidige stafleden Prof. Dr. F. van Bel, Prof. Dr. L.S. de Vries, Dr. M. J.N.L. Benders, drs. C. A. Blok, Dr. H.A.A. Brouwers, drs. M.

van der Heide-Jalving, Dr. C. Koopman-Esseboom, Dr. T.G. Krediet, Dr. P.M.A. Lemmers, Dr. K.J. Rademaker, Dr. J.U.M. Termote, Dr. M.C. Toet en Dr. M.A. Verboon-Majolec, drs. D. C. Vijlbrief, Dr. W.B. de Vries; neonatoloog in opleiding Dr. L. G.M. van Rooij, en de staf- en afdelingssecretaresses Ineke Krijgsman, Karin Warkor, Hanneke Dietz en andere collega's die altijd behulpzaam zijn.

Met veel waardering denk ik aan de goede samenwerking met de teamgenoten van de neonatale follow-up poli vroeger: Dr. Bernard Cats† en Dr. Paula Eken en nu: ons 'opperhoofd' Dr. Corine Koopman-Esseboom, Prof. Dr. Linda de Vries, Prof. Dr. Marian Jongmans, Rian Eijsermans en invallers Dr. Manon Benders, Dr. Petra Lemmers, Dr. Mona Toet; van de afdeling Medische Psychologie en Maatschappelijk werk: drs. Carolien van Stam, Dr. Marion Tanke en Dr. Monica Uniken Venema en medewerkers van poli rood voor de ondersteuning in welke vorm dan ook: de Medisch Ambulante Assistente Zorg Christel Wullems-Diepeveen en collega's (eerder ook I. Borgers-Gerritse) en de medisch dictafonistes R. Gouka-Kaasing en M. Ditewig.

Zonder de hulp van mensen als André Hemelrijk en collega's van het centraal medisch archief bij het opzoeken van eindeloos veel medische statussen en microfilms, en de medisch fotografen Rudy Hövig en collega's (eerder ook Hans Kempkes) o.a. voor het omzetten van figuren in een bepaald bestand ten behoeve van publicaties of presentaties was het onderzoek een stuk lastiger geweest. Rudy bedankt voor je toezegging na de promotieplechtigheid foto's te willen maken.

Collegae kinderfysiotherapeuten van het kinderbewegingscentrum dank ik voor de prettige en stimulerende samenwerking in de periode augustus 1991 t/m december 2002: Dr. Ron van Empelen, Dr. Marja Schoenmakers, Dr. Janjaap van der Net, Rian Eijsermans, Dr. Tim Takken, en de secretaresses Annemiek Apeldoorn, Sonja Raaff en Carla van Rooijen. Drs. Maaike Sprong dank ik voor haar ondersteuning van de neonatale follow-up poli (oktober 2008 t/m juli 2009 en december 2010 t/m mei 2011) waardoor enige ruimte vrijkwam om aan dit proefschrift te werken.

Drs. Jacqueline Nuijsink dank ik voor de prettige samenwerking en interessante discussies. Succes met jouw onderzoek.
Met waardering denk ik ook terug aan de samenwerking met degenen die in de loop der tijd een uitdagende functie buiten het WKZ hebben gevonden: Dr. Vincent Gulmans, Dr. Raoul Engelberts en Dr. Jan Custers. Hans Steenbergen en Annie Lensen, voormalig kinderfysiotherapeuten in het WKZ, dank ik voor de mogelijkheid die zij mij begin 2003 geboden hebben om een dag per week in hun praktijk voor kinderfysiotherapie in Rijswijk te werken omdat ik toen wat tijd over had! Deze bijzonder prettige samenwerking heeft twee jaar geduurd.

Een woord van waardering is er voor de verpleegkundigen van de afdelingen waar ik tot 2003 heb gewerkt zoals Eekhoorn en neonatologie (in het oude WKZ respectievelijk Eskimo en Appel genoemd).

Mijn voormalige 'roomies' Dr. C. Peeters-Scholten, Dr. E.R. van den Tweel, Dr. M.P. Bal, drs. J. Smal, drs. K.M. Korbeeck-van Hof, Dr. L.G.M. van Rooij, Dr. B.J.M. van Kooij, drs. M.J. Vogelaar-Brouwer en de huidige 'roomies' drs. N.E. van der Aa, drs. K.J. Kersbergen en drs. J. Harteman dank ik voor jullie collegialiteit, gezelligheid, kopjes 'capus', eerste hulp bij PC of statistiek problemen en een luisterend oor of meelezend oog. Jullie zijn bijzonder fijne jonge mensen met harten van goud. Mensen om trots op te zijn en met wie het een voorrecht is een kamer te delen. Ook de collega onderzoekers 'next door' onder wie drs. T. Alderliesten, drs. J. Nijman en drs. J.J. Kaandorp dank ik voor jullie interesse in mijn onderzoek en gezelligheid.

De collega's in het Diakonessenhuis te Utrecht dank ik voor de samenwerking gedurende ruim 15 jaren die bijzonder, leerzaam en vormend waren met als afdelingshoofden respectievelijk J.B. den Dekker†, R. Sneep en M.H. van Lijf; als fysiotherapeuten P. Bär, B. Berden-de Bont, M. Blok, M. de Boer, I. Bosga, W. Brakkee, R. Cottaar, P.van Doorn, A. Ebbink†, N. van der Eijk, E. van Genk, S. Gutker de Geus, drs. F. Huijsmans, N. In der Maur, H. de Jong, M. Kock-Verschuur, L. van der Meyden, E. Moons, M. Muller, drs. M. van Niekerk, S. Oomkens,

T. van Oostrum, R. Pook, C. Reijnders, M. Schepman, C. Schlösser, I. Sluis, M. Sterkenburg, N. Visser-de Wolf, H. Vossen, J. Willemse; als ergotherapeuten K. van Beek, I. Lakerveld en T. Verstappen†, en als 'timmerman' J. Nijeboer. Ook JW Doove met wie ik in het centrum Nassau Odijckhof te Driebergen werkte, dank ik voor de goede samenwerking.

Mijn moeder verdient een centrale en ereplaats in dit dankwoord. Zo meelevend, meelezend en zelfs fouten uit de diverse manuscripten halend. Wel toevertrouwd aan een oud-onderwijzeres! Lieve ma, volgens u is het beter zelf iets op te zoeken als je iets niet weet dan het antwoord cadeau te krijgen, omdat de informatie je dan beter bijblijft. Van die wijsheid profiteer ik nog iedere dag. U heeft mij voorgeleefd hoe je positief in het leven kunt staan door niet te lang stil te staan bij nare gebeurtenissen en tegenslagen in je leven, maar je aandacht te richten op je medemens en dat wat het leven de moeite waard maakt. Ik hoop dat het u gegeven is de 13e december aanwezig te kunnen zijn. Dank voor uw aandacht, zorg en onvoorwaardelijke steun. Laten wij nog veel potjes scrabbel breken in een gezamenlijke poging de magische grens van 800 punten te overschrijden.
Aan mijn vader denk ik vanwege zijn oprechte belangstelling die hij tijdens zijn leven toonde voor mijn wel en wee. Het zou hem veel voldoening hebben geschonken dat ik in de voetsporen van grootvader ben getreden die ruim een eeuw geleden als jurist op stellingen promoveerde tot doctor in de Rechtswetenschap aan de Rijksuniversiteit te Utrecht.
De broers en schone zussen, ooms, tantes, nichtjes, neefjes, diverse vrienden en buren in binnen en buitenland dank ik voor hun oprechte belangstelling en zorg voor mijn welzijn.

Mijn altijd belangstellende buurvrouw Riet de Jonge en Annemarie Guldemond, Gerard Steffanie en John Rees dank ik in het bijzonder voor hun medeleven, ondersteuning en zorg door mij regelmatig van een heerlijk bord eten te voorzien, zelfs laat op de avond ('Ja, ik dacht al dat je nog aan het werk was!'), boodschappen voor mij te doen of verhalen aan te horen. Ook de Pingo's (oud-collega's uit het 'Diak' en partners: Nel en

Toby, Hanneke en Jo, Henk en Gerdien, Cecile en Wim, Carla en Wim, Nelletje), Nel In der Maur en Elma Moons dank ik voor jullie luisterend oor, hartelijke medeleven, hand- en spandiensten en niet onderzoekgerelateerde activiteiten om de zinnen te verzetten.

Mijn pianotriogenoten Dr. Marieke Houwert-de Jong, haar vervangster Gemma Habers en drs. Lot Visser dank ik voor de ontspannen en gezellige avondjes musiceren. Sorry, dat ik de laatste tijd niet aanspeelbaar was. Ik zal de cello tijdig uit zijn bekisting halen zodat wij vanaf 2012 weer met passie muziek kunnen maken!

Een speciaal dankwoord wil ik richten tot mijn paranimfen:
Drs. Riekje Sinnecker-Folbert, onze vriendschap begon 42 jaar geleden toen wij aan het begin van onze studie fysiotherapie stonden. Wij hebben door de jaren heen lief en leed gedeeld. Ik mocht 30 jaar geleden getuige zijn op jouw huwelijk met Radboud; het is mij een waar genoegen dat jij straks mijn 'getuige' wil zijn. Dank voor wie je bent, voor je humor en optimisme en voor je geweldige steun in de afgelopen tijd.
Rian Eijsermans, ook wij kennen elkaar al aardig wat jaartjes. Ik bewonder je vakvrouwschap en enorm positieve uitstraling. Nooit is iets je te veel. Dank voor je niet aflatende steun en voor je prachtige 'PROM'-mand die bij menigeen veel nieuwsgierigheid opwekte. Ik heb mijn best gedaan de pakjes niet voortijdig open te scheuren.
Hanneke Vossen, onze vriendschap dateert van eind jaren 70 toen wij collega's werden in het 'Diak'. Helaas maakten persoonlijke omstandigheden je terugtrekking als paranimf noodzakelijk. Dank voor je trouw, interesse in mijn wel en wee en hulp bij zoveel dingen. Ik wens jou en Jo de komende tijd veel sterkte toe.

Pim van Halem, oud lagere schoolgenoot en beeldend tekenaar. Wat was ik nieuwsgierig naar jouw creaties voor de buiten en binnenkant van mijn proefschrift. Al wat je had was het AIMS scoreformulier en de Nederlandstalige samenvatting van mijn proefschrift. Dan ben je een begenadigd kunstenaar als je tot zulke creaties in staat bent. Hartelijk dank voor je inzet, energie en talent die mijn 'boekje' mede tot een prachtig exemplaar hebben gemaakt.

Ronald en Irene Boiten-Mesu. Wat bijzonder dat jullie als grafisch ontwerpers de lay-out van mijn proefschrift met veel genoegen ter hand wilden nemen. Als geen ander weten jullie als ouders van een dochter die ooit bij ons heeft gelegen maar zich prachtig aan het ontplooien is, wat het betekent een kind te krijgen dat direct na de geboorte intensieve zorg nodig heeft. Dank voor jullie enthousiasme, positieve inzet, vakmanschap en bijzonder prettige samenwerking. Ik hoop dat jullie trots zullen zijn op het uiteindelijke resultaat.

Mensje van Keulen, sinds 40 jaar schrijfster, hartelijk dank voor het verlenen van uw toestemming tot gebruik van het bijzonder mooie citaat dat aan het begin van mijn proefschrift te lezen is.

Vooral de afgelopen twee decennia hebben mij geleerd hoe verleden, heden en toekomst met elkaar verbonden zijn. Ik hoop aan die toekomst nog een steentje bij te mogen dragen.
Voorlopig kan het aftellen beginnen: 13-12-11….

LIST OF PUBLICATIONS

1 Harteman J, Groenendaal F, van Haastert IC, Lien KD, Stroink H, Bierings MB, Huisman A, de Vries LS. Atypical timing and presentation of periventricular haemorrhagic infarction in preterm infants: the role of thrombophilia. Dev Med Child Neurol. 2011, in press.

2 Van der Aa NE, Leemans A, Northington FJ, van Straaten HLM, van Haastert IC, Groenendaal F, Benders MJNL, de Vries LS. Does DTI-based tractography at three months of age contribute to the prediction of motor outcome following perinatal arterial ischemic stroke? Stroke. 2011, in press.

3 Van Kooij BJM, van Pul Carola, Benders MJNL, van Haastert IC, de Vries LS, Groenendaal F. Fiber tracking at term displays gender differences regarding cognitive and motor outcome at two years of age in preterm infants. Ped Research. 2011, Aug 18. [Epub ahead of print].

4 Van Kooij BJM, de Vries LS, Ball G, van Haastert IC, Benders MJNL, Groenendaal F, Counsell SJ. Neonatal tract-based spatial statistics findings and outcome in preterm infants. American Journal of Neuro Radiology. May 2011 accepted for publication.

5 De Vries LS, van Haastert IC, Benders MJ, Groenendaal F. Myth: Cerebral palsy cannot be predicted by neonatal brain imaging. Semin Fetal Neonatal Med. 2011;16(5):279-87. Epub 2011 Jun 1.

6 Von Lindern JS, Khodabux CM, Hack KE, van Haastert IC, Koopman-Esseboom C, van Zwieten PH, Brand A, Walther FJ. Long-term outcome in relationship to neonatal transfusion volume in extremely premature infants: a comparative cohort study. BMC Pediatr. 2011 May 28;11:48.

7 van Haastert IC, Groenendaal F, Uiterwaal CS, Termote JU, van der Heide-Jalving M, Eijsermans MJ, Gorter JW, Helders PJ, Jongmans MJ, de Vries LS. Decreasing incidence and severity of cerebral palsy in prematurely born children. J Pediatr. 2011;159(1):86-91.e1. Epub 2011 Mar 2.

8 Claas MJ, de Vries LS, Bruinse HW, van Haastert IC, Uniken Venema MM, Peelen LM, Koopman C. Neurodevelopmental outcome over time of preterm born children ≤750 g at birth. Early Hum Dev. 2011;87(3):183-91. Epub 2011 Jan 8.

9 Van de Weijer-Bergsma E, Wijnroks L, Boom J, de Vries LS, van Haastert IC, Jongmans MJ. Individual differences in developmental trajectories of A-not-B performance in infants born preterm. Dev Neuropsychol. 2010;35(6):605-21.

10 Nuysink J, van Haastert IC, Takken T, Helders PJ. Symptomatic asymmetry in very young infants: a Delphi study on the development of a screening instrument. Physiother Theory Pract. 2011;27(3):194-212. Epub 2010 Sep 8.

11 Claas MJ, Bruinse HW, Koopman C, van Haastert IC, Peelen LM, de Vries LS. Two-year neurodevelopmental outcome of preterm born children ≤ 750 g at birth. Arch Dis Child Fetal Neonatal Ed. 2011;96(3):F169-77. Epub 2010 Jun 7.

12 Groenendaal F, Termote JU, van der Heide-Jalving M, van Haastert IC, de Vries LS. Complications affecting preterm neonates from 1991 to 2006: what have we gained? Acta Paediatr. 2010;99(3):354-8. Epub 2010 Jan 8.

13 van Haastert IC, de Vries LS, Eijsermans MJ, Jongmans MJ, Helders PJ, Gorter JW. Gross motor functional abilities in preterm-born children with cerebral palsy due to periventricular leukomalacia. Dev Med Child Neurol. 2008;50(9):684-9.

14 Ricci D, Romeo DM, Haataja L, van Haastert IC, Cesarini L, Maunu J, Pane M, Gallini F, Luciano R, Romagnoli C, de Vries LS, Cowan FM, Mercuri E. Neurological examination of preterm infants at term equivalent age. Early Hum Dev. 2008;84(11):751-61. Epub 2008 Jul 9.
15 Brouwer A, Groenendaal F, van Haastert IL, Rademaker K, Hanlo P, de Vries L. 11. Neurodevelopmental outcome of preterm infants with severe intraventricular hemorrhage and therapy for post-hemorrhagic ventricular dilatation. J Pediatr. 2008;152(5):648-54. Epub 2007 Dec 26.
16 Nuysink J, van Haastert IC, Takken T, Helders PJM. Symptomatic Asymmetry in the first six months of life: differential diagnosis. Eur J Pediatr. 2008;167(6):613-9. Epub 2008 Mar 4. Review.
17 Van Haastert IC, Eijsermans MJ, de Vries LS. Should new reference values on the AIMS test need to be established for Dutch children? Acta Paediatr. 2007;96(7):1110-1; author reply 1111-2. Epub 2007 May 10.
18 Rademaker KJ, Uiterwaal CS, Groenendaal F, Venema MM, van Bel F, Beek FJ, van Haastert IC, Grobbee DE, de Vries LS. Neonatal hydrocortisone treatment: neurodevelopmental outcome and MRI at school age in preterm-born children. J Pediatr. 2007;150(4):351-7.
19 Van Haastert IC, de Vries LS, Helders PJ, Jongmans MJ. Early gross motor development of preterm infants according to the Alberta Infant Motor Scale. J Pediatr. 2006 Nov;149(5):593-4.
20 Osredkar D, van Haastert I and de Vries LS. Why is the neurological examination so badly neglected in early childhood?: in reply. Pediatrics 2005;116:1048.
21 Rademaker KJ, Uiterwaal CS, Beek FJ, van Haastert IC, Lieftink AF, Groenendaal F, Grobbee DE, de Vries LS. Neonatal cranial ultrasound versus MRI and neurodevelopmental outcome at school age in children born preterm. Arch Dis Child Fetal Neonatal Ed. 2005 Nov;90(6):F489-93. Epub 2005 Jun 14.
22 De Vries LS, van der Grond J, van Haastert IC, Groenendaal F. Prediction of outcome in new-born infants with arterial ischaemic stroke using diffusion-weighted magnetic resonance imaging. Neuropediatrics. 2005;36(1):12-20.
23 Rademaker KJ, Lam JN, van Haastert IC, Uiterwaal CS, Lieftink AF, Groenendaal F, Grobbee DE, de Vries LS. Larger corpus callosum size with better motor performance in prematurely born children. Semin Perinatol. 2004;28(4):279-87.
24 De Vries LS, van Haastert IL, Rademaker KJ, Koopman C, Groenendaal F. Ultrasound abnormalities preceding cerebral palsy in high-risk preterm infants. J Pediatr. 2004;144(6):815-20.
25 Mercuri E, Guzzetta A, Laroche S, Ricci D, van Haastert I, Simpson A, Luciano R, Bleakley C, Frisone MF, Haataja L, Tortorolo G, Guzzetta F, de Vries L, Cowan F, Dubowitz L. Neurologic examination of preterm infants at term age: comparison with term infants. J Pediatr. 2003;142(6):647-55.
26 De Vries LS, Roelants-van Rijn AM, Rademaker KJ, van Haastert IC, Beek FJ, Groenendaal F. Unilateral parenchymal haemorrhagic infarction in the preterm infant. Eur J Paediatr Neurol. 2001;5(4):139-49.
27 Roelants-van Rijn AM, Groenendaal F, Beek FJ, Eken P, van Haastert IC, de Vries LS. Parenchymal brain injury in the preterm infant: comparison of cranial ultrasound, MRI and

neurodevelopmental outcome. Neuropediatrics. 2001;32(2):80-9.
28 Pierrat V, Duquennoy C, van Haastert IC, Ernst M, Guilley N, de Vries LS. Ultrasound diagnosis and neurodevelopmental outcome of localised and extensive cystic periventricular leucomalacia. Arch Dis Child Fetal Neonatal Ed. 2001;84(3):F151-6.
29 Eijsermans MJC, van Haastert IC, Gulmans VAM, Helders PJM. Motor Performance after Bottom-shuffling in Early Childhood. Physiotherapy. 2000;86(2):81-4.
30 De Vries LS, Groenendaal F, van Haastert IC, Eken P, Rademaker KJ, Meiners LC. Asymmetrical myelination of the posterior limb of the internal capsule in infants with periventricular haemorrhagic infarction: an early predictor of hemiplegia. Neuropediatrics. 1999;30(6):314-9.
31 De Vries LS, Rademaker KJ, Groenendaal F, Eken P, van Haastert IC, Vandertop WP, Gooskens R, Meiners LC. Correlation between neonatal cranial ultrasound, MRI in infancy and neurodevelopmental outcome in infants with a large intraventricular haemorrhage with or without unilateral parenchymal involvement. Neuropediatrics. 1998;29(4):180-8.
32 Groenendaal F, van der Grond J, Eken P, van Haastert IC, Rademaker KJ, Toet MC, de Vries LS. Early cerebral proton MRS and neurodevelopmental outcome in infants with cystic leukomalacia. Dev Med Child Neurol. 1997;39(6):373-9.
33 De Vries LS, Groenendaal F, Eken P, van Haastert IC, Rademaker KJ, Meiners LC. Infarcts in the vascular distribution of the middle cerebral artery in preterm and fullterm infants. Neuropediatrics. 1997;28(2):88-96.
34 De Vries LS, Eken P, Groenendaal F, van Haastert IC, Meiners LC. Correlation between the degree of periventricular leukomalacia diagnosed using cranial ultrasound and MRI later in infancy in children with cerebral palsy. Neuropediatrics. 1993;24(5):263-8.

In Dutch journals

1 Claas MJ, van Haastert IC, Bruinse HW, Uniken Venema MMA, de Vries LS en Koopman C. Het testen van de cognitieve en motorische ontwikkeling van kinderen. Wat meten we, wanneer en met welke test? Nederlands Tijdschrift voor Obstetrie en Gynaecologie. 2005;123:380-5.
2 Nuysink J, van Haastert IC, N.L.U. van Meeteren NLU, Helders PJM. Motorische rijping bij zuigelingen verwezen met een voorkeurshouding of asymmetrie; een beknopte beschrijvende studie**.** Ned T Fysiother. 2005;115(4):101-5.
3 Van Haastert IC. 'Een vergelijkende studie van de BOS 2-30 en de AIMS: twee motorische ontwikkelingstests die worden gebruikt bij prematuur geborenen'. Ned T Fysiother. 2001;111(2):52-3. Lezersreactie.
4 De Vries LS, van Haastert IC, Eken P en Groenendaal F. De rol van neonataal kernspinresonantieonderzoek bij het voorspellen van de ontwikkeling van voldragen kinderen met perinatale asfyxie. Tijdschr Kindergeneeskd. 2000;68(6):234-40.
5 Van Haastert IC. 'De motorische ontwikkeling van de zuigeling: variëren, selecteren, leren adapteren.' Kinderfysiotherapie. 2000;10(29):2-3. Boekbespreking.

6 Van Haastert IC, Gulmans VAM, Helders PJM. Dynamics of motor development of preterm infants in the first year of life. Kinderfysiotherapie. 1999;10(24):5-6.
7 Van Haastert IC en Helders PJM. Het effect van een gecorrigeerde omphalocèle op de motorische ontwikkeling van een meisje: een casusbespreking. Kinderfysiotherapie. 1998;3(19):9-12.
8 Groenendaal F, van der Grond J, van Haastert IC, Eken P, Mali WP, de Vries LS. Bevindingen bij cerebrale protonkernspinresonantie-spectroscopie bij pasgeborenen met asfyxie, en psychomotore ontwikkeling. Ned Tijdschr Geneeskd. 1996;140(5):255-9.
9 Van Haastert IC. Te vroeg geboren: indicatie voor kinderfysiotherapeutische interventie? Kleine Maatjes. 1996;18(3):20-1.
10 Engelbert RHH, Schoenmakers MAGC, van Haastert IC en Helders PJM. Loopstoeltjes: panacee of plaag? Tijdsch Kindergeneeskd. 1994;62(6):277-80.

Chapters in books

1 van Haastert IC, de Kleine M. Neonatologie en follow-up: Follow-up van pasgeborenen met een verhoogd risico op ontwikkelingsstoornissen. Hoofdstuk 8 B (p 241-52). In: Kinderfysiotherapie, tweede herziene druk. Maarssen: Elsevier Gezondheidszorg, 2006.
2 Langelaan A, van Haastert IC. Neonatologie. Hoofdstuk 10 (p 205-17). In: Kinderfysiotherapie. Maarssen: Elsevier Gezondheidszorg, 2000.

CURRICULUM VITAE

De auteur van dit proefschrift werd begin oktober 1950 met een watervliegtuig intra-uterien overgeplaatst van Pontianak (Borneo) naar Djakarta, Java, Indonesië, waarna de reis zich voortzette met het vlaggenschip van de Koninklijke Rotterdamsche Lloyd, ms de Willem Ruys, richting Amsterdam. Twee dagen na aankomst, maar twee weken te vroeg, werd zij op 2 november te Hilversum geboren.

Nauwelijks 6 maanden oud onderging zij haar eerste extra-uteriene luchtdoop richting Indonesië waar zij 5 jaar woonde in Pontianak, Medan (Sumatra) en Surabaya (Java).

Haar lagere en middelbare schooltijd bracht zij door in Voorburg (ZH). Na haar eindexamen in 1969 (Huygens Lyceum; Middelbare Meisjes School) ging zij in Utrecht fysiotherapie studeren (directeur Dr. R. Strikwerda†, later Dr. J. P. Schadé). Nog voor het afronden van haar opleiding in april 1975 werkte zij in het verpleeg- en reactiveringcentrum Nassau Odijckhof te Driebergen (hoofd Jan Willem Doove).

Van maart 1976 tot augustus 1991 was zij werkzaam in het Diakonessenhuis te Utrecht, waarvan de laatste tien jaar als waarnemend hoofd (hoofden Jaco B. den Dekker†, Ron Sneep en Martin H. van Lijf). Medio augustus 1991 startte zij haar werkzaamheden in het Wilhelmina Kinderziekenhuis (hoofd Prof. Dr. Paul J.M. Helders).

In de loop der jaren heeft zij diverse cursussen gevolgd om zich vooral vakinhoudelijk te bekwamen (o.a. de Bobath cursus, fysiotherapie en ontwikkelingsstoornissen bij kinderen van 0 tot 2 jaar en de aanvullingscursus kinderfysiotherapie). In de zomer van 1992 volgde een studiebezoek aan het Children's Hospital te Boston, USA bij Prof. Dr. Heidelise Als.

De auteur was jarenlang (bestuurs)lid van de werkgroep 'vroegtijdige onderkenning en behandeling van zuigelingen' en van de landelijke werkgroep neonatologische centra.

Eind 1992 werd zij lid van de Nederlandse Vereniging voor Fysiotherapie in de Kinder en Jeugdgezondheidszorg en begin 1995 werd zij opgenomen in het register van bevoegde kinderfysiotherapeuten. Zij volgde de post HBO opleiding onderzoek, statistiek en kritisch lezen en scholing in wetenschap II en III van de St. Wetenschap en Scholing Fysiotherapie. Zij was deelnemer van de 1e cursus 'Assessment of general movements in preterm and full-term infants' die in Groningen werd gegeven en volgde later de cursus 'Relevance of normal and abnormal muscle tone in the infant neurological examination' te Groningen.

In september 1997 startte zij de deeltijdstudie Pedagogische Wetenschappen aan de Universiteit Utrecht met als specialisatie orthopedagogiek: gehandicaptenzorg. In 2001 behaalde zij haar doctoraal examen.

Naast patiëntenzorg, studie en onderzoek, gaf zij regelmatig les in de kliniek en daarbuiten, en vele lezingen. Als gastdocent is zij verbonden aan de opleiding Professional Master Kinderfysiotherapie van de Hoge School Utrecht en was dat voor korte tijd aan de Transfergroep te Rotterdam. Om collega's bekend te maken met de AIMS reisde zij veelal op zaterdagen door het land om workshops te geven. Ook voor collegae en onderzoekers in het Kinderspital te Zürich (Zwitserland) en recent in Nottingham (United Kingdom) werden workshops verzorgd.

Vanaf begin 2003 is zij in de functie van orthopedagoog werkzaam voor de neonatale follow-up polikliniek van de afdeling neonatologie, Divisie Vrouw en Baby.

Van begin 2003 tot eind 2004 werkte zij een dag in de week in een particuliere praktijk voor kinderfysiotherapie in Rijswijk.

Het besluit een promotietraject te volgen werd definitief genomen toen begin 2006 het indienen van het manuscript over de toepassing van de AIMS bij prematuur geboren kinderen bij The Journal of Pediatrics een feit was.

Appendix A-o Original basic FU protocol for infants and children with perinatal risk factors (1996)

Age *	**Assessment**
TEA	▪ cUS, retinopathy screening and neonatal neurological assessment (e.g. Prechtl, Dubowitz) ▪ Inventory of social background data ▪ Determination of a neonatal risk score
*6 months**	▪ Neurological screening (e.g. Touwen, Amiel-Tison) ▪ Paediatric check-up: health status, growth (weight, height and head circumference) and developmental screening (BSID II, van Wiechen assessment)
*12-18 months**	▪ Neurological screening (Touwen, Amiel-Tison) ▪ Pediatric check-up ▪ BSID II
*24 months**	▪ Paediatric check-up ▪ BSID II ▪ Child Behavior Check List (CBCL) 2-3 years
5 years	▪ Paediatric check-up ▪ Neuromotor screening (Touwen, Movement-ABC) ▪ Revision of the Amsterdam Child-Intelligence Test (RAKIT) ▪ CBCL 4-18
8 years	▪ Paediatric check-up ▪ Neuromotor screening (Touwen, Movement-ABC) ▪ Intelligence assessment ▪ CBCL 4-18

* Corrected for degree of prematurity

Appendix A-1 FU protocol for infants and children born ***preterm*** (2011)

Age	**Assessment**
TEA	▪ History taking ▪ Neonatal neurological assessment (e.g. General Movements, Dubowitz, TIMPSI) ▪ Paediatric check-up: present health status, growth (weight, height, head circumference) ▪ cUS
*6 months**	▪ History taking ▪ Paediatric check-up: present health status and growth ▪ Neuromotor developmental screening (GMDS, van Wiechen assessment, AIMS) ▪ Neurological screening (e.g. Amiel-Tison)
*15 months**	▪ History taking ▪ Paediatric check-up: present health status and growth ▪ Neuromotor developmental screening (GMDS, van Wiechen assessment, AIMS) ▪ Neurological screening (e.g. Amiel-Tison)
24 months	▪ History taking ▪ Paediatric check-up: health status and growth ▪ GMDS or [a] BSITD-III: cognitive and motor subtests ▪ Neurological screening ▪ [a] Child Behavior Check List (CBCL) 1.5-5 years
3.5 years	▪ History taking ▪ Paediatric check-up: health status and growth ▪ GMDS ▪ Neurological screening
5.5 years [a]	▪ History taking ▪ Paediatric check-up: health status and growth ▪ Language screening ▪ Neuromotor screening (GMDS and Movement-ABC)
5.5-6 years [b]	▪ History taking ▪ WPPSI-III NL ▪ CBCL 1.5-5 years (also Teacher Report Form)

[a] GA <30 weeks and/or BW <1000 gram and research studies: PHVD, intra-uterine growth restriction ; [b] psychological assessment

Appendix A-2 FU protocol for infants and children born ***full-term*** (2011)

Age	**Assessment**
3 months	▪ History taking ▪ Neonatal neurological assessment (e.g. General Movements, Amiel-Tison) ▪ Paediatric check-up: present health status, growth (weight, height, head circumference) ▪ cUS
9 months	▪ History taking ▪ Paediatric check-up: present health status and growth ▪ Neuromotor developmental screening (GMDS, van Wiechen assessment and AIMS) ▪ Neurological screening (e.g. Amiel-Tison)
18 months	▪ History taking ▪ Paediatric check-up: present health status and growth ▪ GMDS and AIMS ▪ Neurological screening (Amiel-Tison)
24 months [a]	▪ History taking ▪ Paediatric check-up: health status and growth ▪ BSITD-III: cognitive and motor subtests ▪ Neurological screening ▪ Child Behavior Check List (CBCL) 1.5-5 years
5.5 years [b]	▪ History taking ▪ Paediatric check-up: health status and growth ▪ Neuromotor screening (Movement-ABC)
5.5-6 years [c]	▪ History taking ▪ WPPSI-III NL ▪ CBCL 1.5-5 years (also Teacher Report Form)

[a] research studies: cooling, congenital heart disorders, EPO; [b] after a history of perinatal asphyxia; [c] psychological assessment