

From CLINTEC, Department of Paediatrics
Karolinska Institutet, Stockholm, Sweden

**LONG-TERM NEURODEVELOPMENTAL OUTCOME
AFTER MODERATE NEONATAL ENCEPHALOPATHY
AND AFTER POST-TERM BIRTH
– TWO POPULATION-BASED STUDIES**

Katarina Lindström



**Karolinska
Institutet**

Stockholm 2006

Cover: Picture by Bjørg Tveten Stjernstad. Published with permission.
All previously published papers were reproduced with permission from the publisher.

Published and printed by Repro Print AB
Stockholm, Sweden
© Katarina Lindström, 2006
ISBN 91-7140-702-2

To Yasmin and Josefin

ABSTRACT

Long-term neurodevelopmental outcome in two population-based groups of children with different perinatal events was studied:

A: Children born at term with moderate neonatal encephalopathy (NE) and

B: children born post-term, i.e., at a gestational age of ≥ 42 weeks.

Aims:

A: To study the long-term neurodevelopmental outcome including cognitive functioning after moderate NE and to investigate white matter regions.

B: To evaluate developmental data obtained at the ages of 4 and 5.5 years in children born post-term.

Material and methods:

A: Of all children born in Sweden in 1985, 684 had an Apgar score of < 7 at 5 minutes of age. From the records for these children, those with moderate NE were identified, and the obstetric records were evaluated. The mothers of the children not suffering from cerebral palsy (CP) were interviewed – semistructured and according to rating scales – to obtain information about their child’s development and cognitive functioning, and a subgroup was investigated with Diffusion tensor imaging (DTI) and by performing cognitive tests.

B: Records from the Child Health Centres for the 354 children who were born after 42 weeks gestation in 1991 at Huddinge University Hospital were assessed to extract the developmental data from each child’s check-up at 4 and 5.5 years.

Results:

A: Fifty-six children had had moderate NE (0.57/1000). Most pregnancies were found to be uneventful, but post-term deliveries occurred significantly more often among the mothers giving birth to children with moderate NE than in the general population (19% vs 8%). Ominous FHR patterns were common in these cases. Fifteen of the 56 children had CP or other major neuroimpairments. Of the 41 without CP, 13 did not participate. Of the 28 children without CP, 20 had cognitive dysfunctions, including learning disabilities, impaired social interaction and executive dysfunctions, and 8 had no impairments. DTI, performed in 9 subjects revealed white matter changes in several regions, including the internal capsules, corpus callosum and frontal white matter areas.

B: Definite or suspected neurological disorders/developmental deviations were significantly more common amongst the children born after prolonged pregnancies (13%) than in the comparison group (5.5%).

Conclusions:

A: The present study reveals an unexpectedly high rate of cognitive and neurological disabilities/dysfunctions in term children who have suffered from moderate NE. Of all children participating only 19% had no disabilities or dysfunctions. Changes in the DTI were observed in several white matter regions, even in the absence of CP.

B: Post-term pregnancies were associated with a higher than average rate of neurological disorders or developmental deviations at the age of 4 and/or 5.5 years.

LIST OF PAPERS

- I. **Lindström K**, Hallberg B, Blennow M, Fernell E, Westgren M.
Moderate neonatal encephalopathy in term children is associated with a high rate of cognitive dysfunctions at 15-19 year follow-up; pre- and perinatal risk factors.
(Submitted)
- II. **Lindström K**, Lagerroos P, Gillberg C, Fernell E.
Teenage outcome after being born at term with neonatal encephalopathy.
(Submitted)
- III. Nagy Z, **Lindström K**, Westerberg H, Skare S, Andersson J, Hallberg B, Lilja A, Flodmark O, Lagerkrantz H, Klingberg T, Fernell E.
Diffusion tensor imaging on teenagers born at term with moderate hypoxic ischemic encephalopathy.
Pediatr Res; 2005 Nov;58(5):936-40.
- IV. **Lindström K**, Fernell E, Westgren M.
Developmental data in preschool children born after prolonged pregnancy.
Acta Paediatr; 2005 Sep;94(9):1192-7.

CONTENTS

PREFACE	1
INTRODUCTION.....	3
Perinatal asphyxia.....	3
Molecular/Cellular level.....	3
Structural level.....	3
Clinical level.....	7
Obstetrical aspects	7
Neonatal aspects	7
Neuropaediatric aspects.....	8
Long-term outcome after neonatal encephalopathy	11
Prolonged pregnancy / post-term birth	13
Perinatal outcome	14
Long-term paediatric outcome	14
AIMS	16
MATERIAL AND METHODS	17
Outcome studies of children born at term in 1985 with moderate neonatal encephalopathy (NE) (I-III).....	17
Study I.....	18
Study II.....	19
Study III	19
Outcome after Post-term birth –(IV).....	20
Statistical Analyses.....	21
Ethical considerations.....	21
RESULTS	22
Pre- and perinatal factors (Study I)	22
Data relating to the pregnancy and delivery	24
Data relating to the neonatal period	25
Cognitive dysfunctions without CP (Study II)	25
Neurological diagnoses	27
Cognitive impairments	27
Diffusion tensor imaging (Study III)	28
Post-term birth and developmental aspects (Study IV).....	28
Pregnancy and delivery data.....	28
Neurodevelopmental outcome at pre-school age.....	28
GENERAL DISCUSSION.....	30
Neonatal encephalopathy (Studies I – III).....	30
Post-term birth and developmental aspects (Study IV).....	34
Long-term follow-up studies.....	35
CONCLUSIONS	36
THE DIRECTION OF FUTURE RESEARCH	37
SUMMARY IN SWEDISH-SVENSK SAMMANFATTNING.....	39
ACKNOWLEDGEMENTS	40
REFERENCES	43

LIST OF ABBREVIATIONS

AD/HD	Attention deficit/hyperactivity disorder
ADHD-RS	Attention deficit hyperactivity disorder-rating scale
AS	Apgar score
ASSQ	Asperger syndrome screening questionnaire
CHC	Child health centre
CP	Cerebral palsy
CT	Computed tomography
CTG	Cardiotachogram
DAMP	Deficits in attention, motor control and perception
DCD	Developmental coordination disorder
DTI	Diffusion tensor imaging
EF	Executive functions
FHR	Fetal heart rate
GA	Gestational age
HIE	Hypoxic ischaemic encephalopathy
ICF	International classification of functioning, disability and health
IQ	Intelligence quotient
LMP	Last menstrual period
MMR	Mild mental retardation
MR	Mental retardation
MRI	Magnetic resonance imaging
NE	Neonatal encephalopathy
NICU	Neonatal intensive care unit
OR	Odds ratio
PVL	Periventricular leucomalacia
SGA	Small for gestational age
SMBR	Swedish medical birth register
SMR	Severe mental retardation
WM	White matter

PREFACE

The most magic moment of all — the birth of a child — will always be important. For the parents, however, a whole new phase of worries and concerns is just starting. For the individual, life has just begun. There are many factors determining a child's development and questions will often arise about what role the pregnancy and delivery may have had.

For me it is important to try to eliminate some of the question marks. Almost every day in my work as a neuropaediatrician I get asked questions about what impact pre- and perinatal factors have had on my patients' development. Some of the answers are fairly clear-cut, such as with severe perinatal asphyxia, which is known to be able to have an impact on the future development of a child. Post-term birth, and its relationship with development, is less certain.

The work conducted for this thesis has been a journey in many ways, not least because I have learnt a great deal about myself. Research involves so much more than I had imagined at the outset. The more I have learnt, the more new questions I have arisen. I guess that is the excitement of research — you are never done, there is always more left to explore. The limits are set by the fantasy, creativity, time and stubbornness of the researcher (and sometimes the money...)!

It is fascinating to experience how closely my clinical work and research are linked to each other. Only now do I fully understand the importance of clinical research. I also see the relevance of developmental medicine as an entity. Quality of life and the perspective a person adopts of their life from birth and onwards, that is what it all is about!

I hope you will enjoy reading this book. I hope, too, that you will learn something new and raise some new questions in so doing. I did in writing it.

Katarina Lindström
Tyresö, February 2006

INTRODUCTION

PERINATAL ASPHYXIA

Perinatal asphyxia, derived from the Greek word asphyxis, meaning loss of pulse, refers to a failure in the exchange of respiratory gases, oxygen and carbon dioxide. The definitions of perinatal asphyxia vary and usually include several biochemical and clinical indices [1, 2]. The role and consequences of perinatal asphyxia in infants born at term have been studied extensively [3-5] and is one of the main causes of neurodevelopmental disability [4, 6]. The large body of research now available indicates that multiple causative factors can be involved in perinatal asphyxia, in addition to the obvious perinatal factors [7, 8].

The consequences of perinatal asphyxia can be analysed at three different levels, the molecular/cellular, the structural and the clinical level. These are discussed briefly below.

MOLECULAR/CELLULAR LEVEL

At a micro level, hypoxia is followed by energy depletion, release of excitatory amino acids, accumulation of extracellular glutamate and activation of glutamate receptors. A cascade of deleterious mechanisms occur, involving accumulation of cytosolic calcium and a variety of calcium-mediated deleterious events. After the initial injury, apoptosis (programmed cell death) occurs. [9, 10]. These factors can give rise to a broad spectrum of neurological deficits and impairments.

Several biochemical markers, such as brain specific proteins like S-100 and different cytokines in cerebrospinal fluid (CSF) and serum, have been used to predict the extent of brain injury after perinatal asphyxia [11-16].

STRUCTURAL LEVEL

Brain development and imaging

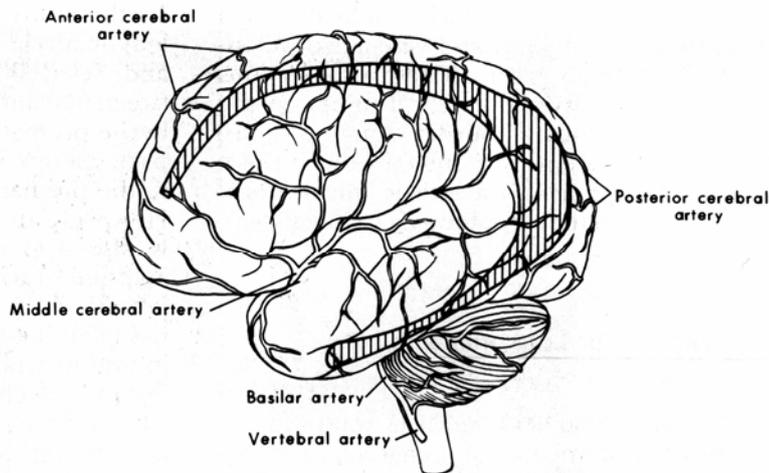
Post-mortem studies and the recent advances in modern imaging techniques, especially magnetic resonance imaging (MRI), have contributed to the understanding of brain structure, development and pathological processes. Nowadays, modern imaging techniques can be used to group the aetiologies behind various neurodevelopmental disorders into a prenatal, perinatal or postnatal period of origin.

Cranial ultrasound and histological post-mortem findings were analysed in full-term neonates with hypoxic ischaemic encephalopathy (HIE) who had died in the perinatal period. Lesions were detected in the periventricular/subcortical white matter (WM), the cortex and the thalamus, and the authors discussed the value of modern cranial ultrasound for detecting intracranial abnormalities in infants with HIE [17].

The role of antenatal, intrapartum and postpartum factors was evaluated in a large MRI and post-mortem study of the brains of full-term children with neonatal encephalopathy (NE) and early neonatal seizures. The findings strongly suggested that events in the immediate perinatal period are most important in neonatal brain injury [18].

In the early stages of brain maturation, in the first and second trimester, pathological processes will result in structural malformations, including migrational disturbances. In the third trimester the process of myelination and the development of neuronal networks occurs, and at this stage, vascular disturbances are decisive for lesions. A lesion ensuing a perinatally acquired circulatory insult is highly dependent on the stage of maturation of the brain at birth, owing to the changing vascular supply of the brain between the second and the third trimester. A vascular lesion occurring between a gestational age (GA) of 24-34 weeks will affect the periventricular zone, while a circulatory insult, such as the predecessor of HIE, occurring at term, will affect other regions, such as the parasagittal area, the basal ganglia, the thalamus, the cerebellum or the brain stem [19-21]. The vascular border zone of the three major cerebral arteries, are particularly vulnerable (Figure 1).

Figure 1. The parasagittal area and the distribution of the major cerebral arteries (reproduced from Neurology of the Newborn, with permission from J.J Volpe)



Among the term infants with cerebral palsy (CP) in a population-based series two children, born at a GA of 37 weeks, with a perinatal aetiology of CP had periventricular leucomalacia (PVL). One of these two children had no other abnormality than PVL and the other had PVL combined with a parasagittal injury. No prenatal risk factors had been recorded. The authors discussed that the findings was in accordance with reports of PVL in term infants – with lower GA – and asphyxia. On the other hand, a parasagittal injury after HIE was revealed in a child born after a GA of 36 weeks [20].

White matter

The process of myelination is starting before birth and continuing up to young adulthood. At birth, the myelination process is observed in the pons and cerebral peduncles, followed by the posterior limb of the internal capsule, optic radiata and splenium of the corpus callosum. Thereafter, the myelination continues in the anterior limb of internal capsule, genu, and finally the white matter (WM) of the frontal, parietal and occipital lobes is formed [22].

WM plays an important role in development, aging and many neurological and psychiatric disorders. The rapid advancement of imaging techniques, such as MRI, is able to provide information about both normal and abnormal WM. Filley has reviewed the contemporary understanding of WM and its disorders from the perspective of behavioural neurology, and states that, with the exception of the corpus callosum and some association systems, relatively little is known of the neurobehavioral affiliations of these tracts [23]. It has been suggested that the myelination of WM in children, especially in the frontal lobes correlates with mature aspects of, for example, executive function.

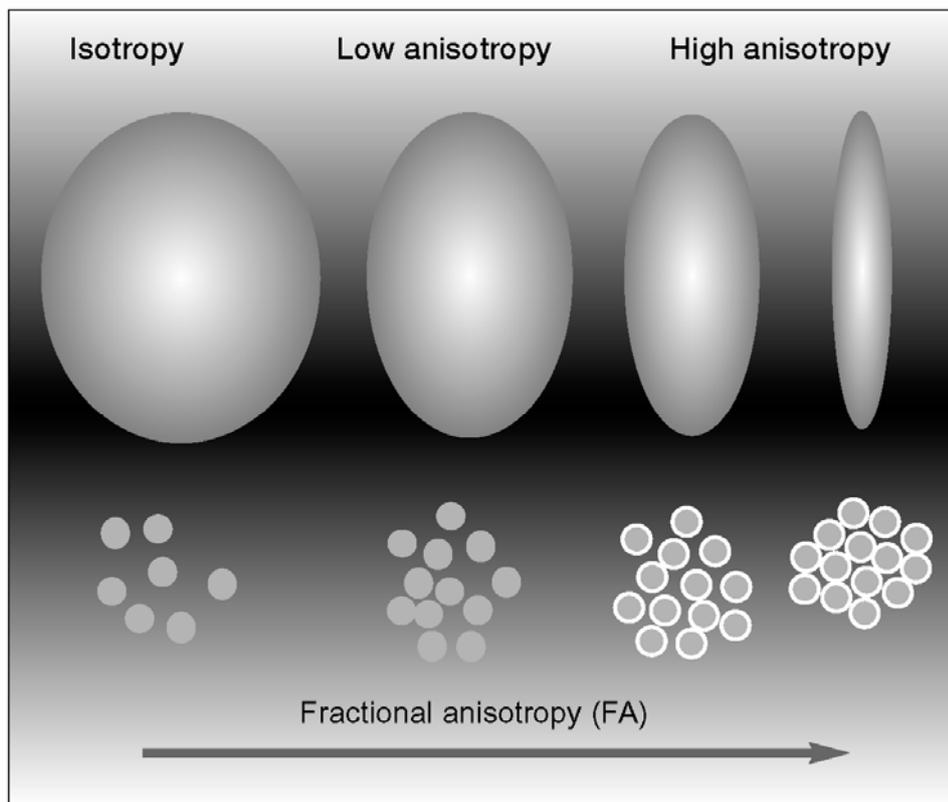
The subcortical WM is characteristically involved after perinatal asphyxia in infants born at term. An abnormal intensity in the posterior limb of the internal capsule revealed in MR images made within 17 days of birth has been shown to correlate with neurodevelopmental impairment at the age of 1 year [24, 25].

Diffusion tensor imaging

Fractional anisotropy Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) is a relatively new technique within the field of magnetic resonance imaging (MRI). Fractional anisotropy DTI can provide information on the microstructure of WM in the brain. It can visualize the location, the orientation and be an indicator of myelination and axonal thickness. The architecture of the axons in parallel bundles and their myelin shield facilitate the diffusion of water molecules along their main direction. Depending on the number, size, arrangement and density of axons, the water will diffuse by different means within the brain. For grey matter, the ellipsoid is a sphere, for WM it is elongated in one direction, cigar-shaped. See Figure 2. From the diffusion tensor, the mean diffusion (corresponding to the size of the ellipsoid) and the degree of anisotropy (describing the shape of the ellipsoid) may be calculated. In the absence of restriction, water diffusion is isotropic, meaning that it is uniform on all directions. Diffusion preferentially oriented in one direction is called anisotropic diffusion. The fractional anisotropy (FA) is a measure of the extent of the anisotropy, and it takes a value between 0 and 1, where 0 represents perfect isotropy and 1 corresponds to one-dimensional diffusion [26].

Figure 2 Illustration of Fractional Anisotropy



The vector can be colour-coded, yielding a cartography of tracts showing position and direction (red for left-right, blue for superior-inferior and green for anterior-posterior); the brightness is weighted according to the tracts' anisotropy.

Fiber tracking DTI

Fiber tracking algorithms can be used to track a fiber along its whole length.

Clinical implications

The DTI technique has been used in studies of several neurological and psychiatric disorders; multiple sclerosis, stroke, Alzheimers, obsessive-compulsive disorder and schizophrenia [27-31]. Alterations in WM has been seen in subjects with attention deficit/ hyperactivity disorder (AD/HD) and also in children born pre-term [32, 33].

CLINICAL LEVEL

Obstetrical aspects

Fetal heart rate

Monitoring of the fetal heart rate (FHR) is a tool for detecting potential asphyxia. Several anomalous types of FHR pattern are associated with the risk of acidemia such as absent or minimal variability, recurrent late decelerations, recurrent severe variable decelerations, persistent or progressive bradycardia (particularly bradycardia below 80 beats per minute) and persistent tachycardia or bradycardia with minimal or absent variability [34].

The positive predictive value for acidemia in fetuses demonstrating abnormal FHR patterns is low [35]. Although there are certain fetal heart rate patterns that are associated with an increased risk of fetal asphyxia, most of the fetuses with these patterns will show no signs of asphyxia at birth. The other side of the coin is that FHR patterns will not discriminate all asphyxial exposures either. Continuous FHR monitoring, however, supplemented by fetal blood gas and lactate assessment can be useful. This will not prevent all cases of moderate or severe asphyxia, but it might prevent mild forms progressing to become moderate or severe ones in some cases [36].

Neonatal aspects

Apgar score

Virginia Apgar, invented the scoring system in the 1950s since which time it has come into use worldwide. The scoring was not initially intended to be a tool for making prognoses or for diagnosing asphyxia. Rather, the score is a description of the child's clinical status after birth, which can be affected by many conditions, including asphyxia [37, 38]. However, the Apgar score has come into use as a marker for asphyxia and been used to predict prognosis. In many studies it has been used as a major outcome measure reflecting complications during birth [6].

Multi-organ involvement after perinatal asphyxia

It is not only the brain that can be affected by asphyxia, multiple organs can suffer. The most common organs affected are the kidneys, the heart/cardiovascular system, the pulmonary system, the liver, and the gastrointestinal systems. Hematological abnormalities and metabolic derangements are also seen. These multi-organ symptoms are often reversible [1, 39].

Hypoxic ischaemic encephalopathy and neonatal encephalopathy

Sarnat and Sarnat presented a classification system in 1976 offering degrees of severity of the neurological symptoms following hypoxia in newborns [40]. This classification of the grade of hypoxic ischaemic encephalopathy (HIE) has since been modified by others [41, 42]. HIE develops during the first days of life after an asphyxial event has occurred and three main grades, mild, moderate and severe, have been distinguished: Mild HIE appears during the first 24 hours and includes jitteriness, a hyperalert status

and irritability, with a low threshold for the Moro response, which may occur spontaneously. Muscle tone is normal, but tendon reflexes can be increased. Consciousness is not impaired. Moderate HIE is characterized by lethargy and dulled senses, lasting for at least 24 hours. Muscle tone at rest is decreased. Seizures usually develop after 12-24 hours. In severe HIE the child is stuporose, muscle tone is flaccid and complex reflexes are absent. Seizures, when present, are difficult to control.

A broader definition of newborn encephalopathy has been proposed since it is unclear what proportion of neurological impairment is due to perinatal hypoxia, how much is caused by antepartal factors, and how different factors might act together pre- and perinatally [43-45]. Neonatal encephalopathy (NE) is the preferred term today, instead of HIE. The causes of NE are heterogeneous. Restriction of intrauterine growth, preeclampsia and an acute intrapartum event all increase the risk of NE [46]. In addition, febrile disease, maternal infection and thyroid dysfunction in the mother increase the risk [7, 8, 47, 48].

Many authors use a broader definition of moderate and severe NE, including seizures alone or any of the following two lasting for longer than 24 hours: Abnormal consciousness, difficulty maintaining respiration, difficulty feeding, abnormal tone and reflexes [8, 49].

The prevalence of perinatal asphyxia/newborn encephalopathy ranges from 1.8 to 7.7/1000 term live births according to the definition used and the population to which it is applied [6, 42, 50-53]. In Sweden the prevalence of HIE in a study by Thornberg was 1.8/1000 in a population of infants born at term with an Apgar score of < 7 at 5 minutes. The prevalence of moderate HIE was 0.57 /1000 [3].

Neuropaediatric aspects

Neurodevelopmental disorders

Neurodevelopmental disorders and deviations include conditions presenting with motor problems, learning difficulties, language impairments, social dysfunctions, attention deficits and/or different types of behavioural symptom. Several types of motor and cognitive dysfunctions underlie these problems, i.e., there are different etiologies, and they present with different degrees of severity. An increasing awareness of cognitive disabilities and the common association between motor and cognitive dysfunctions has gradually evolved in neuropaediatrics in recent years. A close collaboration between neuropsychologists and neuropaediatricians has been fruitful and has increased the understanding of cognitive deficiencies in different types of developmental disorders. This is reflected by the newly proposed definition of cerebral palsy (CP) in which the commonly occurring accompanying conditions are emphasized, such as the different types of cognitive disabilities, vision, hearing and seizure disorders [54].

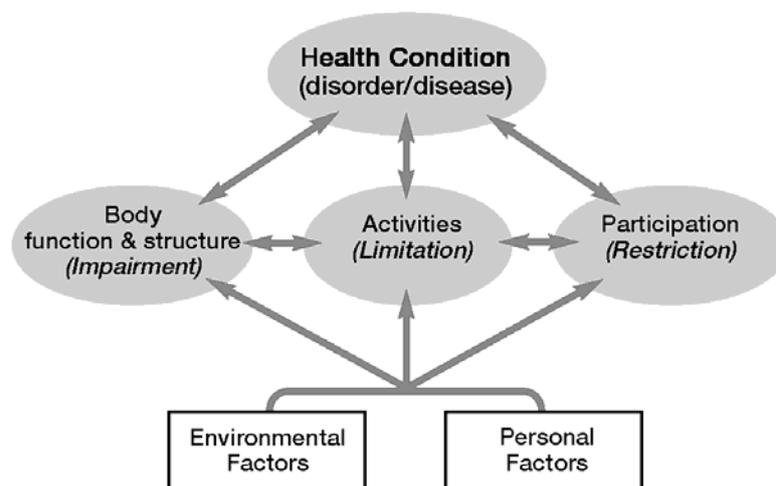
Certain developmental disorders associated with major cognitive dysfunctions can be distinguished, including the following: mental retardation (MR) (learning disabilities in the U.K.), in which the cognitive impairment is characterised by deficiencies in theoretical thinking, autism, in which the cognitive impairments are theory of mind, executive dysfunctions and deficiencies in central coherence — often concomitant with MR — and AD/HD (executive dysfunctions). Cognitive dysfunctions that do not fulfil the criteria for specific diagnoses, such as a general cognitive ability in the lower normal area and corresponding deficits with executive functioning are easily

overlooked or misinterpreted, but such problems may cause severe disabilities in daily life, especially at school age when demands on abilities such as planning, organisation, time perception and working memory increase.

During the last couple of decades, the amount of research in the field of specific cognitive dysfunctions with clinical correlates, such as AD/HD, deficits in attention, motor control and perception (DAMP), developmental coordination disorder (DCD) and autism spectrum disorders has increased tremendously [55-58]. This research has resulted in new insights, including better methods for identifying children with cognitive problems. In addition, knowledge about how to provide appropriate educational intervention has emerged. In Sweden, and in many other countries, child health centres (CHC) have an important role to play in identifying these developmental problems at specific key-ages (Guidelines for Child Health Care in the county of Stockholm, 1991) and the school health care system has been assigned a similar role when it comes to identifying developmental problems that only become evident at school age.

Cognitive capacity is important for functioning in daily life, and may have a profound effect on school achievements, self-confidence and the ability to cope with life in general. Children with neurodevelopmental disorders are, according to the International Classification of Functioning, Disability and Health (ICF), at risk of suffering restrictions on their activity and limitations on their participation in daily life. In the new ICF classification, activity (limitation) and participation (restriction) replaced the previously used terms disability and handicap, respectively [59].

Figure 3. International Classification of Functioning, Disability and Health (ICF)



Aetiologies of neurodevelopmental disorders in term infants

The aetiology of neurodevelopmental disorders may be pre-, peri- or postnatal. In some cases, it is not possible to associate the aetiology with a specific period.

Cerebral palsy

Cerebral palsy (CP) is a broad description of many syndromes with different aetiologies. In recent research on CP epidemiology, conducted in the health care region covering the western part of Sweden, about 35 % of the infants born full-term with CP had a perinatal aetiology [60]. A prenatal origin of the CP was revealed in 38 % of the full-term infants in that study, although it was impossible to determine the aetiology for 27 % of the infants. Among the prenatal causes, CNS malformations and periventricular atrophy were dominant. There are several antenatal risk factors for CP in term infants, including maternal infection, intrauterine infection/inflammation and intrauterine growth restriction. A correlation has been reported between CP and autoimmune and coagulation disorders [61-63]. Imaging studies have helped to improve the understanding of the importance of the timing of the injuries since different structural lesions are strongly correlated to the stage of the brain development at the time when the lesion occurred. The major perinatally acquired lesions in the full-term infant with NE are damage to the parasagittal cortical area, the basal ganglia, thalami and cerebellum. This means that all types of CP may be represented in children born at term with moderate NE.

Learning disabilities/mental retardation

Individuals with learning disabilities/mental retardation are heterogeneous with respect to the aetiology, degree of disability and frequency of additional impairments. Most cases are of prenatal origin. Perinatal events could account for 10 % of all mental retardation [64]. When severe mental retardation is identified and considered to be of perinatal origin, it is associated with CP in almost all cases [65].

Attention and autism spectrum disorders

Several disorders are typified by children with deficits in attention, such as AD/HD, DAMP and autism spectrum disorders. In most cases the aetiologies are of a prenatal or genetic origin.

Experimental data indicate a particular vulnerability of striatal neurons in the developing brain and, in conjunction with the idea that the striatum is important for context recognition and behavior, these data have led researchers to search for subtle striatal lesions, in the form of biochemical changes, in children who have suffered perinatal adverse events [66]. Neonatal complications have been suggested as a riskfactor that may be pathogenic in children with AD/HD [67].

The main cognitive dysfunction in subjects with attention spectrum disorders concerns the executive functions, i.e., giving rise to problems with planning, organization, time-perception, flexibility and working memory. These functions are highly

important for all activities in daily life. However, dysfunctions concerning executive functioning are often overlooked, misunderstood or diagnosed far too late in life. Just recently an association between NE and autism has been reported [68].

Assessments of cognitive functions

In addition to a comprehensive neuropaediatric/developmental history there is most often a need for standardized cognitive tests and specific rating scales.

Tests

Wechsler intelligence scale for children

The third edition of the Wechsler intelligence scale for children, known as WISC-III, is a test of theoretical intelligence. It consists of a verbal and a non-verbal part. The verbal IQ, non-verbal IQ, full-scale IQ are analysed and also four index factors to determine the verbal understanding, freedom from distractibility, perceptual organization and processing speed of children in an age-appropriate manner. The normal range is defined as an IQ in the interval 85-115, a borderline IQ is in the interval 70-85 and mental retardation is defined as corresponding to an IQ below 70, when found in combination with a corresponding measure of the child's adaptive functioning.

Questionnaires/Rating scales

Questionnaires and rating scales are widely used as diagnostic tools to assess developmental and behavioral difficulties. There are a huge number of different scales and we have chosen to use a few that are common in both clinical practice and research. They are easy to use and can be distributed to parents and teachers. In all of these questionnaires, higher scores indicate more problems than lower ones.

LONG-TERM OUTCOME AFTER NEONATAL ENCEPHALOPATHY

The most common studies of the outcome after NE consider a short period [4] [69] and focus on severe deficits, such as severe mental retardation and CP. The mild forms of NE are associated with a normal outcome [5]. The severe forms result in severe neuroimpairments or death [3]. However the prognosis of the moderate grade of encephalopathy is less certain. In the short perspective it is hard to determine whether a child will develop impairments such as cognitive dysfunctions at a later stage.

Despite the dearth of research, some recent investigations are beginning to highlight the need for more comprehensive research. Some of the relevant reports are mentioned briefly here. Gadian et al described three subjects with impairments of episodic memory following encephalopathy [70]. Moster et al conducted a large population-based investigation on a cohort of infants to examine the joint association of low Apgar scores and early neonatal symptoms with a variety of neurodevelopmental impairments and learning difficulties at school-age [71]. Robertson and Finer followed children with

moderate HIE and noted that school performance in subjects like arithmetics, reading and spelling was below average [72]. Maneru and co-workers reported significant differences in tests assessing the attention and executive functions of school-children known to have suffered from moderate perinatal asphyxia [73]. Marlow et al showed similar dysfunctions in preschool children who had had NE [49]. Contradictory data were obtained in a Swedish study conducted on young adults. In this research most subjects had had HIE of moderate form and were found to have had a favorable outcome [74, 75].

Table 1 depicts the outcome from research on children born at term or near term, including those with moderate HIE/NE or with medical records indicating that they could have had HIE/NE although a diagnosis was not made at the time. It should be noted that there are different inclusion criteria, variations in the definition of encephalopathy used and the outcome measures are not directly comparable.

Table 1. Studies including outcome after the age of 7 years or more after suffering moderate HIE/NE. For brief results see text above.

Author	Publication Year	Age at follow-up (in years)
Robertson and Finer [72]	1989	8
Gadian et al [70]	2000	11-13
Maneru et al [73]	2001	15
Moster et al [71]	2002	8-13
Viggedahl et al [74]	2002	19-26
Marlow et al [49]	2005	7

PROLONGED PREGNANCY / POST-TERM BIRTH

Definitions

The standard definition of prolonged pregnancy is at least 42 complete weeks of gestation, i.e., 294 days after the first day of the last menstrual period (LMP) or more. A correct dating of pregnancy is crucial for assessing the likely outcome of post-term birth. Using the LMP method overestimates the number of prolonged pregnancies. The use of ultrasound before 20 weeks of gestation is generally a more accurate method of determining gestational age (GA)[76-78].

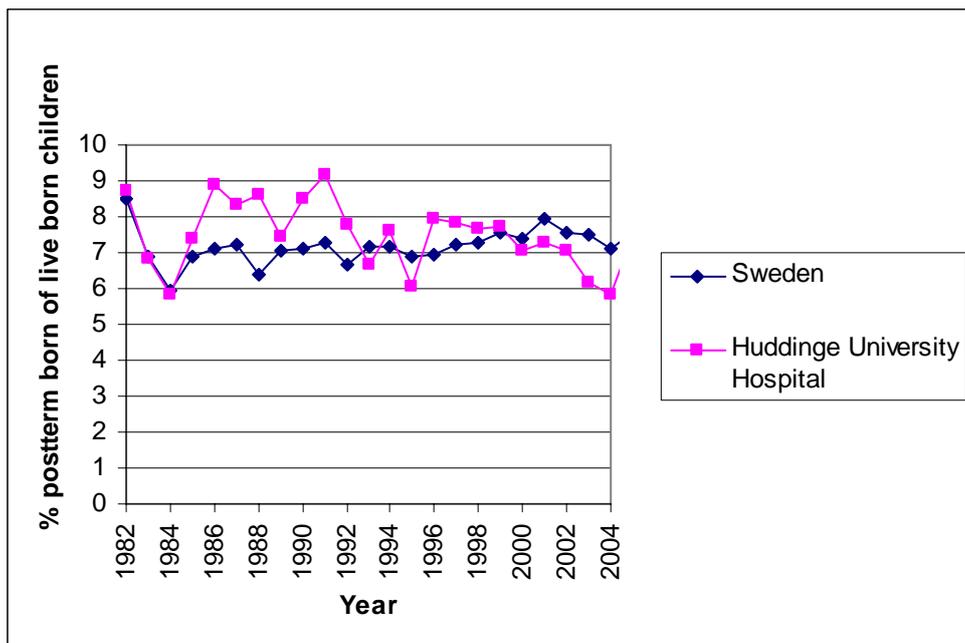
Initiation of labour

The physiology of parturition is not fully understood. Estrogens, progesterone, relaxin, prostaglandins and oxytocin are all believed to be involved in the onset of birth. An intact hypothalamic-pituitary-adrenal (HPA) axis and a healthy placenta seem to be important for normal initiation of labour [79].

Incidence

The incidence of post-term birth varies depending on the definition used and the method of defining the GA at birth. There are also local variations in routines for the induction of labour which can have an impact on the incidence. Incidences between 4 and 14 % are reported [79-81]. The incidence of post-term births in Sweden during the last 20 years has been between 6 and 10% (Fig 4).

Figure 4. Incidence of post-term births in 1982-2004 in Sweden and in Huddinge University Hospital.



Aetiology

The causative factors underlying prolonged pregnancies are still unclear. Hormonal and immunological factors were discussed in a review by [82], and it is known that placental sulphatase deficiency, which is a very rare condition, is associated with prolonged pregnancy. In the fetus, severe abnormalities, such as anencephaly, have been associated with post-term birth, as have chromosomal aberrations like trisomies 16 and 18. Seckel's dwarfism is another condition mentioned. Other factors that have been discussed are primigravidity, use of iron supplementation, genetic factors, hormonal influences and race [79].

Male gender is more common in prolonged pregnancies, with three male deliveries being made for every two female ones [83].

Perinatal outcome

Post-term births are known to be somewhat less likely to have a good outcome than term births, and a substantial body of research can be found in the literature backing this up. Several authors have reported an association between prolonged pregnancy and perinatal mortality and morbidity [84]. The risks for the fetus and the mother of continuing pregnancy beyond 42 weeks are described in a number of articles [85, 86]. Prolonged pregnancy is also associated with an increased stillbirth rate [87].

Perinatal mortality is at its lowest at term and increases for post-term births [88, 89]. Divon and co-workers reported that perinatal mortality already begins to rise at 41 weeks [90]. Little is known about the risk factors associated with mortality in fetuses. The role of maternal hypertension, diabetes and maternal age have been discussed and are considered to have an impact on morbidity, but not to be decisive factors [81]. Maternal complications are generally associated with a larger than average fetal size and fetal complications with a smaller than average fetal size [91].

SGA fetuses born post-term have an increased neonatal morbidity. 20-40 % of post-term fetuses are post-mature, a condition associated with consequences of placental aging. Postmature infants are generally smaller than average. Post-term infants with a low birth weight show increased neonatal mortality [92].

However large fetuses too have higher risks than fetuses of average size, but they have a greater prevalence of traumatic injuries like fractures and paralyses. Post-term infants show complications associated with macrosomia, cephalopelvic disproportion, shoulder dystocia, maternal trauma and postpartum hemorrhage. Fetal distress and meconium release occurs more often in post-term births than term-births [80].

Long-term paediatric outcome

Most outcome studies analyse obstetric and neonatal aspects. The most common outcome measures used are Apgar scores, need for care in NICU and mortality rates. These measures are, however, very unspecific. Luckas has reported more common admission to NICU as an indicator of a less than optimal outcome, but no differences were found to be associated with low Apgar scores in this research [93]. Inconsistent terminology and definitions, variations in the treatments and different population demographics make comparison between the studies performed on the outcome of children with post-term births difficult. The longer outcome studies that have been

made are usually restricted to just the first years of life, and have given few conclusive results [79]. A follow-up of children born post-term made at the age of two revealed that their development was normal [94].

Obstetrical considerations

Prolonged pregnancy is a difficult and controversial problem in obstetrics. The treatments are induction of labour or elective caesarean section. The optimal timing for planned induction is still debatable. Routine induction of labour after 41 complete weeks has been suggested [95]. In recent years most obstetricians have advocated a more active approach in regard to post-term pregnancies. In many countries, routine induction at 41 complete weeks is practiced. However it remains to be established if this approach is associated with improved outcome. Only a few prospective randomized trials have been proposed with the intention of addressing this question [96].

AIMS

The aims of the research presented here were:

To relate clinical pre- and perinatal data to long-term neurodevelopmental outcome in a population-based birth-cohort of children born at term with an Apgar score (AS) of < 7 at 5 minutes and with neonatal encephalopathy (NE).

To investigate the occurrence of various types of cerebral palsy (CP) and to determine whether additional impairments were evident in this population-based group of children with moderate NE.

To study cognitive functioning in late adolescence in a birth cohort of children born at term, with moderate NE, but without CP.

To investigate white matter regions with a specialized MRI technique, diffusion tensor imaging (DTI), in a subgroup of children with moderate hypoxic ischaemic encephalopathy (HIE)/NE, but without CP.

To evaluate developmental data obtained at the ages of 4 and 5.5 years in children born post-term, i.e., at a gestational age (GA) of ≥ 42 weeks.

MATERIALS AND METHODS

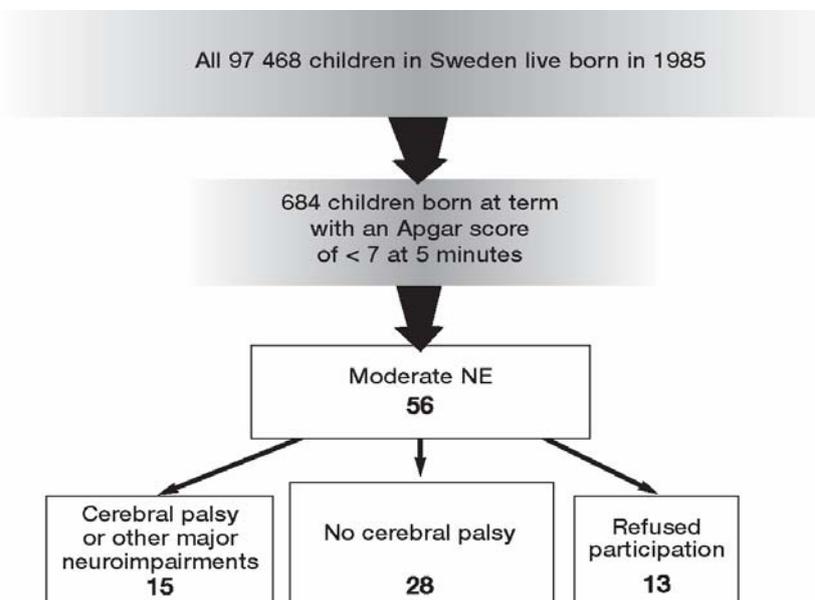
OUTCOME STUDIES OF CHILDREN BORN AT TERM IN 1985 WITH MODERATE NEONATAL ENCEPHALOPATHY (NE) (I-III)

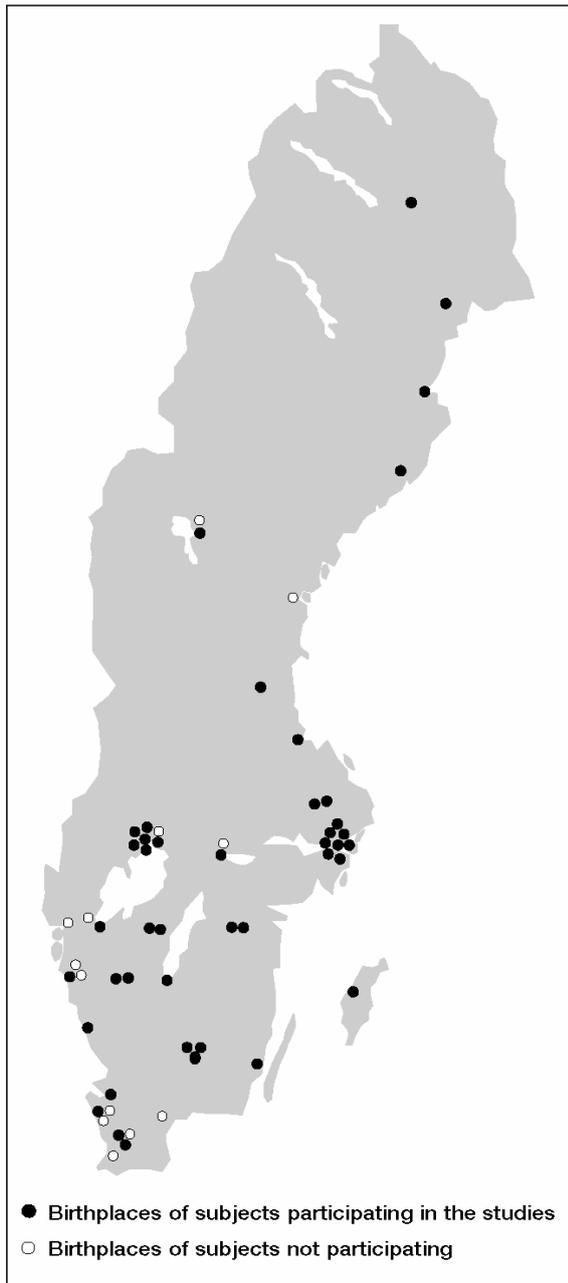
The studies were conducted in Sweden, which had a total population of 8.4 million in 1985, with 97 468 children being live-born in that year. The population was identified from the Swedish Medical Birth Register (SMBR) and consisted of 684 children born at term with an Apgar score (AS) of <7 at 5 minutes of age.

Of the 684 children, 60 had died in the neonatal period and 13 died later (aged from 1 month to 15 years). The relevant clinics were asked to provide the neonatal records for the remaining children, and all available records were scrutinized to identify any children who might have had moderate NE. Fifty-one records could not be found in the local hospital archives. The records of the remaining 560 were evaluated and children with major malformations, chromosomal aberrations, severe perinatal infections, and opioid induced depression were excluded. Records of children who had suspected or definite neurological symptoms during their neonatal period were rated independently, to identify those with moderate NE by one neonatologist or more (BH and MB), who were unaware of the children's developmental outcome. In 13 children the symptomatology was complex, but after discussion agreement was reached in all cases. In two children the clinical symptoms were considered to be borderline between moderate and severe NE; they were assigned to the moderate NE group and included in the study.

Fifty-six children with moderate NE were included for further assessments. The mothers of these children were contacted by letter and asked to participate in a follow up of their child's health and development. Thirteen mothers refused to participate. It was possible to obtain detailed information for 43 of the 56 children. Of these 43, 13 had been diagnosed as having cerebral palsy (CP) and 2 had other major neuro-impairments (one with DAMP and Asperger syndrome, and one with severe mental retardation).

Figure 5 Delineation of the groups





The children were born in different parts of the country. Their birthplaces are marked in Figure 6.

Figure 6. Map of Sweden. Birthplaces of subjects with moderate NE

Study I

Three groups were defined according to the children's outcome, as follows: children with CP, children with cognitive impairments without CP and children without impairments. The obstetrical and neonatal data for these groups were compared to determine whether there were any significant differences between the groups. The maternity records, both from antenatal care and intrapartum care, were evaluated by two independent obstetricians to assess the obstetric risks and management. The information was reviewed, with the reviewers being blind to the outcome. The following antenatal characteristics were considered: diabetes, intrauterine growth restriction (IUGR), hypertension, preeclampsia, renal disease, maternal bleedings after 20 weeks, oligo and polyhydramnios, prolonged rupture of membranes (>24 hours)

and multiple pregnancies. The data were compared to the general statistics for Sweden for that year (from SMBR).

Fetal heart rate tracings were reviewed, and the cardiotocogram (CTG) was assessed and determined to be abnormal if episodes of late or severe variable decelerations and/or decreased variability with the absence of accelerations, and/or tachycardia (more than 160 beats per minute) occurred for periods longer than 30 minutes.

The neonatal records were evaluated to identify those infants who had an AS of < 7 at 10 minutes, were small for gestational age (SGA), needed to be placed in a ventilator, had seizures or needed an extended period of hospitalisation subsequent to their birth.

The relevant neuropaediatric clinics and habilitation units were asked to forward copies of their records for those children who had CP or major neuroimpairments. These records were evaluated to determine the type of CP and/or other neuroimpairments the children had.

Study II

The study group consisted of the 28 subjects (18 boys and 10 girls) without CP or any other major neuroimpairments.

The mothers of the 28 children were interviewed over the telephone using a semi-structured schedule. The questions addressed the child's general health, specific diseases, development, current functioning, in terms of motor ability, speech and language, other general cognitive abilities, interests, social functioning/social interaction and school achievements. Three questionnaires were used to conduct the investigator-based structured interview over the phone: the Conners 10-item scale [97], the ADHD Rating Scale IV [98] and the Asperger Syndrome Screening Questionnaire (ASSQ)[99]. The possible scores for these ranged from 0-30, 0-54, and 0-54, respectively, with higher scores indicating more significant problems.

Siblings of school age were used as the comparison group. The interviews (subject with NE and sibling where appropriate) lasted for 45 – 90 minutes.

Eleven of the 28 subjects were assessed with the WISC-III in connection with the Magnetic Resonance Imaging-Diffusion Tensor Imaging (MRI-DTI) investigation (Study III). Reference data for Swedish school children was used to provide a comparison.

The records from the Child Health Centres (CHC) and school health care service were scrutinized, especially the routine CHC and remarks in the school health records. Data concerning the children's vision and hearing were collected from these records. All the data from the interviews and tests were compiled to obtain the most comprehensive assessment possible of each child's functional profile in the different areas.

Study III

The third investigation was conducted before the first two had been completed. Nineteen of the teenagers who had had moderate NE were contacted and invited to come to the Karolinska University Hospital in Stockholm to participate in the MRI-DTI study. Eight were unable to participate, and thus 11 subjects took part.

All of these teenagers had had seizures during the neonatal period. The DTI-data obtained for two of them were excluded, in one case because the subject had an intraventricular cyst and in the other because the examination was unsatisfactory. Nine were finally included in the analysis.

An age and gender matched comparison group was recruited in Stockholm. The selection criteria for potential candidates were that they were born at term with a birthweight of greater than 2500 g and with no history of perinatal complications or neurological problems.

There were four boys and five girls in each group. Mean age at DTI was 17 years and 2 months in the HIE/NE (4 girls and 5 boys) and 17 years and 5 months in the comparison group.

The subjects underwent a scanning session employing a single shot diffusion-weighted echo planar imaging sequence which was triggered with pulse gating. From each subject 36 slices were collected each with a 3 mm thickness. From the data obtained, the Fractional Anisotropy (FA) could be calculated. A movement correction algorithm was used to minimize the effect of artifacts. Spatial normalization was performed with the SPM software.

Eight of the nine participants had additional clinical MRI scans conducted in their respective local hospitals. These images were evaluated by a neuroradiologist.

OUTCOME AFTER POST-TERM BIRTH – STUDY IV

The study group included all children born in 1991 at Huddinge University Hospital with GA of at least 42 weeks at birth, identified through the SMBR. In all cases, the GA was based on an ultrasound examination conducted in the second trimester. The maternal records were checked manually for verification of the GA at birth.

The records for the children in the post-term group were scrutinized either at the large CHCs or were sent for when the CHC was not visited (either because the CHCs were small or when the record was no longer available at the CHC).

The comparison group was determined by taking the medical records of the children born immediately before and after the index case. The records in the local archives at the CHCs were used. Controls were only searched for at the larger CHCs, while smaller CHCs with only a few cases were not visited. Only children with a GA of ≥ 37 and < 42 weeks and with complete data that could be matched to the SMBR were included in the comparison group.

Data on the growth parameters both from birth and CHC were collected. Obstetric and neonatal data were collected from the SMBR.

The results from the routine 4 and 5.5 year developmental assessments at the CHC were scrutinized and the remarks on each child's development were documented by two neuropaediatricians, one of whom was unaware of the obstetrical history. A definite or suspected neurological or developmental disorder was considered to be present if there were signs of abnormal development in at least one of the following areas: cognition, cognitive language, cognitive behaviour or motor development expressed as:

1. a definite neurological/developmental disorder having been diagnosed, or

2. specific measures having been taken because of a strongly suspected developmental disorder with
 - (a) a referral having been made to a neuropaediatrician/paediatrician, speech pathologist or psychologist for further neurological/developmental assessments
 - (b) further information about the child's development having been collected from the preschool
 - (c) a subsequent evaluation at the CHC having been recommended to get a new developmental assessment in cases that had not passed the CHC check up, or
 - (d) the child having been given specific support at the preschool because of developmental problems, but no other measures having been taken.

STATISTICAL ANALYSES

The following statistical analyses were used:

Studies I and II: A Chi²-test and Fischer's exact test were used, when appropriate, to calculate p-values for the differences in proportion across groups (using Statistica 6.0). In addition, the Mann-Whitney U-test was used in Study II to analyse the differences between the results of the questionnaires for the cases and controls. *T*-test was used for comparisons between means.

Study III: *T* tests were used for analysing movement variables and spatial normalization.

Study IV: Logistic regression analysis with backward elimination (PROC LOGISTIC in SAS) was used to evaluate the independent effects of deviations in development. The p-values and confidence intervals were analysed with the exact statistical interference for odds ratios (using StatXact).

The significance levels were set at $p < 0.05$ throughout.

ETHICAL CONSIDERATIONS

Studies I, II and IV were approved by the local ethical committee of Huddinge University Hospital and Study III was approved by the local ethical committee of Karolinska University Hospital. The participants gave informed consent.

RESULTS

PRE- AND PERINATAL FACTORS IN RELATION TO OUTCOME AFTER MODERATE NE (STUDY I)

Of the 43 subjects with moderate NE, 13 (30%) had CP, 22 (51%) had cognitive dysfunctions without CP and 8 (19%) had no impairments (Figure 7). The gender distribution is presented in Table 2.

Figure 7 Long-term outcome after moderate NE

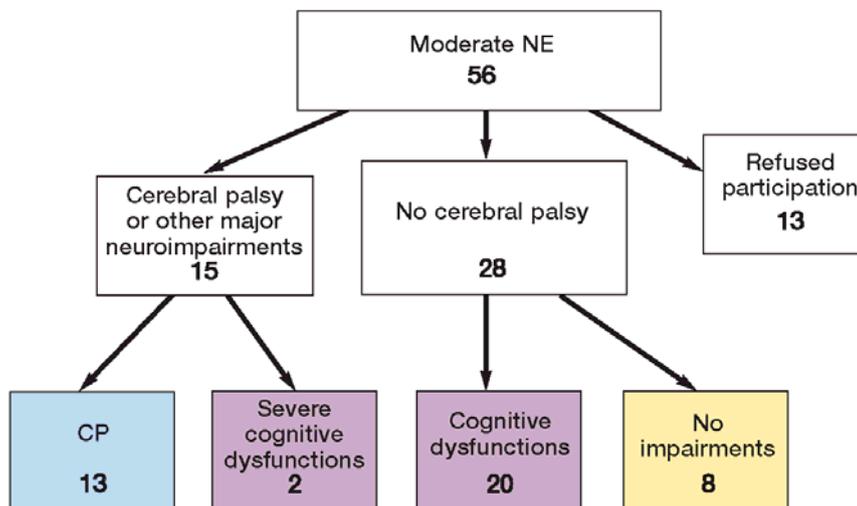


Table 2. Outcome after moderate NE and gender

	Male	Female
CP	6	7
Cognitive dysfunctions without CP	13	9
No impairments	7	1
Complete NE group	26	17

Children with CP

Of the 13 children with CP, different types of motor impairment were represented (Table 3).

Table 3. Types of CP in 13 subjects with moderate NE

Type of CP	Numbers afflicted
Dyskinetic CP	3
Ataxic diplegia	1
Spastic diplegia	1
Spastic hemiplegia	3
Spastic tetraplegia	1
Mixed dyskinetic / tetraplegia	2
Ataxia	2

The majority of the children with CP also had additional impairments (Table 4). Ten of the 13 subjects with CP also had definite cognitive dysfunctions. Eight children had mental retardation (3 of whom had a severe form) and two had marked executive dysfunctions according to their records. Eight children had or had had epilepsy and a definite hearing impairment had been diagnosed in three children. It was not possible to analyse the data on visual impairments in detail.

Table 4. Additional impairments in the 13 subjects with CP

Additional impairments	Numbers afflicted
Mental retardation	8
Cognitive/executive dysfunction	2
Epilepsy	8
Hearing impairment	3

Children with cognitive dysfunctions without CP

This group consisted of 22 children, 20 of whom had cognitive dysfunctions — identified from the interviews with the mothers, including rating scales — and another two with major cognitive impairments that had been identified early in life (one with severe mental retardation (SMR) and one with DAMP and Asperger syndrome. This group is further described in study II.

Group 3: Children without impairments

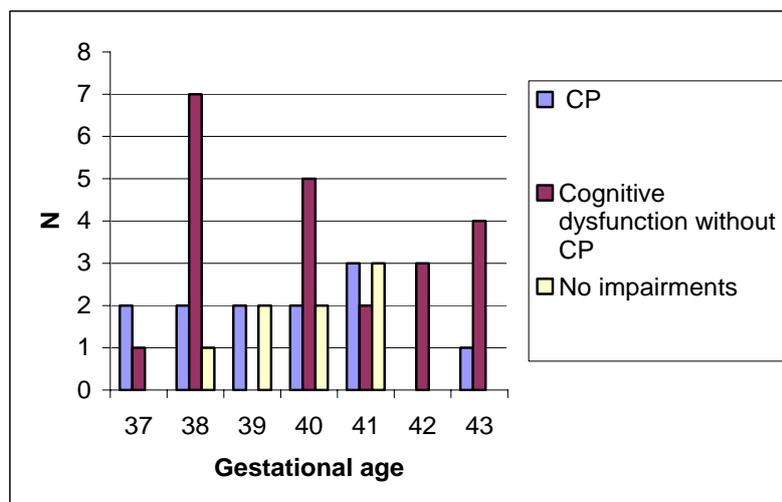
No neurodevelopmental dysfunction was identified in eight of the subjects.

Data relating to the pregnancy and delivery

Pre- and perinatal data are presented separately for the three outcome groups of children classified according to their outcome as discussed above

For one child with CP the pre- and perinatal data were incomplete, so this child has not been included in the presentation. Most mothers had experienced an uneventful pregnancy. Treatment or interventions had been required during pregnancy owing to: preeclampsia/hypertension (n=8), IUGR (n=3), diabetes (n=1), pyelitis (n=1), bleeding at a GA of 34 weeks (n=1) and a twin pregnancy (n=2). The average maternal age in the moderate NE group was higher than in the general population, the respective ages being 30 vs 28 years ($p < 0.001$). Post-term pregnancies (>41 weeks) were common ($8/42=19\%$) and significantly higher than was general for Sweden in that year, 8% ($p < 0.01$). The distribution of GA at birth for the different groups is presented in Figure 8.

Figure 8. Distribution of GA for the moderate NE group



The onset of labour was generally spontaneous, and there were few elective caesarean sections. Caesarean section, instrumental delivery and breech presentation were all more common than in the general population ($p < 0.001$).

There were five cases with severe intrapartum complications: one case of uterine rupture, two cases of abruption of the placenta, one case of severe shoulder dystocia and one case of a fetal bleeding. Maternal fever (> 38.0) was present in four cases. The medium duration of labour was not exceptional (10 h, range 0-36 h), but labour exceeded 24 hours for six of the mothers.

All mothers were monitored by CTG during the intrapartum period, and in 38 cases the CTG tracings were available. Ominous FHR patterns were common and 33 of the 38 tracings showed ominous recordings for 30 minutes or more before the delivery. The corresponding figure for ominous tracings with a duration of at least 90 minutes is 14 out of 38. There were no obvious differences in the recorded variables for those with CP, with cognitive dysfunctions without CP and for subjects without impairments.

Table 5. Pregnancy events and intrapartum complications related to outcome

Complications	CP	Cognitive dysfunctions	No impairments	Total
Preeklampsi/hypertension	2	4	2	8
IUGR	1	2	0	3
Diabetes	0	0	1	1
Bleeding	0	1	0	1
Pyelitis	0	1	0	1
Twins	0	2	0	2
Fever during labour	0	3	1	4
Uterinerupture	1	0	0	1
Abruption placenta	0	2	0	2
Shoulder dystocia	0	0	1	1
Fetal bleeding	0	1	0	1

Data relating to the neonatal period

A prolonged AS of below 7, noted at 10 minutes, was observed in all outcome groups. Two infants were born small for gestational age (SGA). Children who needed ventilator treatment in neonatal intensive care unit (NICU) and children who were hospitalized for more than 14 days were found in all three of the groups composed according to outcome. All of the children with CP had had seizures in the neonatal period, but children with seizures were also found in the other groups. Anticonvulsive treatment with Phenobarbital had been given to 32 children and 24 had been treated with antibiotics.

COGNITIVE DYSFUNCTIONS WITHOUT CP (STUDY II)

Subjects

The mean age at investigation was 16 years and 10 months (SD 1 year and 4 months) and age range was 15 years –19 years and 1 month.

Of the 28 subjects, 14 (50 %) had siblings of school age. One child had 2 siblings yielding a comparison group of 15 children. The mean age for this group (5 boys, 10 girls) was 14 years and 2 months (SD 2 years) and age range was 10 years and 11 months –17 years and 5 months. The sibling group was significantly younger than the probands ($p < 0.01$).

The interviews lasted for 45 – 90 minutes. A summary of the cognitive dysfunctions in the NE cases without CP is presented in table 6. In the table it is noted who are tested and investigated with MRI and DTI within the study.

Table 6. Subjects with moderate NE without CP

No	Sex	Cognitive dysfunction	Other neurological diagnoses	Hearing impairment	Tested in study	DTI study	MRI in study
1	M	IQ< 70, EF	no	yes	yes	yes	yes
2	F	Borderline IQ, EF	no	no	yes	yes	yes
3	F	IQ<70	no	yes	yes	yes	yes
4	F	EF	no	no	yes	yes	yes
5	M	EF	no	no	yes	yes	yes
6	F	IQ<70	no	no	yes	yes	yes
7	M	Borderline IQ, DAMP	no	no	yes	yes	no
8	M	0	no	no	yes	yes	yes
9	F	Borderline IQ, EF	no	no	yes	yes	yes
10	M	IQ<70	no	no	yes	no	no
11	M	0	Intraventricular cyst	no	yes	no	no
12	F	EF	no	no	no	no	no
13	F	EF	Brachial palsy	no	no	no	no
14	F	Dyscalculia, EF	Epilepsy	no	no	no	no
15	M	EF	no	no	no	no	no
16	M	0	no	no	no	no	no
17	F	EF	no	no	no	no	no
18	M	MMR	no	no	no	no	no
19	M	Borderline IQ, AD/HD	no	yes	no	no	no
20	M	0	no	no	no	no	no
21	M	0	no	no	no	no	no
22	M	Borderline IQ	no	no	no	no	no
23	M	Borderline IQ	Pes equinovarus	yes	no	no	no
24	M	Borderline IQ, EF	no	no	no	no	no
25	M	Borderline IQ, EF	no	no	no	no	no
26	M	0	no	yes	no	no	no
27	F	0	no	no	no	no	no
28	M	0	no	no	no	no	no

M = Male

F = Female

EF = Executive functioning

MMR = Mild mental retardation

AD/HD = Attention deficit/ hyperactivity disorder

DAMP = Deficits in attention, motor control and perception

Borderline IQ=IQ 70-85

Neurological diagnoses

Specific neurological diagnoses (n=8) that had been reported previously for the children with NE were: hearing impairment (n=5), brachial plexus palsy (n=1), pes equinovarus (n=1), and "benign epilepsy" (n=1). No visual impairments were reported. In one teenager, an asymptomatic ventricular cyst was revealed at the DTI examination.

Cognitive impairments

Five of the 28 (18%) children had IQs of ≤ 70 . No child in the comparison group attended any type of special school for children with learning disabilities. Three of the 11 children in the moderate NE group who were tested with WISC-III had IQs between 71 and 85, i.e., borderline intelligence. Special educational support, indicative of borderline intelligence had been given to a further five children, giving a total of eight children with presumed or documented borderline intelligence out of 28 (28%) and a total rate of mild learning disability/borderline intelligence of 13/28 (46%). Special educational support includes a child having the resources allocated to him or her to enable a person to provide assistance at school, as well as repeating a school-year, participating in a small group or attending a special school. Two children (13%) in the sibling comparison group had indications of a borderline IQ, which is in accordance with normative data. The difference between the non-CP moderate NE and the sibling comparison group concerning mild learning disability/borderline intelligence was significant ($p < 0.05$).

Of the 28 subjects in the NE group, two had a previous clinical AD/HD or DAMP diagnosis and one had dyscalculia. Eight children (29%) had some indication of motor control problems. There were no motor problems reported in the group of siblings. . When problems of a degree that interfered with the child's daily life were examined from the data obtained from the interviews, a significantly difference was observed for the children comprising the NE group and their comparison siblings. These difficulties included short-term memory, perception of time and difficulty making friends or interacting with peers.

Table 7. Cognitive dysfunctions/impairments

Dysfunction	NE group n = 28	Comparison siblings n = 15	p-value
IQ < 70 / borderline IQ	13	2	< 0.05
DAMP or AD/HD	2	0	ns
Motor control	8	0	ns
Short-term memory	18	2	< 0.002
Time perception	14	1	< 0.005
Orientation	8	1	ns
Interacting with peers	10	0	< 0.01

ns = not significant

There were also significant differences between the NE subjects/the participants who had had NE and the siblings who formed the comparison group when the following were examined: the Conners scale ($p < 0.003$), the Inattention Subscale of the AD/HD Rating Scale-IV ($p < 0.006$) and the ASSQ ($p < 0.003$).

Eight out of 28 children (29%) in the moderate NE group and 12/15 (80%) in the sibling group had no reported problems ($p < 0.01$)

DIFFUSION TENSOR IMAGING (STUDY III)

In several white matter areas the fractional anisotropy (FA) was lower in the group with moderate NE/HIE. The areas included the internal capsules bilaterally in the posterior limb and on the right in the anterior limb, the posterior and anterior corpus callosum as well as frontal inferior WM areas. Two of the eight subjects for whom clinical MR images were available exhibited changes indicating PVL and one additional child had borderline PVL. One subject had cortical and subcortical changes.

POST-TERM BIRTH AND DEVELOPMENTAL ASPECTS (STUDY IV)

Subjects

The study group comprised 354 children born post-term ($GA \geq 42$ weeks). They constituted 8.9% of the total live births at the Huddinge University Hospital in 1991. Records for 321 children (190 boys and 131 girls) were found at the CHCs. Two children had died, one during the first day of life and the other at the age of 3 in an accident. Four families had moved abroad. The records could not be found for 27 children. The comparison group consisted of 379 children (196 boys, 183 girls).

Pregnancy and delivery data

The parity and maternal age did not vary between the groups. The numbers of induced deliveries were higher in the post-term group, as were dystocia and instrumental deliveries. There were no significant differences in the sectio rate, children born SGA, low AS, traumatic injuries or neonatal complications. In the material there was one child with HIE.

The head circumference at the age of one year was larger in the post term group. The weight and length did not differ.

Neurodevelopmental outcome at pre-school age

Definite or strongly suspected neurological or developmental disorders were more common amongst the children born after prolonged pregnancies than in the comparison group. About 13 % ($n=42$) of the children born post-term had definite neurological / developmental disorder or had been subjected to further assessments. The corresponding rate in the comparison group was 5.5% ($n=21$). The results are presented in Table 8.

Table 8. Neurodevelopmental outcome according to the records from the CHC

	Post- term n = 42	Comparison group n = 21
Neurological / developmental disorder	12	7
Developmental deviation, children referred for further assessment	19	11
Extra support	4	2
New assessment at CHC recommended	7	1

Twelve children in the post-term group presented definite neurological/developmental disorders and seven in the comparison group (Table 9).

Table 9. Definite neurological /developmental deviations

	Post- term n = 12	Comparison group n = 7
Severe mental retardation (with or without autism)	3	
Severe psychomotor retardation	3	3
Neuromuscular involvement	5	
Congenital hearing impairment		1
Seizure disorder	1	3

Logistic regression analysis showed Odds Ratio (OR) of 2.20 for developmental deviations. Boys exhibited more deviations than girls.

GENERAL DISCUSSION

NEONATAL ENCEPHALOPATHY (STUDIES I – III)

Delineation of the series

Studies I and II were mainly focused on the clinical aspects of moderate NE. Study III concentrated on the structural, WM, aspects of the brain.

The clinical series is population-based and was conducted on a well-defined birth cohort of children born at term ($GA \geq 37$ weeks) in 1985 from an entire country (Sweden) and relates to a long-term follow-up of those who had NE. The follow-up was made after a much longer interval (15-19 years) than in most outcome studies of NE.

It should be noted that this investigation has limitations. It involves children who were born at a time when cerebral monitoring was less accurate than the imaging available today and when neurophysiology and laboratory facilities to monitor acidosis and infection markers were not always available. The inclusion criteria in the present study were based on the AS, and were followed by a clinical classification referring to the degree of encephalopathy, conducted in accordance with the method laid down by Sarnat and Sarnat [40]. We have insufficient knowledge about the proportion of newborn encephalopathy that is exclusively perinatal and asphyxial in origin. We therefore decided to use the term NE instead of HIE in Studies I and II. The wide variety of outcomes in children with moderate NE could be related to several factors. Besides adverse perinatal and perinatal events, and although known causes of low AS were excluded, such as malformations, neuromuscular disorders, known congenital infections and opioid-induced depression, several prenatal putative risk factors might have been present and influenced the outcome.

The organization of the Swedish health care system and the existence of the Swedish Medical Birth Register (SMBR) enabled the vast majority of records from the different hospital clinics to be retrieved and information extracted from them. The attrition rate was low (7.1%), and we can assume that most of the records that could not be identified belonged to children who had not been treated in neonatal units, and thus had not suffered from NE.

The classification of the children into NE groups was retrospective, and was done using clinical records that had not specifically been kept with the intention of conducting research. However, the information given in the neonatal records was considered to be sufficiently comprehensive for a retrospective categorization to be made of whether the infants had or had not had moderate NE. The neonatologists involved in the classification were unaware of the children's long-term outcome.

We have no evidence that the children whose mothers refused to allow them to participate, differed from the group of children included in the investigation

To validate our prevalence of moderate NE, a comparison was performed with a population-based study including all term infants born between 1985 and 1991 in the city of Gothenburg [3].

The prevalence found in our investigation, of 7/1000 (684/97468) children born at term with an AS of < 7 at 5 minutes was found to be similar to that reported by Thornberg et al (6.9/1000) [3]. However, the prevalence of moderate NE, of 0.57/1000

(56/97468) measured in our study was somewhat higher than the corresponding prevalence of moderate HIE found in their study, which was 17/42203, corresponding to 0.4/1000. Considering their discussion in which they mention that a number of the "non-determined" cases with HIE might well have moderate HIE, our figure probably accords reasonably well.

Main findings:

Pre and perinatal factors in relation to outcome after moderate NE (Study I)

Data from this study revealed that there is only a limited possibility to predict the outcome for a child, in terms of whether or not it will have CP, cognitive impairments without CP or no impairments, from the child's pre and perinatal history.

Obstetrical data

Most mothers had experienced an uneventful pregnancy and most of them went into labour spontaneously. Prolonged pregnancy was common and failure of parturition to be initiated could be regarded as a subtle sign of poor coordination between the mother and the fetoplacental unit. Fetuses in breech presentation are known to be at a high risk of long-term neurological morbidity, and breech presentation was more common amongst those included in this investigation than in the population as a whole [100-102].

Several mothers demonstrated ominous FHR patterns over sustained periods of time. Obviously, some of them experienced suboptimal care. It has not been within the scope of the present study to assess these circumstances, but we speculate that complications associated with management and medico-legal issues may sometimes have had an impact on how the long-term prognosis of these children has been regarded.

At the time when the children included in the present study were born (1985), there was an overwhelming preference among obstetricians in Sweden to limit the caesarian section-rate to a "reasonable" level of about 10 %. The existence of such a policy is well illustrated in the present study, where it is obvious that the obstetricians often preferred to deliver the mother vaginally despite poor progress and ominous FHR patterns. Since that time, obstetric care has changed dramatically, and nowadays patients with fetuses in breech presentations and post-term deliveries are mostly managed in a more active way, often including elective caesarean sections. Thus, hopefully, the number of children with NE will decline in the future.

Neonatal data

The most severely affected children had more often suffered from seizures, had a higher need for assisted ventilation and had required longer neonatal hospitalization than the ones without impairments at follow up. However, in regard to pre- and perinatal prognostic risk factors, the material is too limited to enable a statistically valid comparison to be made between the groups with different outcomes, and it is not, therefore, conclusive. We conclude that pre and perinatal risk factors do not permit a valid assessment to be made of the prognosis in individual cases. Few children had had neonatal and/or recent neuroimaging investigations made. Furthermore many of these children were born in hospitals with limited resources in terms of technical equipment. The results, therefore, reflect the situation as it was in 1985. Routines in neonatal care

have changed since then, and, as yet it is not possible to know what these changes mean for the outcome, however one can presume that the long-term prognosis will have improved on average as better monitoring is available making it more obvious when intervention is the appropriate course of action.

Children with CP

All of the various types of CP were represented among the 13 children in the group with CP. This indicates that several neuropathological mechanisms have been operating in the pre- and/or perinatal periods. Thus, considering the entire group of those with CP, it is evident that various areas of the brain had been involved and with different degrees of severity of the ensuing cerebral damage. Only 6/13 children had dyskinetic or tetraplegic CP, or a mixed form of these two severe types of CP, indicating a vascular disturbance to the basal ganglia and/or the cerebral cortex, i.e., the parasagittal area where the main cerebral circulation supply ends.

The children with diplegia subsequent to damage of the periventricular area might have a strong prenatal component, i.e., it is likely, that the damage occurred between the 24th and 34th week of gestation.

Cerebral palsy has traditionally been defined as “a disorder of movement and posture due to a defect or lesion of the immature brain” [103]. This definition has resulted in the motor aspects being concentrated on to a considerable extent. Owing to an increased awareness of the prevalent occurrence of other impairments in children with CP, however, a new definition of cerebral palsy has been suggested [54]. This definition has been proposed with the intention of considering different aspects of the cognitive dysfunctions of the children with CP. Cognitive dysfunctions are extremely common in children with CP, and cognitive dysfunctions may be more disabling than the motor impairments.

Since the material presented represents just a small group, one must consider that the results indicate the direction in which research could take in the future.

Cognitive dysfunctions without CP (Study II)

There were only a few participants in Study II, even though it was population-based, and many of the children were not seen personally or individually clinically examined at the time of the follow-up. However, our comprehensive data, including a thorough parental interview, information from records and tests support the idea that cognitive dysfunctions are common after moderate NE.

The comparison group consisted of siblings of school age. Given the age of the participants, this means that the siblings were younger than those who had had NE, but it had the advantage that the comparison children shared the same social environment as the index children/participants. Despite the younger ages of the siblings, the teenagers in the moderate NE group were reported to have significantly more problems. There is no indication in other populations that some of the problems associated with AD/HD or DAMP, including those measured by the Conners, ADHD-RS and ASSQ, increase over time for the relevant age range, thereby supporting the conclusion that there is a very large discrepancy between children with NE and their siblings. Furthermore, it should be mentioned that the group comprised of the sibling controls was of such an age that learning disabilities would already have been recognised.

We must consider that there is a risk of recall bias since parents are more prone to express extra concern and report more problems in a child with neonatal complications. However, we believe that we have minimised such effects by using our comprehensive approach.

Most follow-up studies of children suffering from NE focus on severe disabilities, such as CP and severe mental retardation, and are usually conducted when the children are still relatively young .

Severe and visible neurological impairments are easily recognised and usually diagnosed early on. Cognitive dysfunctions without motor involvement, however, might be overlooked.

In contrast to common belief, the participants who had suffered from moderate NE, but had not developed CP, displayed an unexpectedly high prevalence of cognitive dysfunctions. A long-term follow-up revealed that the overwhelming majority had major and/or cognitive dysfunctions. The impairments reported in this subgroup ranged from learning disability and learning problems through motor control problems, problems with short-term memory, time perception attention and with peer relations.

Nearly half of the group (13/28) had test results or school placements indicative of IQs in the borderline or disabled range. Moreover, the number of teenagers with symptoms related to inattention was significantly higher in the moderate NE group than for the siblings.

In modern society, where cognitive skills are highly regarded and increasingly demanded, impaired cognitive function may be regarded as a major handicap. For a child with a cognitive dysfunction, secondary social stigmatisation might be a major burden.

It is difficult to compare the results with previous studies owing to the inclusion criteria, the different follow-up periods and the different designs of the studies.

Clinical implications

We conclude that it is time to reconsider the use of motor functioning as the primary measure of neurological outcome after asphyxia. Several studies have reported cognitive deficits even in subjects without motor impairments [4]. The belief that cognitive impairment cannot exist in the absence of cerebral palsy has been invalidated.

The introduction of a routine long term follow-up conducted by a paediatrician/neuro paediatrician and a clinical child psychologist should be considered for children who have suffered from moderate NE, with assessments being made of cognitive and motor functions. Whether they have developed a motor disability or not, the children should be followed at least to school-age, although some developmental functions, such as cognitive abilities, cannot be fully assessed until school-age at the earliest. It is important that the children's families, medical personnel and teachers are aware of the potential problems following moderate NE.

There is a need to emphasise the significance of cognitive dysfunctions in neuropaediatrics, and the introduction of a term such as developmental paediatrics might be considered in Sweden, as it has elsewhere. The assessment and identification of developmental deficits might have an important impact on the children's functional independence and quality of life.

Diffusion Tensor Imaging (Study III)

DTI is a new technique that has not been used previously in long-term follow-up studies after NE.

The lower fractional anisotropy (FA) values, indicative of smaller, fewer, less well organized and less well myelinated axons, or a combination of these factors, were seen in specific regions of the internal capsule and the corpus callosum. Thus, in the group of adolescents with moderate NE, but without CP, structural abnormalities were revealed in WM areas. How these changes correlate to the clinical picture has to be investigated. Some of the changes in WM were unilateral and this fact could be a result of the small number of participants.

Changes in the callosal size have been seen in models with asphyxiated animals [104]. The corpus callosum is particularly involved in cognitive functions such as processing speed and visuospatial functions and is vulnerable to hypoxic events [105]. Mañeru and collaborators used MRI to study adolescents with antecedents of mild and moderate NE related to perinatal asphyxia [106]. The subjects had no apparent neurological sequelae, but the corpus callosum was found to be smaller in adolescents who had sustained perinatal, moderate NE, a finding that accords with our study.

In a MRI investigation by Rutherford and collaborators, 18 term infants with hypoxic ischaemic encephalopathy (HIE) were investigated for up to two months following their birth. Among the findings they reported, loss of signal in the posterior limb of the internal capsules, which was associated with the subsequent development of major structural changes in the brain [24].

POST-TERM BIRTH AND DEVELOPMENTAL ASPECTS (STUDY IV)

This investigation, based on the routine assessments made at CHCs, revealed that children born post-term are at risk of having developmental deviations more frequently than children born at term.

One strength of this research was the accuracy of the dating of gestation, since all pregnancies were dated by ultrasound. The study was population-based and a relatively large number of children were included and followed up to 5.5 years of age. Most of the literature concerning children born post-term deal with morbidity and mortality in the neonatal period. More boys than girls were born post-term in our investigation, as has been found to be the case previously [83]. One weakness, from a neuropaediatric point of view, is that the follow-up period is short as the children were of pre-school age and definite dysfunctions may not become evident until later.

The association between post-term birth and developmental deviations is unclear. It is not possible to distinguish between pre, peri and postnatal causative factors with our material. Large prospective studies would be needed for this. A comprehensive evaluation of relevant pre, peri and postnatal factors might be helpful in improving the general understanding of the aetiologies of prolonged pregnancies. Although it can be considered to be a side-issue, it would be a good start for the general understanding of problems associated with prolonged pregnancies to better comprehend how labour is initiated, and, more specifically, to determine what factors associated with the child are of importance for this.

LONG-TERM FOLLOW-UP STUDIES

The research conducted for this thesis has demonstrated the importance of population based long-term follow-up after both moderate NE and post-term birth.

With respect to the follow up study of children with moderate NE, one problem is associated with inevitable change in neonatal conditions, because current, neonatal conditions are different from those contemporary to the period in which these children were born. This means that the findings are not necessarily valid for the current neonatal situation.

Information from long-term outcome studies is important for selecting candidates for neuroprotective treatments, such as hypothermia and headcooling, and several pharmacological interventions [107-111]. Moreover, long-term clinical follow-up of neurodevelopmental aspects will also be decisive for the evaluation of these protective measures.

CONCLUSIONS

It is difficult to predict the long term outcome after moderate NE from pre- and perinatal data and it is noted that, whilst most of the pregnancies were uneventful, prolonged pregnancies were more common amongst the children with moderate NE than in the general population.

Various types of CP were evident in the participants who had had moderate NE, indicating different etiologies.

Cognitive dysfunctions — with or without CP — are common in the group of teenagers born at term with an AS of < 7 at 5 minutes with moderate NE who were investigated in the research presented here. The cognitive dysfunctions apparent after moderate NE without CP were: major learning disabilities/mental retardation, impaired social interaction and executive dysfunctions, including difficulties with short-term memory, attention and time-perception.

Changes in the white matter were found in teenagers with moderate HIE/NE, even in the absence of CP.

Prolonged pregnancies were associated with a higher rate of neurological disorders or developmental deviations evident in a follow up study made at the age of 4 and 5.5 years.

THE DIRECTION OF FUTURE RESEARCH

Neonatal encephalopathy

A considerable amount of research is dedicated to improving the understanding of the mechanisms operating at a molecular/cellular level, in an attempt to find brain-specific markers that can help to predict the neurodevelopmental outcome and to select candidates for neuroprotection. At present several potentially useful treatment strategies are being evaluated [107]. If studies on the outcome of NE and the potential benefits of neuroprotection are to be conducted to maximum advantage, our data indicate that long-term follow-up almost into adulthood is needed to assess functions such as cognitive behaviour. Clinical prospective studies will certainly be needed in the future to establish how and how early potential problems could be identified.

Advances in imaging techniques have played an important role in improving the understanding of the processes by which injury is developed on the structural level. If it is to be possible to evaluate what these structural findings mean to the clinical picture, longer-term studies are required, including imaging, and incorporating relevant laboratory and neurophysiological data. It is indisputable that the prediction of future cognitive capacity is more complicated than the prediction of eventual motor function. An association has been shown between adverse short-term neurodevelopmental outcome after NE and imaging [24]. However, it is not yet possible to produce images that we know will help to predict cognitive outcome.

Further studies involving advanced techniques such as DTI might help us to understand some of the mechanisms underlying cognitive dysfunctions.

More collaborative studies are needed between the molecular/cellular, the structural and the clinical research fields if substantial steps forward are to be made. A multidisciplinary approach is desirable. Broader questions can be addressed, when looking beyond the Apgar scores. Finally, it is not impossible that asphyxia in the perinatal period might have an impact on the adult brain and aging.

Post-term birth

More studies of the relationship between developmental outcome and prolonged pregnancy are needed. As yet, neither the onset of labour nor the mother-placenta-fetus relation are understood. What factors related directly with the child initiate labour? There might be specific neurodevelopmental disorders that correlate to post-term birth. Another unknown concerns the issue of what induction at an earlier GA means for the long-term development of a child. Larger randomized controlled studies are needed; these will be hard, if not impossible, to perform.

Long-term follow up studies

There will always be a need for long-term studies of the outcome of different perinatal events and of complications during pregnancy and childbirth. Routines, the accepted mode of care, the interventions made and the management of pregnancies and childbirth all change over time and from one country to another. New treatments develop and their effects need to be evaluated.

How long-term follow-up studies should be performed in the future is an open question. Modern IT techniques will enable comprehensive handling of electronic medical record systems and should facilitate the large-scale compilation of data; hopefully this will facilitate follow-up studies, as well as the transfer and interpretation of data. The present study also illustrates another possibility, the value of self-reporting systems.

SUMMARY IN SWEDISH

– SVENSK SAMMANFATTNING

I den här avhandlingen ingår långtidsuppföljningar av två grupper barn:

A Barn/ungdomar som haft måttlig neonatal encefalopati och

B: barn som fötts överburna, dvs efter 42 fullbordade graviditetsveckor.

A. Långtidsprognosen hos barn som haft asfyxi vid födelsen och utvecklat måttliga neurologiska symtom, så kallad måttlig neonatal encefalopati är oklar. Enligt tidigare studier utvecklar ca 30-50 % av barnen cerebral pares men hur det går för övriga på längre sikt är mer oklart.

I en populationsbaserad studie avseende barn födda i Sverige 1985 har de fullgångna barn som haft Apgar poäng < 7 vid 5 min identifierats. De som haft kliniska tecken på måttlig neurologisk påverkan, så kallad neonatal encefalopati, NE har inkluderats i studien (n=56). Av dessa 56, avböjde 13 medverkan. Tretton hade cerebral pares och två annat svårt neurologiskt funktionshinder. Hos de 13 barnen med cerebral pares var olika typer av CP representerade vilket talar för att olika etiologiska faktorer kan vara inblandade. Mödrarna till de 28 barn/ungdomar som ej hade CP intervjuades per telefon. Intervjun innefattade en omfattande neuropediatrik anamnes och skattningsskalor. Ungdomarna var i åldrarna 15-19 år vid uppföljningen. BVC och skolhälsovårdsjournaler rekvirerades liksom läkarjournaler i förekommande fall. Elva av barnen som kom för den radiologiska studien genomgick begåvningsstest.

Majoriteten av barnen som ej har CP uppvisade kognitiva funktionsnedsättningar. Andelen barn med IQ under 70 eller svag teoretisk begåvning (IQ 70-85) var signifikant högre än i jämförelsegruppen som utgjordes av syskon i skolålder. Exekutiva svårigheter var vanliga. Ungdomarna uppvisade svårigheter med uppmärksamhet, korttidsminne, tidsuppfattning och i kontakter med kamrater. Endast 8/28 (19%) var utan funktionsnedsättningar.

De flesta graviditeter var normala. Det var i gruppen med måttlig NE signifikant ökad mängd barn födda överburna. Utifrån pre- och perinatale faktorer är det svårt att uttala sig om prognosen på lång sikt i det enskilda fallet.

Nio av barnen som haft NE men ej CP har undersökts med en speciell magnetkamerateknik, så kallad diffusion tensor imaging (DTI) som möjliggör analys av hjärnans vita substans. Som jämförelsegrupp har ungdomar matchade för ålder och kön använts. Denna undersökning har visat förändringar i vit substans i flera områden.

B. Överburna barn, barn som fötts efter 42 veckor eller längre, har tidigare i stora material vistats ha en ökad dödlighet och sjuklighet i nyföddhetsperioden. Hur det går på längre sikt vad gäller neurologisk funktion/psykomotorisk utveckling är mer osäkert. Alla barn som fötts överburna 1991 på Huddinge Universitetssjukhus har identifierats via det medicinska födelseregistret. BVC journaler och mödravårdsjournaler har analyserats.

Denna genomgång visar en association mellan överburenhet och neurologisk utvecklingsavvikelse vid 4 års resp 5,5 årskontrollen på BVC.

ACKNOWLEDGEMENTS

This work is a result of a true teamwork in many ways and I would like to express my sincere gratitude to:

All the children/teenagers and parents participating in the studies, without you this would not have been possible!

Elisabeth Fernell, my supervisor, for your neverending enthusiasm, support, encouragement and friendship. For sharing your broad knowledge in the field of neuropaediatrics. Thanks for all the fun we had along the way!

Magnus Westgren, my co-supervisor, for dynamic thinking, encouragement, help in desperate situations. Thanks for all inspiring discussions.

Agne Larsson and Claude Marcus, the former and current professors at the department of Paediatrics for creating a scientific environment.

Ulla Nordström and Märta Fredriksson at the department of Paediatrics for superb secreterial assistance.

Charlotte Palme-Kilander and Ragnar Tunell for initiating the NE study.

Boubou Hallberg and Mats Blennow for invaluable help with evaluating the neonatal records.

Michael Divon, Lennox Hill Hospital in New York, for initiating the post-term study.

Zoltan Nagy and Helena Westerberg for all the nice weekends at MR-centre in the DTI-study. Thanks also to the rest of the cowriters in the DTI-study.

Peter Lagerroos, the most flexible male psychologist I know. Without you the DTI study had not been able to perform as smoothly as it did.

Christopher Gillberg for being such a brilliant cowriter.

Petra Otterblad Olausson and collaborators, Swedish Medical Birth Register for providing data.

Kerstin Wolff for evaluating the obstetrical records in the NE study.

Nurses at all the CHCs in the postterm study, for help with finding all the records.

Gudrun Hagberg, Göteborg and Magnus Backheden, LIME, KI for statistical assistance.

Suzy Lidström for revision of the English texts. Thanks for working so fast.

Björg Tveten Stjernstad for letting me use your beautiful picture to the cover of my book.

Birgir Jacobsson and Ann-Britt Bohlin, former heads of the Children's Hospital, for great leadership.

All nice colleagues and staff - past and present - at Children's hospital through the years. Kajsa Bohlin and Torun Torbjörnsdotter for great support to a confused PhD-student.

STUDS-teamet i Botkyrka for nice Wednesdays and Fridays (Soon I'm back!).

Nurses at Storkens BVC for nice collaboration.

Klas Theorell, Per Sandstedt, Kerstin Dahlström, Katarina Wide, my past and present heads for the Department of Neuropaediatrics - for creating a great atmosphere to work in.

All in the staff at the Department of Neuropaediatrics, Children's hospital, Huddinge, all remembered, no one forgotten! Thank you all for the laughs in the lunchroom!

All in the staff at the habilitation unit in Botkyrka. Thanks for all the years of working together.

All colleagues at the Department of Neuropaediatrics at Astrid Lindgren Children's Hospital for nice collaboration.

Kerstin, Gunilla M, Katarina W, Maud, Kjell, Per S- for being such nice colleagues, thanks for your support.

Karin N, colleague and friend, being the best and most tolerant room-mate one could ever have. Thanks for sharing the ups and downs in life, for all the laughs and tears. Mona-Lisa, colleague and friend, part-time room-mate, for being so generous, for coaching and outstanding support whenever I need it.

All friends, old and new, including friends in Struulan, syjuntan, "biogänget", friends from school, friends from medical school and neighbours. You all mean a lot to me!

All babysitters all these years, without you this had been impossible!!!

My family and relatives including my parents, my brother Allan with Mirja, Mattias and Lina. My parents in law- Kyllikki and Ingemar, my brother in law Peter and Elisabeth. Thank you all for support and being the ones you are.

Marjatta and Hardy, my parents - for all help, for being such good grandparents, for always being there when I need it the most.

Finally, my own family:

Björn, my husband, for tolerance and patience all these years.

Yasmin och Josefin, my daughters for all the joy you're bringing - for being the ones you are- you are the best!!!

The studies were supported by grants from the Sunnerdahl Foundation, the Folke Bernadotte Foundation, the RBU Foundation, Stiftelsen Samariten, the First of May Flower Annual Campaign, Swedish Society of Medicine, Frimurare Barnhuset in Stockholm and Stiftelsen Allmänna BB:s Minnesfond..

REFERENCES

1. Carter BS, Haverkamp AD, Merenstein GB: **The definition of acute perinatal asphyxia.** *Clin Perinatol* 1993, **20**:287-304.
2. Hankins GD, Speer M: **Defining the pathogenesis and pathophysiology of neonatal encephalopathy and cerebral palsy.** *Obstet Gynecol* 2003, **102**:628-636.
3. Thornberg E, Thiringer K, Odeback A, Milsom I: **Birth asphyxia: incidence, clinical course and outcome in a Swedish population.** *Acta Paediatr* 1995, **84**:927-932.
4. Dilenge ME, Majnemer A, Shevell MI: **Long-term developmental outcome of asphyxiated term neonates.** *J Child Neurol* 2001, **16**:781-792.
5. Robertson CM, Finer NN: **Long-term follow-up of term neonates with perinatal asphyxia.** *Clin Perinatol* 1993, **20**:483-500.
6. Nelson KB, Ellenberg JH: **Apgar scores as predictors of chronic neurologic disability.** *Pediatrics* 1981, **68**:36-44.
7. Badawi N, Kurinczuk JJ, Keogh JM, Alessandri LM, O'Sullivan F, Burton PR, Pemberton PJ, Stanley FJ: **Intrapartum risk factors for newborn encephalopathy: the Western Australian case-control study.** *Bmj* 1998, **317**:1554-1558.
8. Badawi N, Kurinczuk JJ, Keogh JM, Alessandri LM, O'Sullivan F, Burton PR, Pemberton PJ, Stanley FJ: **Antepartum risk factors for newborn encephalopathy: the Western Australian case-control study.** *Bmj* 1998, **317**:1549-1553.
9. Volpe JJ: **Perinatal brain injury: from pathogenesis to neuroprotection.** *Ment Retard Dev Disabil Res Rev* 2001, **7**:56-64.
10. Johnston MV: **Excitotoxicity in perinatal brain injury.** *Brain Pathol* 2005, **15**:234-240.
11. Savman K, Blennow M, Gustafson K, Tarkowski E, Hagberg H: **Cytokine response in cerebrospinal fluid after birth asphyxia.** *Pediatr Res* 1998, **43**:746-751.
12. Blennow M, Hagberg H, Rosengren L: **Glial fibrillary acidic protein in the cerebrospinal fluid: a possible indicator of prognosis in full-term asphyxiated newborn infants?** *Pediatr Res* 1995, **37**:260-264.
13. Blennow M, Savman K, Ilves P, Thoresen M, Rosengren L: **Brain-specific proteins in the cerebrospinal fluid of severely asphyxiated newborn infants.** *Acta Paediatr* 2001, **90**:1171-1175.
14. Hagberg H, Thornberg E, Blennow M, Kjellmer I, Lagercrantz H, Thiringer K, Hamberger A, Sandberg M: **Excitatory amino acids in the cerebrospinal fluid of asphyxiated infants: relationship to hypoxic-ischemic encephalopathy.** *Acta Paediatr* 1993, **82**:925-929.
15. Thornberg E, Thiringer K, Hagberg H, Kjellmer I: **Neuron specific enolase in asphyxiated newborns: association with encephalopathy and cerebral function monitor trace.** *Arch Dis Child Fetal Neonatal Ed* 1995, **72**:F39-42.
16. Thorngren-Jerneck K, Alling C, Herbst A, Amer-Wahlin I, Marsal K: **S100 protein in serum as a prognostic marker for cerebral injury in term newborn infants with hypoxic ischemic encephalopathy.** *Pediatr Res* 2004, **55**:406-412.
17. Eken P, Jansen GH, Groenendaal F, Rademaker KJ, de Vries LS: **Intracranial lesions in the fullterm infant with hypoxic ischaemic encephalopathy: ultrasound and autopsy correlation.** *Neuropediatrics* 1994, **25**:301-307.
18. Cowan F, Rutherford M, Groenendaal F, Eken P, Mercuri E, Bydder GM, Meiners LC, Dubowitz LM, de Vries LS: **Origin and timing of brain lesions in term infants with neonatal encephalopathy.** *Lancet* 2003, **361**:736-742.
19. Rivkin MJ, Volpe JJ: **Hypoxic-ischemic brain injury in the newborn.** *Semin Neurol* 1993, **13**:30-39.

20. Krageloh-Mann I, Petersen D, Hagberg G, Vollmer B, Hagberg B, Michaelis R: **Bilateral spastic cerebral palsy--MRI pathology and origin. Analysis from a representative series of 56 cases.** *Dev Med Child Neurol* 1995, **37**:379-397.
21. Inder TE, Volpe JJ: **Mechanisms of perinatal brain injury.** *Semin Neonatol* 2000, **5**:3-16.
22. Paus T, Collins DL, Evans AC, Leonard G, Pike B, Zijdenbos A: **Maturation of white matter in the human brain: a review of magnetic resonance studies.** *Brain Res Bull* 2001, **54**:255-266.
23. Filley CM: **White matter and behavioral neurology.** *Ann N Y Acad Sci* 2005, **1064**:162-183.
24. Rutherford MA, Pennock JM, Counsell SJ, Mercuri E, Cowan FM, Dubowitz LM, Edwards AD: **Abnormal magnetic resonance signal in the internal capsule predicts poor neurodevelopmental outcome in infants with hypoxic-ischemic encephalopathy.** *Pediatrics* 1998, **102**:323-328.
25. 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.
26. Le Bihan D, Mangin JF, Poupon C, Clark CA, Pappata S, Molko N, Chabriat H: **Diffusion tensor imaging: concepts and applications.** *J Magn Reson Imaging* 2001, **13**:534-546.
27. Ge Y, Law M, Grossman RI: **Applications of Diffusion Tensor MR Imaging in Multiple Sclerosis.** *Ann N Y Acad Sci* 2005, **1064**:202-219.
28. Mukherjee P: **Diffusion tensor imaging and fiber tractography in acute stroke.** *Neuroimaging Clin N Am* 2005, **15**:655-665, xii.
29. Moseley M, Bammer R, Illes J: **Diffusion-tensor imaging of cognitive performance.** *Brain Cogn* 2002, **50**:396-413.
30. Kubicki M, Westin CF, McCarley RW, Shenton ME: **The Application of DTI to Investigate White Matter Abnormalities in Schizophrenia.** *Ann N Y Acad Sci* 2005, **1064**:134-148.
31. Szeszko PR, Ardekani BA, Ashtari M, Malhotra AK, Robinson DG, Bilder RM, Lim KO: **White matter abnormalities in obsessive-compulsive disorder: a diffusion tensor imaging study.** *Arch Gen Psychiatry* 2005, **62**:782-790.
32. Ashtari M, Kumra S, Bhaskar SL, Clarke T, Thaden E, Cervellione KL, Rhinewine J, Kane JM, Adesman A, Milanaik R, et al: **Attention-deficit/hyperactivity disorder: a preliminary diffusion tensor imaging study.** *Biol Psychiatry* 2005, **57**:448-455.
33. Nagy Z, Westerberg H, Skare S, Andersson JL, Lilja A, Flodmark O, Fernell E, Holmberg K, Bohm B, Forssberg H, et al: **Preterm children have disturbances of white matter at 11 years of age as shown by diffusion tensor imaging.** *Pediatr Res* 2003, **54**:672-679.
34. Fahey J, King TL: **Intrauterine asphyxia: clinical implications for providers of intrapartum care.** *J Midwifery Womens Health* 2005, **50**:498-506.
35. Miller FC: **Prediction of acid-base values from intrapartum fetal heart rate data and their correlation with scalp and funic values.** *Clin Perinatol* 1982, **9**:353-361.
36. Low JA, Pickersgill H, Killen H, Derrick EJ: **The prediction and prevention of intrapartum fetal asphyxia in term pregnancies.** *Am J Obstet Gynecol* 2001, **184**:724-730.
37. Peevy KJ, Chalhub EG: **Occult group B streptococcal infection: an important cause of intrauterine asphyxia.** *Am J Obstet Gynecol* 1983, **146**:989-990.
38. Catlin EA, Carpenter MW, Brann BSt, Mayfield SR, Shaul PW, Goldstein M, Oh W: **The Apgar score revisited: influence of gestational age.** *J Pediatr* 1986, **109**:865-868.
39. Perlman JM: **Systemic abnormalities in term infants following perinatal asphyxia: relevance to long-term neurologic outcome.** *Clin Perinatol* 1989, **16**:475-484.
40. Sarnat HB, Sarnat MS: **Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study.** *Arch Neurol* 1976, **33**:696-705.

41. Fenichel GM: **Hypoxic-ischemic encephalopathy in the newborn.** *Arch Neurol* 1983, **40**:261-266.
42. Finer NN, Robertson CM, Richards RT, Pinnell LE, Peters KL: **Hypoxic-ischemic encephalopathy in term neonates: perinatal factors and outcome.** *J Pediatr* 1981, **98**:112-117.
43. Nelson KB, Leviton A: **How much of neonatal encephalopathy is due to birth asphyxia?** *Am J Dis Child* 1991, **145**:1325-1331.
44. Leviton A, Nelson KB: **Problems with definitions and classifications of newborn encephalopathy.** *Pediatr Neurol* 1992, **8**:85-90.
45. Bax M, Nelson KB: **Birth asphyxia: a statement.** *World Federation of Neurology Group.* *Dev Med Child Neurol* 1993, **35**:1022-1024.
46. Impey L, Greenwood C, Sheil O, MacQuillan K, Reynolds M, Redman C: **The relation between pre-eclampsia at term and neonatal encephalopathy.** *Arch Dis Child Fetal Neonatal Ed* 2001, **85**:F170-172.
47. Badawi N, Kurinczuk JJ, Mackenzie CL, Keogh JM, Burton PR, Pemberton PJ, Stanley FJ: **Maternal thyroid disease: a risk factor for newborn encephalopathy in term infants.** *Bjog* 2000, **107**:798-801.
48. Adamson SJ, Alessandri LM, Badawi N, Burton PR, Pemberton PJ, Stanley F: **Predictors of neonatal encephalopathy in full-term infants.** *Bmj* 1995, **311**:598-602.
49. 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**:F380-387.
50. Ergander U, Eriksson M, Zetterstrom R: **Severe neonatal asphyxia. Incidence and prediction of outcome in the Stockholm area.** *Acta Paediatr Scand* 1983, **72**:321-325.
51. Badawi N, Keogh JM, Dixon G, Kurinczuk JJ: **Developmental outcomes of newborn encephalopathy in the term infant.** *Indian J Pediatr* 2001, **68**:527-530.
52. Palme-Kilander C: **Methods of resuscitation in low-Apgar-score newborn infants--a national survey.** *Acta Paediatr* 1992, **81**:739-744.
53. Levene ML, Kornberg J, Williams TH: **The incidence and severity of post-asphyxial encephalopathy in full-term infants.** *Early Hum Dev* 1985, **11**:21-26.
54. Bax M, Goldstein M, Rosenbaum P, Leviton A, Paneth N, Dan B, Jacobsson B, Damiano D: **Proposed definition and classification of cerebral palsy, April 2005.** *Dev Med Child Neurol* 2005, **47**:571-576.
55. Landgren M, Pettersson R, Kjellman B, Gillberg C: **ADHD, DAMP and other neurodevelopmental/psychiatric disorders in 6-year-old children: epidemiology and co-morbidity.** *Dev Med Child Neurol* 1996, **38**:891-906.
56. Gillberg C: **Deficits in attention, motor control, and perception: a brief review.** *Arch Dis Child* 2003, **88**:904-910.
57. Kadesjo B, Gillberg C: **Developmental coordination disorder in Swedish 7-year-old children.** *J Am Acad Child Adolesc Psychiatry* 1999, **38**:820-828.
58. Kadesjo B, Gillberg C, Hagberg B: **Brief report: autism and Asperger syndrome in seven-year-old children: a total population study.** *J Autism Dev Disord* 1999, **29**:327-331.
59. (WHO) WHO: **International Classification of Functioning, Disability and Health (ICF)** Geneva. 2001.
60. Himmelman K, Hagberg G, Beckung E, Hagberg B, Uvebrant P: **The changing panorama of cerebral palsy in Sweden. IX. Prevalence and origin in the birth-year period 1995-1998.** *Acta Paediatr* 2005, **94**:287-294.
61. Grether JK, Nelson KB: **Maternal infection and cerebral palsy in infants of normal birth weight.** *Jama* 1997, **278**:207-211.
62. Jacobsson B, Hagberg G: **Antenatal risk factors for cerebral palsy.** *Best Pract Res Clin Obstet Gynaecol* 2004, **18**:425-436.
63. Meberg A, Broch H: **Etiology of cerebral palsy.** *J Perinat Med* 2004, **32**:434-439.

64. Paneth N, Stark RI: **Cerebral palsy and mental retardation in relation to indicators of perinatal asphyxia. An epidemiologic overview.** *Am J Obstet Gynecol* 1983, **147**:960-966.
65. Hagberg B, Kyllerman M: **Epidemiology of mental retardation--a Swedish survey.** *Brain Dev* 1983, **5**:441-449.
66. Toft PB: **Prenatal and perinatal striatal injury: a hypothetical cause of attention-deficit-hyperactivity disorder?** *Pediatr Neurol* 1999, **21**:602-610.
67. Ben Amor L, Grizenko N, Schwartz G, Lageix P, Baron C, Ter-Stepanian M, Zappitelli M, Mbekou V, Joobor R: **Perinatal complications in children with attention-deficit hyperactivity disorder and their unaffected siblings.** *J Psychiatry Neurosci* 2005, **30**:120-126.
68. Badawi N, Dixon G, Felix JF, Keogh JM, Petterson B, Stanley FJ, Kurinczuk JJ: **Autism following a history of newborn encephalopathy: more than a coincidence?** *Dev Med Child Neurol* 2006, **48**:85-89.
69. Dixon G, Badawi N, Kurinczuk JJ, Keogh JM, Silburn SR, Zubrick SR, Stanley FJ: **Early developmental outcomes after newborn encephalopathy.** *Pediatrics* 2002, **109**:26-33.
70. Gadian DG, Aicardi J, Watkins KE, Porter DA, Mishkin M, Vargha-Khadem F: **Developmental amnesia associated with early hypoxic-ischaemic injury.** *Brain* 2000, **123 Pt 3**:499-507.
71. Moster D, Lie RT, Markestad T: **Joint association of Apgar scores and early neonatal symptoms with minor disabilities at school age.** *Arch Dis Child Fetal Neonatal Ed* 2002, **86**:F16-21.
72. Robertson CM, Finer NN, Grace MG: **School performance of survivors of neonatal encephalopathy associated with birth asphyxia at term.** *J Pediatr* 1989, **114**:753-760.
73. Maneru C, Junque C, Botet F, Tallada M, Guardia J: **Neuropsychological long-term sequelae of perinatal asphyxia.** *Brain Inj* 2001, **15**:1029-1039.
74. Viggedal G, Lundalv E, Carlsson G, Kjellmer I: **Follow-up into young adulthood after cardiopulmonary resuscitation in term and near-term newborn infants. II. Neuropsychological consequences.** *Acta Paediatr* 2002, **91**:1218-1226.
75. Kjellmer I, Beijer E, Carlsson G, Hrbek A, Viggedal G: **Follow-up into young adulthood after cardiopulmonary resuscitation in term and near-term newborn infants. I. Educational achievements and social adjustment.** *Acta Paediatr* 2002, **91**:1212-1217.
76. Gardosi J: **Dating of pregnancy: time to forget the last menstrual period.** *Ultrasound Obstet Gynecol* 1997, **9**:367-368.
77. Mongelli M, Opatola B: **Duration and variability of normal pregnancy. Implications for clinical practice.** *J Reprod Med* 1995, **40**:645-648.
78. Rowlands S, Royston P: **Estimated date of delivery from last menstrual period and ultrasound scan: which is more accurate?** *Br J Gen Pract* 1993, **43**:322-325.
79. Shea KM, Wilcox AJ, Little RE: **Postterm delivery: a challenge for epidemiologic research.** *Epidemiology* 1998, **9**:199-204.
80. Usher RH, Boyd ME, McLean FH, Kramer MS: **Assessment of fetal risk in postdate pregnancies.** *Am J Obstet Gynecol* 1988, **158**:259-264.
81. Eden RD, Seifert LS, Winegar A, Spellacy WN: **Maternal risk status and postdate pregnancy outcome.** *J Reprod Med* 1988, **33**:53-57.
82. Rath W: **[Prolonged pregnancy--prostaglandins as the cause of labor onset].** *Z Geburtshilfe Perinatol* 1994, **198**:207-214.
83. Divon MY, Ferber A, Nisell H, Westgren M: **Male gender predisposes to prolongation of pregnancy.** *Am J Obstet Gynecol* 2002, **187**:1081-1083.
84. Stubblefield PG, Berek JS: **Perinatal mortality in term and post-term births.** *Obstet Gynecol* 1980, **56**:676-682.
85. Lagrew DC, Freeman RK: **Management of postdate pregnancy.** *Am J Obstet Gynecol* 1986, **154**:8-13.
86. Olesen AW, Westergaard JG, Olsen J: **Perinatal and maternal complications related to postterm delivery: a national register-based study, 1978-1993.** *Am J Obstet Gynecol* 2003, **189**:222-227.

87. Ingemarsson I, Kallen K: **Stillbirths and rate of neonatal deaths in 76,761 postterm pregnancies in Sweden, 1982-1991: a register study.** *Acta Obstet Gynecol Scand* 1997, **76**:658-662.
88. Hilder L, Costeloe K, Thilaganathan B: **Prolonged pregnancy: evaluating gestation-specific risks of fetal and infant mortality.** *Br J Obstet Gynaecol* 1998, **105**:169-173.
89. Cotzias CS, Paterson-Brown S, Fisk NM: **Prospective risk of unexplained stillbirth in singleton pregnancies at term: population based analysis.** *Bmj* 1999, **319**:287-288.
90. Divon MY, Haglund B, Nisell H, Otterblad PO, Westgren M: **Fetal and neonatal mortality in the postterm pregnancy: the impact of gestational age and fetal growth restriction.** *Am J Obstet Gynecol* 1998, **178**:726-731.
91. Campbell MK, Ostbye T, Irgens LM: **Post-term birth: risk factors and outcomes in a 10-year cohort of Norwegian births.** *Obstet Gynecol* 1997, **89**:543-548.
92. Zwerdling MA: **Factors pertaining to prolonged pregnancy and its outcome.** *Pediatrics* 1967, **40**:202-212.
93. Luckas M, Buckett W, Alfirevic Z: **Comparison of outcomes in uncomplicated term and post-term pregnancy following spontaneous labor.** *J Perinat Med* 1998, **26**:475-479.
94. Shime J: **Influence of prolonged pregnancy on infant development.** *J Reprod Med* 1988, **33**:277-284.
95. Rand L, Robinson JN, Economy KE, Norwitz ER: **Post-term induction of labor revisited.** *Obstet Gynecol* 2000, **96**:779-783.
96. Hannah ME, Huh C, Hewson SA, Hannah WJ: **Postterm pregnancy: putting the merits of a policy of induction of labor into perspective.** *Birth* 1996, **23**:13-19.
97. Conners CK: **A teacher rating scale for use in drug studies with children.** *Am J Psychiatry* 1969, **126**:884-888.
98. duPaul GJ PT, Anastopoulos AD, Reid R: **AHD rating scale IV. Checklist, norms and clinical interpretations.** New York, Guilford Press. 1998.
99. Ehlers S, Gillberg C, Wing L: **A screening questionnaire for Asperger syndrome and other high-functioning autism spectrum disorders in school age children.** *J Autism Dev Disord* 1999, **29**:129-141.
100. Westgren LM, Ingemarsson I: **Breech delivery and mental handicap.** *Baillieres Clin Obstet Gynaecol* 1988, **2**:187-194.
101. Herbst A, Thorngren-Jerneck K: **Mode of delivery in breech presentation at term: increased neonatal morbidity with vaginal delivery.** *Acta Obstet Gynecol Scand* 2001, **80**:731-737.
102. Krebs L, Langhoff-Roos J, Thorngren-Jerneck K: **Long-term outcome in term breech infants with low Apgar score--a population-based follow-up.** *Eur J Obstet Gynecol Reprod Biol* 2001, **100**:5-8.
103. Bax MC: **Terminology and Classification of Cerebral Palsy.** *Dev Med Child Neurol* 1964, **11**:295-297.
104. Kohlhauser C, Mosgoller W, Hoyer H, Lubec B: **Myelination deficits in brain of rats following perinatal asphyxia.** *Life Sci* 2000, **67**:2355-2368.
105. Verger K, Junque C, Levin HS, Jurado MA, Perez-Gomez M, Bartres-Faz D, Barrios M, Alvarez A, Bartumeus F, Mercader JM: **Correlation of atrophy measures on MRI with neuropsychological sequelae in children and adolescents with traumatic brain injury.** *Brain Inj* 2001, **15**:211-221.
106. Maneru C, Junque C, Salgado-Pineda P, Serra-Grabulosa JM, Bartres-Faz D, Ramirez-Ruiz B, Bargallo N, Tallada M, Botet F: **Corpus callosum atrophy in adolescents with antecedents of moderate perinatal asphyxia.** *Brain Inj* 2003, **17**:1003-1009.
107. Thoresen M, Whitelaw A: **Therapeutic hypothermia for hypoxic-ischaemic encephalopathy in the newborn infant.** *Curr Opin Neurol* 2005, **18**:111-116.
108. Azzopardi D, Robertson NJ, Cowan FM, Rutherford MA, Rampling M, Edwards AD: **Pilot study of treatment with whole body hypothermia for neonatal encephalopathy.** *Pediatrics* 2000, **106**:684-694.

109. Battin MR, Dezoete JA, Gunn TR, Gluckman PD, Gunn AJ: **Neurodevelopmental outcome of infants treated with head cooling and mild hypothermia after perinatal asphyxia.** *Pediatrics* 2001, **107**:480-484.
110. Vannucci RC, Perlman JM: **Interventions for perinatal hypoxic-ischemic encephalopathy.** *Pediatrics* 1997, **100**:1004-1014.
111. Shankaran S, Laptook A: **Challenge of conducting trials of neuroprotection in the asphyxiated term infant.** *Semin Perinatol* 2003, **27**:320-332.