BIOLOGICAL AND SOCIAL FACTORS

IN THE DEVELOPMENT OF

THE VERY LOW BIRTHWEIGHT CHILD

Cover illustration: Martijn Dragt, Anouk Roosmalen and Patricia van Veen

at 3.6 years of age.

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IN THE DEVELOPMENT OF

THE VERY LOW BIRTHWEIGHT CHILD

BIOLOGISCHE EN SOCIALE FACTOREN

IN DE ONTWIKKELING VAN

HET KIND MET EEN ZEER LAAG GEBOORTEGEWICHT

PROEFSCHRIFT

ter verkrijging van de graad van doctor

aan de Erasmus Universiteit Rotterdam

op gezag van de Rector Magnificus

Prof. Dr. C.J. Rijnvos

en volgens het besluit van het College van Dekanen.

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Nynke Weisglas-Kuperus

geboren te Rotterdam.

Aan alle toekomstige kinderen met een zeer laag geboortegewicht

The prematurely born infant emerges into a hectic, cold, noisy, and bright environment filled with mysterious equipment and peopled by masked strangers who try to help. Almost everything done to or for the infant is painful, and that pain can certainly be felt, although it cannot be communicated. The infant who must have endotracheal tube cannot cry and is not fed by mouth for weeks. His or her feet are slashed periodically for blood samples. The infant's respirator roars away at night and day keeping his or her lungs inflated and sustaining life - but at what price?

(J. F. Lucey, 1985)

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CHAPTER 1

INTRODUCTION

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1.1 BACKGROUND

Only 0,6 % of all live-born children in the Netherlands have a birthweight less than 1500 grams. Although few in number, these very low birthweight (VLBW) infants constitute a major workload for neonatal intensive care units. Because of their immaturity, VLBW infants are at risk from a wide range of hazards which can cause death or neonatal damage. The introduction of neonatal intensive care has greatly improved their chances of survival. Worldwide the survival of VLBW infants has trebled since 1960, and the handicap rate stabilized [1,2]. However, the surviving infants have a high incidence of hemorrhagic and ischemic cerebral lesions. Handicaps such as cerebral palsy, mental retardation, severe visual and hearing impairments are found in 5 to 15% of the surviving infants. Less severe impairments such as minor neurological dysfunction, mild developmental delays, behavioral and learning problems, and poor school performance are found in up to 60%. With the increased survival rate, neurodevelopmental disabilities may thus occur in an increasing number of VLBW survivors. Pediatricians are now faced with questions related to the quality of life of those infants. Prevention of morbidity in the neonatal period as well as later in life has therefore become an important goal of neonatal intensive care.

VLBW infants are not only at biological but also at psychosocial risk. Due to preterm birth, these infants have to adapt earlier to extra-uterine life. Being treated by neonatal intensive care, their early environment is very different from healthy full-term infants. Neonatal intensive care also implies many caretakers and separation from the parents. Parents have to relate to their, often severely ill, newborn infant in the environment of a neonatal intensive care unit with all its high technology. Moreover, the parents may be uncertain for a very long time whether their child will survive or die, whether it will survive healthy or handicapped. This may affect the parent-child relationship. Any of these factors is traumatic and can thus affect the child's development. In addition the incidence of VLBW is associated with socio-demographic risk factors (eg. single motherhood, low occupational or educational status, poverty) which in themselves may be related to a less favorable outcome. Prenatal, intrapartum, neonatal and socio-environmental factors play their part in a complex transactional

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process [3], determining the ultimate outcome in the individual child.

Neonatal intensive care is not only stressful for the child and its parents. The cost is also high. In the Netherlands financial resources in health care are cut down. Around F50.000 have to be invested in neonatal intensive care for one single surviving infant. Major handicaps, however, require an investment of F1.000.000 to F2.000.000 per child in terms of chronic care. Less severe impairments involve larger numbers of children and are therefore also expensive. Neonatal intensive care thus creates difficult ethical and economic dilemmas for parents, pediatricians and society in general.

With the increasing number of surviving VLBW infants, a new generation of infants will grow up, which would not have had a chance of survival before the introduction of neonatal intensive care. Learning from long-term evaluation after hospital discharge is therefore an obligation. Follow-up of VLBW infants is essential for the child and its parents to enable early detection of handicaps and timely therapeutic intervention. Early detection of handicaps is also vital to evaluate perinatal management, in order to try to prevent possible causes of neurodevelopmental disabilities in the future. Most major handicaps can be detected in the first year of life. Less severe impairments, such as minor neurological dysfunction, school and behavioral problems, may go undetected until later in childhood, but may also be more amenable to intervention. It is not yet certain at what age follow-up can give a reasonably confident assessment of these minor impairments. Therefore long-term follow-up is essential. With a decreasing budget, however, it is difficult to follow the increasing number of VLBW infants intensively throughout childhood. Early identification of infants at risk and early intervention would allow a more efficient utilization of existing resources.

Longitudinal follow-up studies on VLBW children can be multi-centered or hospital-based. Multi-centered studies have the advantage of covering the whole population in one area, involving a large number of infants. In the Netherlands such a large epidemiological study on VLBW infants has been conducted in 1983 (Project Onderzoek Prematuritas en Small for gestational age, POPS). The POPS has given us valuable information about mortality and morbidity of VLBW infants in the Netherlands [4-6]. However, this large epidemiological survey was mostly based on routine clinical evaluations and the interobserver variability was high. Therefore this study could not provide detailed information about the complex interaction between biological and

social factors and about possible clues for intervention in that process. A hospital-based study of VLBW infants, all treated by neonatal intensive care and consequently at highest developmental risk, is more suitable to collect such detailed information.

1.2 AIMS OF THE STUDY

In this thesis a prospective longitudinal follow-up study will be described from birth to 3.6 years of age in 79 high-risk VLBW children. The aim of the study was to find answers to the following questions:

1. What is the predictive value of standardized assessments in the neonatal period, at 1 and 2 years of age, for neurodevelopmental outcome at 3.6 years of age?

2. What is the effect of biological and social factors on the development of high-risk VLBW children and how do these factors interact?

3. Is there any relationship between specific biological and social factors and specific neurodevelopmental disabilities and if so, how can these disabilities be prevented in the future?

1.3 PATIENTS AND METHODS

The study group consisted of all preterm VLBW children (birthweight < 1500 grams, gestational age < 36 weeks) admitted to the Neonatal Intensive Care Unit of the Sophia Children's Hospital in Rotterdam between August 1, 1985 and August 1, 1986 within 48 hours after birth (n = 114). Twenty-three infants (20%) died in the neonatal period or in the first year of life. Twelve children (10%) were not available for the whole follow-up period. Of the remaining 79 children, in addition to regular pediatric care, detailed assessments were made during their stay in neonatal intensive care as well as at the age of 1, 2 and 3.6 years. An overview of the assessment procedures is presented in Table 1.1.

1.4 STRUCTURE OF THE THESIS

In the following chapters of this thesis the different assessments will be described at different ages in detail and consequences of these findings will be discussed:

Table 1.1 Assessment procedures

TYPE OF ASSESSMENT	AGE OF ASSESSMENT			
	Neonatal	1 Year	2 Years	3.6 Years
Perinatal Conditions	Obstetrical Optimality Birthweight Gestational Age Neonatal Optimality			
Neurology	Cerebral Ultrasound Neurological Examination	Neurological Examination	Neurological Examination	Neurological Examination
Visual Functions		Visual Acuity Visual Fields Optokinetic Nystagmus Strabismus	Visual Acuity Visual Fields Optokinetic Nystagmus Strabismus	
Hearing				Audiometry Tympanometry
Development		Bayley: -Mental Scale -Motor Scale	Bayley: -Mental Scale -Motor Scale	K-ABC: -Intelligence -Achievement McCarthy: -MotorScale Language: -Comprehension -Expression
Behavior				Clinician Report Parent Report: -CBCL -GBO
Social Factors	Socio-demographic Risk	HOME Inventory		HOME Inventory

Chapter 2 gives an overview of the follow-up results at different ages and describes which assessments are useful in order to identify handicaps in pediatric practice.

Chapter 3 describes in detail which assessments, before discharge from the neonatal intensive care, will predict outcome most accurately.

Chapter 4 and 5 describe the interaction between biological and social factors in the cognitive development and behavioral outcome of the VLBW child.

Chapter 6 and 7 describe minor impairments such as minor neurological dysfunction, inattention and activity in relation to neonatal conditions, cognitive outcome and the home environment .

Chapter 8 and 9 describe hearing loss and visual impairments in relation to neonatal conditions and developmental outcome.

Chapter 10 gives a summary of all findings. Final conclusion and recommendations for the future are made.

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CHAPTER 2

EARLY ASSESSMENT AND NEURODEVELOPMENTAL OUTCOME
IN VERY LOW BIRTHWEIGHT INFANTS, IMPLICATIONS FOR PEDIATRIC PRACTICE

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EARLY ASSESSMENT AND NEURODEVELOPMENTAL OUTCOME
IN VERY LOW BIRTHWEIGHT INFANTS, IMPLICATIONS FOR PEDIATRIC PRACTICE

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2.1 SUMMARY

To determine which assessments are useful at what age in order to identify handicaps in VLBW children, neonatal cerebral ultrasound findings, neurological examinations and the mental scale of the Bayley Infant Scales of Development at 1 and 2 years of age were examined in relation to neurodevelopmental outcome at 3.6 years of age in a cohort of 79 high-risk very low birthweight infants. At age 3.6 a minor handicap was found in 9 (11%) and a major handicap in 4 (5%) children. Cerebral palsy was found in 9 (11%) children at age 3.6 and could only be diagnosed reliably at age 2. For short term follow-up, as feedback to the neonatologist, the positive predictive value of intraparenchymal damage, as detected by neonatal cerebral ultrasound, was better than the positive predictive value of a definitely abnormal neurological examination at age 1. Visual handicaps (n = 4, 5%) and severe hearing deficits (n = 1, 1%) were all detected in the first year of life. A mental handicap was found in 7 (9%) children. It was impossible to predict mental handicaps for the individual child. Only 35% of the children with a mental delay at age 2 had a mental handicap at age 3.6 whereas 35% had a normal cognitive outcome. Pediatricians therefore should be cautious in the interpretation of developmental test results in infancy. Long-term follow-up is essential for the child and its parents.

2.2 INTRODUCTION

In present times 85 % of the infants born with birthweights less than 1500 grams (VLBW) will survive without handicap (1,2). Nevertheless VLBW infants are still much more prone to handicaps than healthy fullterm children. Follow-up of VLBW infants is

essential for the child and its parents to enable early detection of handicaps and timely therapeutic intervention. Early detection is also vital to evaluate perinatal management, in order to try to prevent handicaps in the future.

Several types of assessment are possible at an early age. Neonatal cerebral ultrasound scanning is common practice now in neonatal intensive care units and abnormalities have been associated with neurodevelopmental outcome (3-4). In pediatric practice neurological examinations are standard. However, follow-up of VLBW children is mostly not pursued past the age of 15-18 months, unless specific problems arise. Developmental tests are widely used in the clinical evaluation of cognitive development in young infants and children. Unfortunately many children make important changes in their developmental quotient (5). Moreover not all developmental sequelae will be diagnosed in infancy because subtle developmental deficits may not be apparent until later in life.

Long term follow-up is, however, difficult and expensive. It is usually impossible for the pediatric practitioner to perform all assessments at different ages. Moreover unnecessary labeling and treatment of a child as handicapped may initiate a harmful sequence of events, even if the treatment per se is benign. In this study we therefore wanted to determine which assessments at what age are useful in pediatric practice to identify handicaps. Neonatal cerebral ultrasound findings, neurological examinations and the mental scale of the Bayley Infant Scales of Development at 1 and 2 years of age were examined in relation to neurodevelopmental outcome at 3.6 years of age.

2.3 PATIENT AND METHODS

Study group

This study is part of a larger longitudinal study on VLBW infants (6). The study group consisted of all preterm VLBW children (birthweight <1500 grams, gestational age <36 weeks) who were admitted to the Neonatal Intensive Care Unit of the Sophia Children's Hospital in Rotterdam (a regional tertiary intensive-care unit) between August 1, 1985 and August 1, 1986 within 48 hours after births (n=114). Twenty-three infants (20%) died in the neonatal period or in the first year of life. Twelve children (10%) were not available for the whole follow-up period because of migration (N=6), lack of interest (N=3) or inability (N=3) to cooperate on the part of the parents. Of the

remaining 79 children there were 34 boys and 45 girls. There were no children with major congenital anomalies. Gestational age ranged from 25 to 35 weeks (mean 30, ±2SD). Birthweights ranged from 690 to 1495 grams (mean 1136, ±213 SD). Obstetrical and neonatal conditions were recorded on an obstetrical and neonatal scale and are presented in detail elsewhere (4).

Neonatal cerebral ultrasound

Neonatal cerebral ultrasound findings were classified as follows: Normal (group 0); abnormal without ventriculomegaly (group 1); abnormal with ventriculomegaly (group 2); and abnormal with intraparenchymal damage (group 3).

Neurology

A standardized neurological examination (7-8) was done at the corrected ages of 1, 2 and 3.6 years. Findings were classified as normal, mildly and definitely abnormal. A child was classified as definitely abnormal when a neurological disorder, such as cerebral palsy, was diagnosed. A child was classified as mildly abnormal when minor neurological signs, such as minor left-right differences or mild hypertonia, were present but could not be attributed to a traditional neurological diagnosis.

Cognition

At a corrected age of 1 and 2 years cognition was assessed with the mental scale of the Dutch version of the Bayley Scales of Infant Development (9). A mental developmental index less than -1SD below the mean (MDI>84) was considered as normal, of -1SD to -2SD (MDI 84-68) as a mild delay and of more than -2SD below the mean (MDI<68) as a definite delay.

At a corrected age of 3.6 years the Dutch adaptation of the Kaufman Assessment Battery for Children (K-ABC) (10-11) was used. The K-ABC measures intelligence (the Mental Processing Composite, MPC) and achievement (the Achievement Scale). An index of more than -2SD below the mean (< 70) on both the intelligence and the achievement scale was considered as a mental handicap, an index of -1SD to -2SD (85-70) on both scales was considered as a mild cognitive delay. The remaining children were considered to have a normal cognitive outcome.

Handicap

A handicap was defined, according to the WHO definition (12), as " a disadvantage for a given individual, resulting from an impairment or a disability, that limits or prevents the fulfillment of a role that is normal for that individual." Impairment is disturbance at organ level; disability is the consequence for function and activity; and handicap is the social disadvantage experienced by the individual as a result of the disability. A handicap was considered minor when it did not require extensive caretaking; and major when it let to a life of dependency or institutionalization (1). In our study group a child was considered as being handicapped when one of the following conditions was found at 3.6 years of age: cerebral palsy, a mental handicap, a severe visual or hearing impairment.

Data analysis

The statistical package Statgraphics 4.0 was used. Univariate statistical analysis was performed to study associations between separate items. A p value of <.05 was considered significant.

2.4 RESULTS

Results of the assessments at 0, 1, 2 and 3.6 years of age are presented in Table 2.1.
- Cerebral ultrasound: Of the 79 children 22 had a normal and 57 abnormal scan (20 without ventriculomegaly, 30 with ventriculomegaly and 7 with intraparenchymal damage).
- Neurology: The prevalence of mildly and definitely abnormal neurological examinations at age 1, 2 and 3.6 remained relatively stable. At 3.6 years of age 50 of the 79 children were classified as normal, 20 as mildly and 9 as definitely abnormal (6 quadriplegia, 2 hemiplegia and 1 hypotonia). Five of these 9 children were mildly handicapped and able to walk without aid while 4 were severely handicapped and confined to a wheelchair.
- Cognition: At 1 and 3.6 years of age a developmental index could be calculated in all 79 cases. At 2 years of age, 2 children (with normal development at age 1 and mild delay at age 3.6) refused to cooperate. The prevalence of mild and definite mental delay was higher at age 2 than at age 1 and 3.6. The mean Mental Developmental

Table 2.1 Results of the assessments at 0, 1, 2 and 3.6 years of age (n=79).

TYPE OF ASSESSMENT		AGE OF ASSESSMENT			
		Neonatal	1 Year	2 Years	3.6 Years
Cerebral Ultrasound:	-Normal/Ventriculomegaly - -Ventriculomegaly + -Intraparenchymal Damage	42 (53%) 30 (34%) 7 (9%)			
Neurology:	-Normal -Mildly Abnormal -Definitely Abnormal		49 (62%) 20 (25%) 10 (13%)	54 (68%) 16 (20%) 9 (12%)	50 (63%) 20 (25%) 9 (12%)
Cognition:	-Normal -Mildly Abnormal -Definitely Abnormal		61 (77%) 10 (13%) 8 (10%)	38 (49%) 22 (29%) 17 (22%)	61 (77%) 11 (14%) 7 (9%)

Index was 96 (±19 SD, range 52-137) at age 1 and 86 (±26 SD, range 52-141) at age 2. At age 3.6 the mean index on the Intelligence scale was 87 (±13 SD, range 55-113) and 86 (±14 SD, range 55-115) on the Achievement scale.

- A handicap was found in 8 of the 45 girls (18%) and 5 of the 34 boys (15%). Nine children had a minor (11%) and 4 (5%) had a major handicap. Eight of the 13 children had one handicap (4 children with cerebral palsy, 3 children with a mental handicap, 1 child with a visual handicap) and 5 children had multiple handicaps (2 children with cerebral palsy, a mental and a visual handicap, 1 child with cerebral palsy, a mental handicap, severe bilateral hearing loss and a visual handicap, 1 child with cerebral palsy and a mental handicap, 1 child with cerebral palsy and a visual handicap). All severe hearing and visual impairments were detected in the first year of life

The relationship of the 0, 1 and 2 years assessments with cerebral palsy and mental handicaps at 3.6 years of age is given in Table 2.2. Children with a cerebral palsy at age 3.6 had significantly more intraparenchymal damage, as detected by neonatal cerebral ultrasound, and significantly more definitely abnormal neurological examinations and definite mental delays at age 1 and 2. Children with a mental handicap at age 3.6 had significantly more definite mental delays at age 1 and 2. Intraparenchymal damage as detected by neonatal cerebral ultrasound better predicted cerebral palsy at age 3.6 (positive predictive value 86%) than a definitely abnormal neurological examination at age 1 (positive predictive value 70%). In the individual child, cerebral palsy could only be reliably diagnosed at age 2. A mental delay at age 1 (positive predictive value 62%) better predicted a mental handicap at age 3.6 than a mental delay at age 2 (positive predictive value 35%). Details of the neurological examination at 1, 2 and 3.6 years of age are presented in Figure 2.1. Details of the

cognitive development at 1, 2 and 3.6 years of age are presented in Figure 2.2.
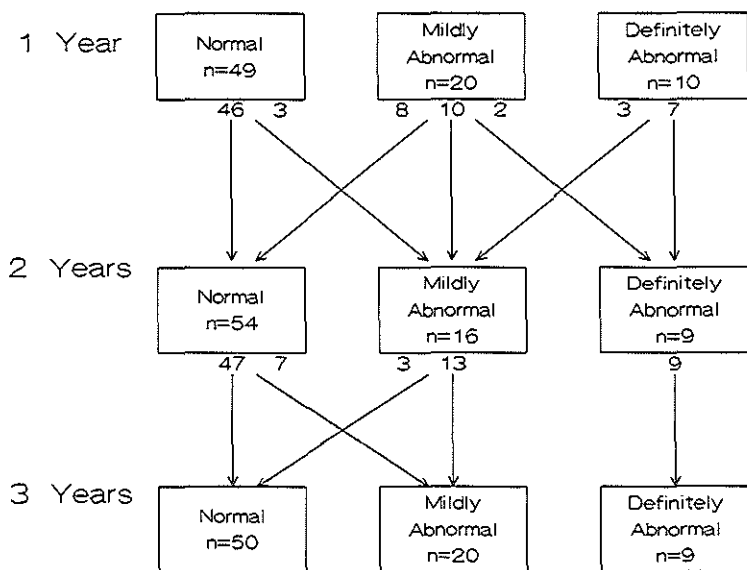
Figure 2.1 Neurological classification at 1, 2 and 3.6 years of age.
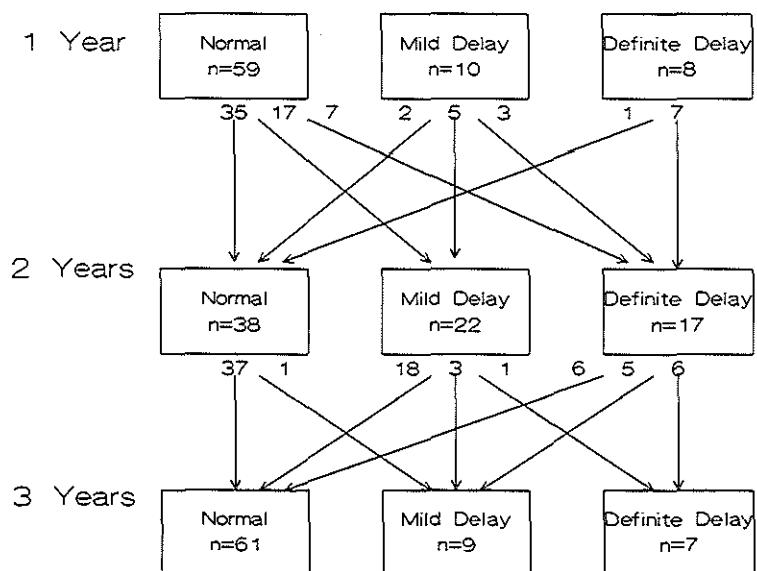
Figure 2.2 Cognition at 1, 2 and 3.6 years of age.

Table 2.2 Relationship of the assessments at age 0, 1 and 2 with cerebral palsy and mental handicaps at 3.6 years of age.

AGE OF ASSESSMENT		NEURODEVELOPMENTAL OUTCOME AT 3.6 YEARS OF AGE			
		Cerebral Palsy		Mental Handicap	
		Absent	Present	Absent	Present
Neonatal	Cerebral Ultrasound:				
	-Normal/Ventriculomegaly-	42(100%)	0(0%)	40(95%)	2(5%)
	-Ventriculomegaly+	27(90%)	3(10%)	28(93%)	2(7%)
	-Intraparenchymal Damage	1(14%)	6(86%)***	4(57%)	3(43%)*[1]
1 Year	Neurology:				
	-Normal/Mildly Abnormal	67(97%)	2(3%)	65(94%)	4(6%)
	-Definitely Abnormal	3(30%)	7(70%)***	7(70%)	3(30%)*[1]
	Mental Developmental Index:				
	-≥68	68(96%)	3(4%)	69(97%)	2(3%)
	-<68	2(25%)	6(75%)***	3(38%)	5(62%)***
2 Years	Neurology:				
	-Normal/Mildly Abnormal	70(100%)	0(0%)	67(96%)	3(4%)
	-Definitely Abnormal	0(0%)	9(100%)***	5(56%)	4(44%)**
	Mental Developmental Index:				
	-≥68	57(95%)	3(5%)	59(98%)	1(2%)
	-<68	11(65%)	6(35%)**	11(65%)	6(35%)***

Fisher's Exact, *=p<0.05, **=p<0.01, ***=p<0.001.
[1] Not significant when corrected for the number of analysis, using Bonferroni correction.

2.5 DISCUSSION

In our study of VLBW infants, all treated by neonatal intensive care, the mortality rate was 20%, the prevalence of minor handicaps at 3.6 years of age was 11% and of major handicaps was 5%. Comparing our results with the results of an epidemiological study of all VLBW born in the Netherlands in 1983 (POPS-project), we observe some differences. In the POPS study the mortality rate was 28%, the prevalence of minor handicaps at 5 years of age was 8% and of major handicaps was 6.5% (1). In this epidemiological study, all VLBW infants in the Netherlands, treated in regional hospitals as well as by neonatal intensive care, were included. Our results suggest that neonatal intensive care can increase the survival rate of VLBW infants with a stable handicap rate. These results are promising, since the likelihood of a handicap is greater in VLBW infants requiring intensive care than in those without major neonatal illness (13).

Although the frequency of neurologically mildly and definitely abnormal children remained relatively stable, the neurological classification in the individual child changed in time. Our data demonstrate that in the absence of a definitely abnormal neurological examination or a definite mental delay at age 1, it is highly unlikely that there will be

cerebral palsy at age 3.6 (negative predictive value 96-97%). While with a definitely abnormal neurological examination or a definite mental delay at age 1, it is highly likely that there will be cerebral palsy at age 3.6 (positive predictive value 70-75%). As in other studies (14-18), the diagnosis of cerebral palsy at age 1 was not a static condition and a reliable diagnosis of cerebral palsy in the individual child did not occur until 2 years of age in our study group. For neurological outcome the positive predictive value of intraparenchymal damage (86%), as detected by neonatal cerebral ultrasound, was better than the positive predictive value of a definitely abnormal neurological examination at age 1 (75%). Neonatal cerebral ultrasound is thus more useful than the 1 year assessment for early prediction and evaluation of perinatal management.

In neurologically mildly abnormal children, the neurological status fluctuated in time and no individual prediction was possible. Approximately one third of the infants classified as mildly abnormal at 1 and 2 years of age were normal by 3.6 years of age, while one sixth of the infants who were neurologically normal at 1 and 2 years of age were classified as mildly abnormal at 3.6 years of age. These subtle neurological findings in preschool children are important, because they could be manifestations of brain damage and indicators of later learning deficits (16,19). Moreover minor neurological deficits may not all manifest themselves in infancy and early childhood. Recent studies (20-21) have demonstrated that the prevalence of minor neurological dysfunction increases until puberty. Repetitive evaluations are necessary to identify all children with these more subtle neurological problems.

The fundamental question to answer before a developmental delay is categorized as a disorder, is whether it is associated with impairment of current or future functioning. As in other studies of high-risk children (5,22), there was a significant relationship between mental developmental test results at different ages. However, many children made large developmental quotient changes from ages 1 to 2 and from ages 2 to 3.6 and the predictive value for the individual child was low. The results of the mental assessment at age 2 should have our special attention. Only 35% of 2-year-old children with a mental delay had a mental handicap at age 3.6 while 35% were normal. The prediction of cognition from early test results for the individual child, may thus not be valid. Pediatricians therefore should be cautious in the interpretation of these test results to prevent unnecessary parental concern. Long-term developmental follow-up is essential.

We conclude that for short term follow-up as feedback for the neonatologist, who requires monitoring of their treatment regime, neonatal cerebral ultrasound findings are as effective as a neurological examination at 1 year of age. Neurological assessment in the second year is appropriate for reliably diagnosing cerebral palsy in the individual child. Long term follow-up is necessary to identify children with minor neurological dysfunction and children with a mental handicap. In the use of developmental test results in infancy to predict later development, two facts should not be overlooked. Social factors play an important role in cognitive development (23). Moreover what can be assessed developmentally early in the child's life is far more limited than what can be assessed at a later time. Mild mental delay as well as minor neurological dysfunction at preschool age, found frequently in this very low birthweight population, may represent a substrate for future specific learning disabilities. In order to reveal the significance of these subtle findings, more detailed studies and follow-up until school age are essential. In addition studies on the interaction of social factors and neonatal cerebral damage in the development of the VLBW child are necessary.

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CHAPTER 3

NEONATAL CEREBRAL ULTRASOUND, NEONATAL NEUROLOGY
AND PERINATAL CONDITIONS AS PREDICTORS
OF NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTHWEIGHT INFANTS

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NEONATAL CEREBRAL ULTRASOUND, NEONATAL NEUROLOGY
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3.1 SUMMARY

To determine the assessment(s) before discharge from the intensive care unit, that will predict outcome most accurately, a prospective longitudinal study in a cohort of 79 high risk VLBW children was conducted from birth to 3.6 years of age. Birthweight, gestational age, obstetrical and neonatal optimality, neonatal neurological examinations and neonatal cerebral ultrasound were studied in relation to outcome. The best predictor for outcome was a simple cerebral ultrasound classification according to the presence or absence of ventriculomegaly and intraparenchymal damage of any cause. Infants with normal neonatal cerebral scans or abnormal scans without ventriculomegaly almost invariably had a normal neurological outcome. In infants with cerebral lesions with ventriculomegaly the incidence of normal neurological outcome decreased to less than 50%. Intraparenchymal damage was associated with cerebral palsy as well as other (mental and sensori) handicaps in over 85% of the cases. Neonatal neurological examinations at preterm age had additional value in predicting neurological outcome especially in the group with ventriculomegaly. Neither birthweight, nor gestational age, obstetrical or neonatal optimality were independent variables in the prediction of outcome in high risk VLBW children at 3.6 years of age.

3.2 INTRODUCTION

Over the last decades neonatal intensive care has greatly improved the chances for survival of infants born with birthweights less than 1500 grams (VLBW infants). With this improved survival the prevention of morbidity in the neonatal period as well as

later in life has become an important goal of neonatal intensive care. Handicaps such as cerebral palsy, mental retardation, visual and hearing impairment have been found in 6-14% of VLBW survivors [12,30,34]. Disabilities such as minor neurological dysfunction, mild developmental delay, behavioral and learning problems have been found in up to 60% of surviving infants [7,16,18]. Early identification of infants who might develop a major handicap is important for the decision whether or not to continue intensive care treatment. Furthermore it is increasingly difficult to follow all VLBW infants intensively throughout childhood. Early identification of infants at risk for a handicap would allow a more efficient utilization of existing resources.

VLBW infants have a high incidence of peri- and intraventricular hemorrhages (PIVH). In early neonatal ultrasound studies, with linear array equipment, associations of PIVH with poor neurodevelopmental outcome have been shown. The predictive value for the individual child was low, however, since some infants with major cerebral lesions were normal or mildly handicapped, while others with minor or no cerebral lesions were handicapped at follow-up [8,38,5]. PIVH should be distinguished from periventricular leucomalacia (PVL), an ischemic lesion probably resulting from a decreased blood flow in the water shed areas. Infants with cystic periventricular leucomalacia also have a high incidence of handicaps [10,14,36,37]. More recently the use of high resolution ultrasonography has led to a more accurate detection of neonatal cerebral lesions, particularly ischemic lesions other than cavitating PVL. Structural lesions of the brain detected by high resolution sector scanning may be more predictive of longterm neurodevelopmental outcome than linear aray findings [20,5]. Only few follow-up studies have described the neurodevelopmental outcome of children with various cerebral lesions detected by present day equipment. Also there is still no common agreement on the respective role of the different types of cerebral lesions in neurodevelopmental outcome and the best classification method [20]. Some authors have shown that grades of PIVH were a better predictor of outcome than grades of PVL [4]. Others concluded that cystic PVL showed a better correlation with outcome than PIVH [10,15]. Low [22] concluded that a three part classification of PIVH, persistent ventriculomegaly and parenchymal damage should be used to predict outcome most accurately.

Neonatal neurological examinations at term corrected age in combination with neonatal cerebral ultrasound findings can contribute to a more accurate prediction of

neurological outcome than either neonatal cerebral ultrasound or neonatal neurological examination alone [9,31]. However at term corrected age many children have already been discharged from our neonatal intensive care unit. Moreover, in these studies neurodevelopmental assessment was done during the first 2 years of life. At that age neurodevelopmental deficits may not yet be clinically evident.

Because of those reasons we conducted a prospective longitudinal follow-up study in a cohort of 79 high risk VLBW children from birth to 3.6 years of age. We wanted to find an answer to the following questions:

1. Which classification method of neonatal cerebral ultrasound findings will predict outcome most accurately?

2. What is the predictive value of neonatal neurological examinations at preterm age?

3. Can clinical and/or laboratory parameters, other than neonatal cerebral ultrasound findings and neonatal neurology, improve the prediction of outcome?

3.3 PATIENTS AND METHODS

Study group

This study is part of a larger longitudinal study on VLBW infants [39]. The total study group consisted of all preterm VLBW children (birthweight <1500 grams, gestational age <36 weeks), admitted to the Neonatal Intensive Care Unit of the Sophia Children's Hospital in Rotterdam (a regional tertiary intensive-care unit) between August 1, 1985 and August 1, 1986 within 48 hours after births (n = 114). Twenty-three infants (20%) died in the neonatal period or in the first year of life. Twelve children (10%) were not available for the whole follow-up period because of migration (N = 6), lack of interest (N = 3) or inability (N = 3) to cooperate on the part of the parents. Of the remaining 79 children 34 were boys and 45 girls. There were no children with major congenital anomalies. Neonatal treatment in our intensive care unit ranged from 7 to 160 days (M = 35). Gestational age was determined by maternal dates, and/or early ultrasound, and/or postnatal clinical assessment [3] and ranged from 25 to 35 weeks (M = 30, SD = 2). Birthweights ranged from 690 to 1495 grams (M = 1136, SD = 213).

Obstetrical and neonatal conditions were recorded in an obstetrical and neonatal scale based on the optimality concept of Prechtl [13,19,21,25,27]. The scales were adapted to our study group of high risk VLBW infants. Items were chosen to represent

the most frequent complications of prematurity. Criteria for optimality were defined according to common clinical practice. The obstetrical scale consisted of 30 and the neonatal of 14 items (Table 3.1). One point was deducted for each non optimal criteria. For each infant the number of optimal items was counted. The obstetrical score ranged from 3 to 15 (M = 7.7,SD = 2.5) and the neonatal from 0 to 9 (M = 4.1,SD = 2.2).

Table 3.1 Obstetrical and neonatal optimality scale

OBSTETRICAL AND NEONATAL SCALE	CRITERIA FOR OPTIMALITY	FREQUENCY OF OPTIMALITY n=79 (%)
OBSTETRICAL SCALE		
1. Age Mother	18-30 yrs	55 (70%)
2. Marital status at delivery	married	66 (83%)
3. Parity	1-3	26 (33%)
4. Previous abortion or fetal loss	none	57 (72%)
5. Previous infertility (>2yr)	absent	75 (95%)
6. Induced ovulation or IVF	absent	76 (96%)
7. Vaginal bleeding	absent	62 (78%)
8. Blood group incompatibility	absent	79 (100%)
9. Infections in pregnancy	absent	61 (77%)
10. Anaemia (Hb<110g/l)	absent	57 (72%)
11. Echo	normal	70 (89%)
12. Hypertension (diast>85 mmHg))	absent	44 (56%)
13. Preeclampsia (diast>90mmHg,prot>0.05 g/24h)	absent	53 (67%)
14. Preexisting maternal illness	absent	68 (86%)
15. X ray during the first 20 weeks	absent	79 (100%)
16. Tocolysis	absent	48 (61%)
17. Place of birth	inborn	55 (70%)
18. Multiple birth	absent	68 (86%)
19. Abnormal presentation	absent	71 (90%)
20. Instrumental delivery, Caesarean section	absent	39 (48%)
21. CTG	normal	43 (54%)
22. Rupture of membranes (> 24h before birth)	absent	68 (86%)
23. Colonization of birth canal	absent	75 (95%)
24. Amniotic fluid	clear	71 (90%)
25. Birthweight (Usher and McLean)	>+2SD,<-2SD	51 (65%)
26. Head circumference (Usher and McLean)	>+2SD,<-2SD	64 (81%)
27. Sexe	female	45 (57%)
28. Apgar score 1 min	≥7	33 (42%)
29. Apgar score 5 min	≥7	65 (82%)
30. Intrapartum sedation	absent	32 (40%)
NEONATAL SCALE		
1. Ventilatory assistance	absent	25 (32%)
2. IRDS (clinical and X ray characteristics)	absent	43 (54%)
3. BPD (oxygen treatment>28 days)	absent	50 (63%)
4. Apnoea	<10/day	32 (40%)
5. PDA (confirmed by ultrasound)	absent	60 (76%)
6. Pneumothorax	absent	76 (96%)
7. Hyperbilirubinemia(>150 umol/l)	absent	36 (46%)
8. Sepsis/meningitis(bloodcult.+)	absent	69 (87%)
9. Seizures	absent	76 (96%)
10. Shock (Versmold 1981)	absent	70 (89%)
11. Hypoglycemia(Gluc <2.0)	absent	47 (59%)
12. Hypocalcaemia(Ca <1.75)	absent	60 (76%)
13. Anaemia at admission(Ht<0.5)	absent	61 (77%)
14. Necrotizing enterocolitis	absent	79 (100%)

IRDS=Idiopathic Respiratory Distress Syndrome, BPD=Broncho Pulmonary Dysplasia, PDA=Persistent Ductus Arteriosus

Neonatal cerebral ultrasound

Neonatal cerebral ultrasound scanning was performed 2-4 times in the first week of life and 1-2 times weekly thereafter until discharge. All scanning was done through the anterior fontanel with an Advanced Technology Laboratories or a Diasonics scanner with 5.0 and 7.5 MHz transducers. Scans were scored by an experienced neonatologist on a form modified from Kuban, with additional items to enable a more exact classification of parenchymal lesions [2] and were classified as follows:

- Hemorrhagic lesions: Periventricular and intraventricular hemorrhages were classified according to the method of Papile et al. [24]. (PIVH I to IV).

- Ischemic lesions: Cystic periventricular leucomalacia was characterized by intense bilateral flaring of the paraventricular areas, followed by polycystic degeneration (PVL 3). Flaring without visible cystic changes was considered to be a sign of less severe periventricular leucomalacia (PVL 1 without ventriculomegaly, PVL 2 with ventriculome-galy) [14,20].

- Other cerebral lesions included congenital or acquired subependymal cysts unrelated to hemorrhage, congenital or acquired ventricular dilatation without preceding hemor-rhage or leucomalacia, or combinations of these lesions.

- Ventriculomegaly was defined by a rounded outline of the ventricular cavity plus a ventricle-brain ratio > 0.35 on a coronal cut at the middle cranial fossa.

Since the size and shape of the lesion can change in time, the results as classified here are the most extensive lesions seen in the neonatal period.

Neonatal neurology

The neonatal neurological examination was carried out according to Prechtl [26] and was performed weekly by` two experienced neonatologists (W.B. and W.F.) until discharge, including all items feasible according to the clinical condition of the child. A summary, consisting of the evaluation of posture, motility, pathological movements, tonus, threshold responses, tendon reflexes, moro and states was made. Of these 9 items a neonatal neurological optimality score was calculated, the lowest score obtained during admission was used for this analysis. One point was deducted for each non optimal symptom and for each infant the number of optimal symptoms was counted.

Neurodevelopmental assessment at 3.6 years of age

A neurodevelopmental assessment was performed at the corrected age of 3.6 years ($\pm$ 2 weeks) by a developmental pediatrician (N.W.) who was not aware of the obstetrical or neonatal findings. Interval complications were collected. The assessment at 3.6 years of age consisted of:

- A standardized neurological examination adapted from Touwen [32]. Findings were classified as normal, minor neurological dysfunction (MND) or abnormal. A child was classified as abnormal when a neurological disorder, such as cerebral palsy was diagnosed. A child was classified as MND when minor neurological signs, such as minor left-right differences or mild hypertonia, were present but could not be attributed to a traditional neurological diagnosis and did not lead to an overt handicapping condition.

- Cognition was assessed by the Dutch adaptation of the Kaufman Assessment Battery for Children (K-ABC) [17,23]. The K-ABC measures Intelligence (the Mental Processing Composite, MPC) and Achievement (the Achievement Scale). Children with a score less than - 2SD (<70) below the mean on both scales were considered to have a mental handicap. Children with a score less than -1SD (<85) below the mean on both scales were considered to have a mildly abnormal cognitive development. The remaining children were considered to have a normal cognitive outcome.

- A handicap was defined as a disability that would probably prevent the child from going to a normal school or cause interference with normal function. A handicap was diagnosed when one of the following conditions was found at 3.6 years of age: a neurological disorder, a mental handicap, a severe visual or hearing impairment.

Data analysis

The statistical package Statgraphics 4.0 was used for analysis. Univariate statistical analysis was performed to study associations between separate items. In addition stepwise multiple regression analyses were performed to determine the best perinatal predictors (eg. birthweight, gestational age, obstetrical and neonatal optimality, neonatal neurology and neonatal cerebral ultrasound) to outcome and to determine the best outcome variable (eg. neurology, cognition, all handicaps). A p value of <0.05 was considered as significant.

3.4 RESULTS

Neonatal cerebral ultrasound

Twenty-two children (28%) had normal and 57 children (72%) had abnormal neonatal cerebral ultrasound. In Table 3.2 neonatal cerebral ultrasound findings are presented in detail. There was no significant difference in neonatal cerebral ultrasound findings of the 12 children who did not complete the whole follow-up and the 79 children in follow-up.

Table 3.2 Neonatal cerebral ultrasound findings

NEONATAL CEREBRAL ULTRASOUND		TOTAL n (%)
Normal		22 (28%)
Hemorrhagic lesions:	PIVH I-II	7 (9%)
	PIVH III	6 (7%)
	PIVH IV	3 (4%)
Ischemic lesions:	PVL 1	5 (6%)
	PVL 2	9 (11%)
	PVL 3	2 (3%)
Hemorrhagic and ischemic lesions:	PIVH I-III + PVL 2	4 (5%)
	PIVH III+ PVL 3	2 (3%)
Other lesions:	Ventriculomegaly -	8 (10%)
	Ventriculomegaly +	11 (14%)
TOTAL		79 (100%)

Neonatal neurology

The neonatal neurological optimality score ranged from 1 to 9. A summary of the neonatal neurological findings is given in Table 3.3. Since generalized hypotonia was present in 90% of the infants, hypotonia was excluded from further analysis by classifying all infants with a score of 8-9 as normal. Infants with a neonatal neurological optimality score less than the 25th percentile (<5) were considered as deviant and with a score of 5-7 as mildly abnormal. Of the 79 infants, 37 (47%) had a normal neonatal condition throughout admission, 26 (33%) infants were mildly abnormal and 16 (20%) infants were deviant. All neonatally neurologically deviant infants had an apathy syndrome, none of these children was hyperexcitable or had a hemisyndrome.

Table 3.3 Neonatal neurological findings

NEONATAL NEUROLOGY		TOTAL n (%)
Posture:	Normal	79 (100%)
	Abnormal	0 (0%)
Motility:	Normal	49 (62%)
	Hypokinesis	29 (37%)
	Hyperkinesis	1 (1%)
Pathological Movements:	Absent	68 (86%)
	Tremors	7 (9%)
	Overshooting movements	2 (3%)
	Convulsions	2 (3%)
Tonus:	Normal	8 (10%)
	Hypotonia	71 (90%)
Responses:	Normal	55 (70%)
	Low/absent	24 (30%)
Threshold Responses:	Normal	56 (71%)
	High	23 (29%)
Tendon Reflexes:	Normal	62 (78%)
	Low	17 (22%)
Moro Response:	Normal	64 (81%)
	Weak/absent	15 (19%)
States:	Normal	70 (89%)
	Difficult to arouse	9 (11%)
TOTAL		79 (100%)

Neurodevelopmental assessment at 3.6 years of age

- Neurology: At 3.6 years of age 50 of the 79 children were classified as normal, 20 as MND and 9 as abnormal (6 quadriplegia, 2 hemiplegia and 1 hypotonia).

- Cognition: The mean index on the Intelligence scale was 87 (SD 13) and 86 (SD 14) on the Achievement scale. Seven children (9%) scored < 70 on both scales of the K-ABC and were thus considered as mentally handicapped.

- A handicap was found in 8 of 45 girls (18%) and 5 of the 34 boys (15%). Eight of the 13 children had one handicap (4 children with a cerebral palsy, 3 children with a mental handicap, 1 child with a visual handicap) and 5 children had multiple handicaps. Details of the neurodevelopmental assessment are presented elsewhere[39].

Neonatal cerebral ultrasound and outcome

Neonatal cerebral ultrasound in relation to neurodevelopmental outcome is given in Table 3.4. None of the 22 infants with normal neonatal ultrasound compared to 6 of the 7 children with intraparenchymal damage due to hemorrhagic and/or ischemic lesions (PIVH IV and/or PVL 3) were classified as neurologically abnormal at 3.6 years of age (p < 0.001). Two of the 22 infants with normal ultrasound compared to 14 of the 30 infants with ventriculomegaly without intraparenchymal damage were classified as MND at 3.6 years of age (p < 0.001). No statistical significant relationship between neonatal cerebral ultrasound findings and cognition at age 3.6 could be established. However, only 1 of the 22 infants with normal neonatal ultrasound had a mental handicap, while 3 of the 7 infants with intraparenchymal damage showed an intelligence score of less than 70 (p < 0.05). Two of the 22 infants with normal ultrasound showed a handicap as compared to 6 of the 7 infants with intraparenchymal lesions (p < 0.001).

Taking into consideration that ventriculomegaly and intraparenchymal damage were important predictors for outcome at age 3.6, we also classified the infants according to a more simplified ultrasound scoring system: Normal (Group 0, n = 22), abnormal without ventriculomegaly (Group 1, n = 20), abnormal with ventriculomegaly but without intraparenchymal damage (Group 2, n = 30) and abnormal with intraparenchymal damage (Group 3, n = 7). Neurodevelopmental outcome of the infants defined in these four categories is given in Table 3.5. In a stepwise multiple regression analysis of the outcome variables (neurology, cognition and all handicaps) included as independent variables and the simplified neonatal cerebral ultrasound classification as the dependent variable, the neurological examination was the only significant independent outcome variable (p < 0.001) explaining 32% of the variance. Neurologically abnormal at age 3.6 were none of the children with normal or abnormal neonatal cerebral ultrasound without ventriculomegaly (negative predictive value 100%), 3 of the 30 children with abnormal cerebral ultrasound with ventriculomegaly (positive predictive value 10%) and 6 of the 7 children with intraparenchymal damage (positive predictive value 86%).

Table 3.4 Neonatal cerebral ultrasound in relation to neurodevelopmental outcome at 3.6 years of age.

NEONATAL CEREBRAL ULTRASOUND	NEURODEVELOPMENTAL OUTCOME								
	NEUROLOGY			COGNITION			HANDICAP		TOTAL
	Normal	MND	Abnormal	Normal	Mildly Abnormal	Definitely Abnormal	Absent	Present	
Normal	21	1	0	17	4	1	20	2	22
Hemorrhagic lesions									
PIVH I-II	5	2	0	6	1	0	7	0	7
PIVH III	2	3*¹	1	4	1	1	5	1	6
PIVH IV	0	0	3***	2	0	1	0	3**	3
Ischemic lesions									
PVL 1	4	1	0	5	0	0	5	0	5
PVL 2	4	5**	0	8	0	1	8	1	9
PVL 3	1	0	1	1	0	1	1	1	2
Hemorrhagic and ischemic lesions									
PIVH I-III + PVL 2	0	3**	1	3	1	0	3	1	4
PIVH III + PVL 3	0	0	2**	1	0	1	0	2*¹	2
Other lesions									
Ventriculomegaly -	6	2	0	6	1	1	7	1	8
Ventriculomegaly +	7	3	1	8	3	0	10	1	11
TOTAL	50	20	9	61	11	7	66	13	79

Fisher's Exact   * = p<0.05,   ** = p<0.01,   *** = p<0.001
¹ Not significant when corrected for the number of analyses using Bonferroni correction

Table 3.5 Simplified neonatal cerebral score in relation to neurodevelopmental outcome at 3.6 years of age.

NEONTATAL CEREBRAL ULTRASOUND	NEURODEVELOPMENTAL OUTCOME								TOTAL
	NEUROLOGY			COGNITION			HANDICAP		
	Normal	MND	Abnormal	Normal	Mildly Abnormal	Definitely Abnormal	Absent	Present	
Group 0: Normal	21	1	0	17	4	1	20	2	22
Group 1: Ventriculomegaly -	15	5	0	17	2	1	19	1	20
Group 2: Ventriculomegaly +	13	14***	3	23	5	2	26	4***	30
Group 3: Intraparenchymal Damage	1	0	6***	4	0	3*[1]	1	6***	7
TOTAL	50	20	9	61	11	7	66	13	79

Fisher's Exact * = p<0.05, ** = p<0.01, *** = p<0.001
[1] Not significant when corrected for the number of analyses using Bonferroni correction

Table 3.6 Summary of the neonatal neurological examinations in relation to neurodevelopmental outcome at 3.6 years of age.

NEONATAL NEUROLOGY	NEURODEVELOPMENTAL OUTCOME								
	NEUROLOGY			COGNITION			HANDICAP		TOTAL
	Normal	MND	Abnormal	Normal	Mildly Abnormal	Definitely Abnormal	Absent	Present	
Posture: Normal Abnormal	50 0	20 0	9 0	61 0	11 0	7 0	66 0	13 0	79 0
Motility: Normal Abnormal	38 12	10 10	1 8***	40 21	7 4	2 5	46 20	3 10**[1]	49 30
Pathological Movements: Absent Abnormal	44 6	17 3	7 2	52 9	11 0	5 2	58 8	10 3	68 11
Tonus: Normal Hypotonia	7 43	1 19	0 9	7 54	1 10	0 7	8 58	0 13	8 71
Responses: Normal Low	44 6	10 10**	1 8***	47 14	6 5	5 2*[1]	52 14	3 10***	55 24
Threshold Responses: Normal High	41 9	13 7	2 7***	48 13	6 5	2 5*[1]	52 14	4 9**[1]	56 23
Tendon Reflexes: Normal Low	46 4	14 6*[1]	2 7***	54 7	6 5*[1]	2 5**[1]	58 8	4 9***	62 17
Moro Response: Normal Low	47 3	15 5*[1]	2 7***	54 7	7 4	3 4*	60 6	4 9***	64 15
States: Normal Difficult to arouse	47 3	19 1	4 5***	56 5	9 2	5 2	63 3	7 6***	70 9
TOTAL	50	20	9	61	11	7	66	13	79

Fisher's exact test, * = p<0.05, ** = p<0.01, *** = p<0.001
[1] Not significant when corrected for the number of analyses using Bonferroni correction

Table 3.7 Classification of neonatal neurology in relation to neurodevelopmental outcome at 3.6 years of age.

NEONATAL NEUROLOGY	NEURODEVELOPMENTAL OUTCOME								
	NEUROLOGY			COGNITION			HANDICAP		TOTAL
	Normal	MND	Abnormal	Normal	Mildly Abnormal	Definitely Abnormal	Absent	Present	
Normal	31	5**¹	1	29	6	2	34	3	37
Mildly Abnormal	15	11**¹	0	25	1	0	26	0	26
Definitely Abnormal	4	4*¹	8***	7	4	5*¹	6	10***	16
TOTAL	50	20	9	61	11	7	66	13	79

Fisher's exact test, * = p<0.05, ** = p<0.01, *** = p<0.001
¹ Not significant when corrected for the number of analyses using Bonferroni correction

Neonatal neurology and outcome

The summary of the neonatal neurological examinations in relation to neurodevelopmental outcome is given in Table 3.6. When corrected for chance findings, children classified as neurologically abnormal at 3.6 years of age had significantly more symptoms of the apathy syndrome, except hypotonia, than children classified as neurologically normal. Cognitive assessment was not significantly related to the results of the neonatal neurological examinations.

The classification of neonatally neurologically normal, mildly abnormal and deviant infants in relation to neurodevelopmental outcome is given in Table 3.7. In a stepwise multiple regression analysis of the outcome variables (neurology, cognition and all handicaps) included as independent variables and the neonatal neurological classification as the dependent variable, the neurological examination was the only significant independent outcome variable ($p < 0.001$) explaining 23% of the variance. Neurologically abnormal at age 3.6 were 1 of the 63 infants with a normal or mildly abnormal neonatal neurological condition (negative predictive value 2%) and 8 of the 16 children whith a definitely abnormal neonatal neurological condition (positive predictive value 50%).

Neonatal cerebral ultrasound and neonatal neurology

Neonatal cerebral ultrasound in relation to neonatal neurology is presented in Table 3.8. Children with ventriculomegaly (group 2) had significantly more mildly abnormal neonatal neurological examinations than children with normal ultrasound. Children with intraparenchymal damage (group 3) were significantly more neonatally neurologically deviant than children with normal ultrasound.

Table 3.8 Neonatal neurology and neonatal cerebral ultrasound

NEONATAL CEREBRAL ULTRASOUND	NEONATAL NEUROLOGY			
	Normal	Mildly Abnormal	Definitely Abnormal	Total
Group 0: Normal	16	4	2	22
Group 1: Ventriculomegaly -	11	8	1	20
Group 2: Ventriculomegaly +	9	13*	8*	30
Group 3: Intraparenchymal Damage	1	1	5**	7
TOTAL	37	26	16	79

Fisher's exact test, * = p<0.05, ** = p<0.01, *** = p<0.001

Prediction of outcome

To determine which parameters best predicted outcome, stepwise multiple regression analyses were done. Birthweight, gestational age, obstetrical and neonatal optimality score, neonatal cerebral ultrasound and neonatal neurology were considered for inclusion as predictors to neurological outcome at 3.6 years. Neurological outcome was predicted best by neonatal cerebral ultrasound (p<0.00001) together with neonatal neurology (p=0.0006) explaining 45 % of the variance. Definitely abnormal neonatal neurology contributed to a better prediction of abnormal neurology at 3.6 years of age in the group with abnormal neonatal cerebral ultrasound with ventriculomegaly. Mildly abnormal neonatal neurology contributed to a better prediction of minor neurological dysfunction at 3.6 years of age in the group with abnormal neonatal cerebral ultrasound with ventriculomegaly (Table 3.9). Neither birthweight, nor gestational age or the obstetrical and neonatal optimality score were independent variables in the prediction of outcome. Including birthweight, gestational age, obstetrical and neonatal optimality as predictors to neonatal cerebral ultrasound and neonatal neurology, neonatal optimality alone best predicted neonatal cerebral ultrasound findings (p<0.001) explaining 18% of the variance. Neonatal neurology was best predicted by the neonatal optimality score (p<0.00001) and birthweight (p=0.03) together explaining 29% of the variance. A stepwise multiple regression analysis of the individual items of the neonatal optimality score, cerebral ultrasound and neonatal neurology as predictors to neurological outcome at 3.6 years of age revealed that none of the individual items significantly contributed as an independent variable to the prediction of neurological outcome.

Table 3.9 Neonatal neurology and neonatal cerebral ultrasound in relation to neurological outcome

NEONATAL CEREBRAL ULTRASOUND	NEONATAL NEUROLOGY	NEUROLOGICAL OUTCOME			
		Normal	MND	Abnormal	Total
Group 0/1 Group 2 Group 3	Normal	25 6 0	2 3 0	0 0 1	27 9 1
Group 0/1 Group 2 Group 3	Mildly Abnormal	9 5 1	3 8** 0	0 0 0	12 13 1
Group 0/1 Group 2 Group 3	Definitely Abnormal	2 2 0	1 3*[1] 0	0 3** 5***	3 8 5
TOTAL		50	20	9	79

Fisher's exact test, * = p<0.05, ** = p<0.01, *** = p<0.001
[1] Not significant when corrected for the number of analyses using Bonferroni correction

3.5 DISCUSSION

In our study serial ultrasound scanning with modern equipment resulted in a very high incidence and large variety of cerebral abnormalities. Scans were entirely normal in only 28% of the infants. Hemorrhagic lesions were found in 28% and ischemic lesions in 28% of the infants. Lesions other than PIVH and PVL were seen in 24% of the infants. These other lesions were either present from birth or appeared in the first week of life, suggesting a prenatal or perinatal origin.

Neurodevelopmental assessment at 3.6 years of age showed that 6 of the 7 children with intraparenchymal damage had cerebral palsy, 4 of them with other handicaps. The number of children with MND was higher in the group with ventriculomegaly than in the group with normal neonatal cerebral ultrasound. These results prompted us to classify neonatal cerebral ultrasound findings in a simplified scoring system. This simple classification was the best predictor for neurodevelopmental outcome. Infants with normal neonatal cerebral scans or abnormal scans without ventriculomegaly almost invariably had a normal neurological outcome. The incidence of normal neurological outcome decreased to less than 50% in infants with cerebral lesions with ventriculomegaly. Intraparenchymal damage was associated with a handicap in over 85% of the cases. Nevertheless, some infants with normal scans may develop a handicap while some infants with gross parenchymal damage may show relatively minor disabilities. This limits the value of neonatal cerebral ultrasound as a reliable method to decide whether withdrawal of intensive care would be a realistic option.

The purpose of our study was to evaluate the predictive value of neonatal cerebral ultrasound and neurological examinations in the intensive care setting. Normal neonatal neurological findings at preterm age were highly predictive of later normal neurological outcome and definitely abnormal findings indicated an increased risk of abnormal neurological outcome. The positive predictive value of the neonatal neurological examination (50%) in our study was comparable to the positive predictive value of neonatal neurological examinations at term age (38-64%) found in other studies [1,9]. As in previous studies [9,31], neonatal neurology in combination with cerebral ultrasound best predicted neurological outcome especially in the group of children with ventriculomegaly. However the greatest extent of the neonatal cerebral ultrasound

lesions not always coincided with the severity of the neonatal neurological condition.

The available neurological assessment techniques for high risk preterm infants, treated by intensive care, are still not fully satisfactory [29]. In our study repeated neurological examinations according to Prechtl were chosen, although this examination was originally designed for term infants, and the results of the neonatal neurological examination at preterm age differ from those found at term corrected age. Signs of depression of the central nervous system and the apathy syndrome (eg. hypokinesia, low responsivity, high threshold, low tendon reflexes, low Moro and low states) were mainly found and were significantly related to outcome. Hypotonia is probably the most common neurological 'symptom' in VLBW infants treated in an intensive care unit. Not surprisingly it was found in 90% of our infants and not related to outcome. Therefore it was excluded from further analysis. Only one child was hyperkinetic without other signs of neonatal neurological dysfunction and none of the infants had signs of a hemisyndrome at preterm age.

Recently Ferrari et al. [11] have demonstrated that repeated observations of the quality of general movements in high risk preterm infants might represent better complex neural function than signs of depression of the central nervous system. In his study all preterm infants with brain damage, as detected by cerebral ultrasound, demonstrated an abnormal quality of general movements. The positive predictive value for outcome was 70% as compared to 50% in our study. Therefore systematic observation of spontaneous motor activity should be included in the neurological assessment of preterm infants. For purposes of standarisation, it would also have been preferable to reexamine all infants at term age. This was, however, for practical reasons not possible because of earlier discharge.

We applied the concept of optimality to obstetrical and neonatal conditions. In the Groningen Perinatal Project correlations between obstetrical optimality and neonatal neurology [33] have been found. In our population of high risk VLBW infants the neonatal and not the obstetrical score was related to cerebral ultrasound and neonatal neurology. Ventilatory assistance and BPD are often described as conditions associated with a higher prevalence of handicaps [35]. In our study these neonatal conditions were associated with an increased incidence of neonatal cerebral damage and neonatal neurological abnormalities. These neonatal conditions, however, were no independent variables in the prediction of outcome. Since bodyweight may account for the results in

items in which muscle power is important [28], birthweight was an independent variable in the prediction of neonatal neurology. The obstetrical and neonatal scale in our study consisted of simple items generally known in VLBW infants and could be answered by yes or no. A qualitative assessment based on potential mechanisms of brain cell injury like the Nursery Neurobiologic Risk Score [6] might be more valuable in predicting outcome.

We conclude that present-day cerebral ultrasound scanning of VLBW infants enables identification of a large variety of lesions. A simple classification according to the presence or absence of ventriculomegaly and intraparenchymal involvement of any cause is helpful in defining groups of children who are at low, intermediate and high risk for neurodevelopmental deficits. Neonatal neurological examinations have additional value in predicting neurological outcome especially in the group with ventriculomegaly on neonatal cerebral ultrasound scans. However accurate prediction of outcome for the individual child still remains impossible. Large portions of variance in neurological outcome, and even more so in cognitive outcome, are not explained by neonatal cerebral ultrasound or neonatal neurological examinations. Mental and sensori handicaps occur more frequently in children with cerebral palsy, especially in the group with intraparenchymal damage on neonatal cerebral ultrasound. The reason why infants with no signs of neonatal cerebral damage as detected by cerebral ultrasound and neonatal neurological examinations may develop a handicap while infants with gross parenchymal damage and abnormal neonatal neurology may show relatively minor disabilities, cannot be answered by this study. Therefore more studies on the protective factors in the development of VLBW infants are needed.

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CHAPTER 4

THE EFFECTS OF BIOLOGICAL AND SOCIAL FACTORS
ON THE COGNITIVE DEVELOPMENT OF VERY LOW BIRTHWEIGHT CHILDREN

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THE EFFECTS OF BIOLOGICAL AND SOCIAL FACTORS
ON THE COGNITIVE DEVELOPMENT OF VERY LOW BIRTHWEIGHT CHILDREN

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4.1 SUMMARY

In order to investigate the interaction between biological and social factors in the cognitive development of very low birth weight (VLBW) children, a longitudinal follow-up study was conducted from birth to 3.6 years of age in a cohort of 79 high risk VLBW infants. Neonatal cerebral ultrasound and a neurological score were used as indicators of biological risk. A socio-demographic risk score and the HOME Inventory were used as indicators of social risk. Cognitive development was assessed at ages 1 and 2 years by the mental scale of the Bayley Scales of Infant Development and at age 3.6 years by the Kaufman Assessment Battery for Children. The mean mental index at 1 year of age was 96 (SD 19), at 2 years of age 86 (SD 26) and at 3.6 years of age for intelligence 87 (SD 13) and for achievement 86 (SD 14). In a stepwise multiple regression analysis of biological as well as social factors, the neurological score alone was the best predictor for cognitive development at 1 year of age, explaining 46% of the variance. From 2 years of age onward the best predictors for cognitive development were the neurological score together with the home environment explaining 46% of the variance for the mental developmental index at age 2, 34% for intelligence and 56% for achievement at age 3.6. Children at high biological risk were able to catch up on their cognitive delay in a highly stimulating home environment. Children at low as well as high biological risk in a less stimulating home environment showed a decline in cognitive development. For these children early intervention programs might be important in the prevention of cognitive disabilities.

4.2 INTRODUCTION

Infants born with birthweights less than 1500 grams (VLBW infants) have a higher incidence of developmental deficits than have full term infants.[1-6] A downward trend in cognitive development in preschool years has been described.[7-11] In some studies this downward trend was related to neonatal cerebral damage[8-10], in others to social risk factors.[7,11]

VLBW is associated with socio-demographic risk factors (eg. single motherhood, poverty) which in themselves may be related to less favorable cognitive outcome. Sameroff[12] concluded that a cumulative social risk index better predicted cognitive outcome than any single social risk factor. The pattern for these disadvantaged children is one of relative decline on intellectual test scores in the second year of life.[13] At the same time VLBW infants, treated by intensive care, are at high risk for events which might cause brain damage. The concept of biological risk highlights an early stage of vulnerability prior to the actual emergence of a permanent neurodevelopmental disorder. The ability of children at biological risk to cope and adapt may be more limited and fragile, and interactions between caregivers and these children can be easily disrupted. VLBW infants, being at biological risk, might be even more vulnerable to social risk than normal babies[7,11]. The transactional model of development emphasizes this dynamic interplay between the child's biology and the child's environment[15].

In this paper we describe a longitudinal prospective follow-up study from birth to 3.6 years of age and address the following questions:

1. What is the contribution of biological and social factors to the cognitive development of VLBW children from 1 to 3.6 years of age?

2. Are VLBW children at high biological risk more vulnerable to social factors than VLBW children at low biological risk?

3. Which elements in the VLBW child's home environment are important for cognitive development and at what age?

4.3 PATIENTS AND METHODS

Study group

This study is part of a larger longitudinal study on VLBW children.[16] The study group consisted of all preterm VLBW children (birthweight < 1500 grams, gestational age < 36 weeks) who were admitted to the Neonatal Intensive Care Unit of the Sophia Children's Hospital in Rotterdam (a regional tertiary intensive-care unit) between August 1, 1985 and August 1, 1986 within 48 hours after birth (n = 114). Twenty-three infants (20%) died in the neonatal period or in the first year of life. Twelve children (10%) were not available for the whole follow-up period because of migration (n = 6), lack of interest (n = 3) or inability to cooperate (n = 3) on the part of the parents. Of the remaining 79 children there were 34 boys and 45 girls. There were no children with major congenital anomalies. Birthweights ranged from 690 to 1495 grams (M = 1136, SD 213). Gestational ages ranged from 25 to 35 weeks (M = 30.4, SD 2.3).

Cognitive development

At a corrected age of 1 and 2 years cognition was assessed with the mental scale of the Dutch version of the Bayley Scales of Infant Development.[17] These scales have a mean value of 100 and a SD of 16.

At a corrected age of 3.6 years the Dutch adaptation of the Kaufman Assessment Battery for Children[18-19] was used. This cognitive battery measures Intelligence (the Mental Processing Composite, MPC) and Achievement (the Achievement Scale). Both scales have a mean value of 100 and a SD of 15. An index of more than -2SD (< 70) below the mean on both the intelligence and the achievement scale was considered as a definite cognitive delay. An index of more than -1SD (< 85) below the mean on both the intelligence and the achievement scale was considered as a mild cognitive delay. The remaining children were considered to have a normal cognitive outcome.

Biological factors

Neonatal cerebral ultrasound findings are described in detail elsewhere and were classified as follows[16]:

- Group 0: Normal.

- Group 1: Abnormal (PIVH I-II, periventricular flaring and/or other lesions) without ventriculomegaly.

- Group 2: Abnormal (PIVH III, periventricular flaring and/or other lesions) with ventriculomegaly.

- Group 3: Abnormal (PIVH IV and/or PVL) with intraparenchymal damage.

A standardized neurological examination (adapted from Touwen[20-21]) was done at the corrected age of 1, 2 and 3.6 years old. Findings were classified as normal (score 0), mildly abnormal (score 1) or definitely abnormal (score 2). Children were classified as definitely abnormal when a traditional neurological diagnosis such as cerebral palsy could be made. Children were classified as mildly abnormal when minor neurological signs, such as minor left-right differences or mild hypertonia, were present but could not be attributed to a traditional neurological diagnosis.

Social factors

Socio-demographic variables were grouped together in a socio-demographic risk score of four variables: the occupational status of the family, the mother's educational status, family support and ethnic background. One point was given for each risk factor. The occupational status of the parents was scored on a six-step occupation scale.[22] Whenever parents had occupations with different classifications, the highest class was chosen. Class 0 to 2 (unemployed to manual employees) was considered as a risk factor. The mother's educational status was also divided into 6 classes.[23] Class 1 to 2 (special education or primary school finished only) was considered as a risk factor. Although family support involves many dimensions, high risk was simply defined as the absence of a father in the home at birth. In addition ethnic background was included as a risk factor because of adaptation and language problems in non-Dutch families living in the Netherlands.

The child's home environment was assessed by the Dutch version of the HOME Observation for the Measurement of the Environment[24-25] at ages 1 and 3.6. The HOME Inventory at 1 year consists of 45 items (maximal total score 45) representing six categories of social stimulation important in infant development. The HOME Inventory at 3.6 years consists of 55 items (maximal total score 55) and seven categories of social stimulation important in toddler development. At both ages the subscores of the different categories and a total score were computed.

Data analysis

The statistical package Statgraphics 4.0 was used. Univariate statistical analysis was performed to study associations between separate items. Stepwise multiple regression analysis was used to determine how well biological (neonatal cerebral ultrasound and neurological score) and social factors (socio-demographic risk score and home environment) predicted cognitive development at ages 1, 2 and 3.6 years. A p value of <.05 was considered significant.

4.4 RESULTS

Cognitive development is summarized in Table 4.1. There was a downward trend of almost 10 points in mean developmental indices from ages 1 to 2, but no further decline from 2 to 3.6 years of age. At 3.6 years of age 61 (79%) had a normal cognitive outcome, 11 (14%) a mild and 7 (9%) a definite cognitive delay.

Table 4.1 Cognitive Development.

COGNITIVE ASSESSMENTS		Mean (SD)	Range
1 Year	Mental Developmental Index (MDI)	96 (19)	52-137
2 Years	Mental Developmental Index (MDI)	86 (26)	52-141
3.6 Years	Intelligence (MPC) Achievement (ACH)	87 (13) 86 (14)	55-113 55-115

There was a siginificant correlation between the cognitive assessments at 1, 2 and 3.6 years of age (Table 4.2).

Table 4.2 Correlations of the cognitive assessments at 1, 2 and 3.6 years of age.

COGNITIVE		1 Year	2 Years	3.6 Years	
ASSESSMENTS		MDI	MDI	MPC	ACH
1 Year	MDI	-	.50***	.61***	.29*
2 Years	MDI	-	-	.65***	.69***
3.6 Years	MPC	-	-	-	.65***
	ACH	-	-	-	-

Pearson correlation coefficient, *=p<0.05, ***=p<0.001

Twenty-two of the 79 children (28%) had normal (Group 0) and 57 (72%) abnormal neonatal cerebral ultrasound findings; 20 (25%) without ventriculomegaly (Group 1), 30 (38%) with ventriculomegaly (Group 2) and 7 (9%) with intraparenchymal damage (Group 3). The neurological classification changed over time. In order to use all available information for further analysis, the results of the neurological examinations at 1, 2 and 3.6 years of age were summarized in a total neurological score from 0 to 6 points. Forty-one of the 79 children (52%) had a neurological score of 0 and could thus be considered as completely normal; 9 children (11%) had a neurological score of 5 or 6, all were definitely abnormal at 3.6 years of age; the remaining 29 children (37%) with a neurological score of 1 to 4 were classified as abnormal on one or more examinations but not as definitely abnormal at 3.6 year of age and could thus be considered as neurologically at risk. Neonatal cerebral ultrasound and the neurological score were significantly correlated (Spearman rank correlation coefficient .56, $p < 0.0001$) and are summarized in Table 4.3.

Table 4.3 Neonatal cerebral ultrasound and neurology.

NEONATAL CEREBRAL ULTRASOUND	NEUROLOGY			
	Score 0 n (%)	Score 1-4 n (%)	Score 5-6 n (%)	TOTAL n (%)
Group 0: Normal	18 (82%)	4 (18%)	0 (0%)	22 (28%)
Group 1: Ventriculomegaly -	13 (65%)	7 (35%)	0 (0%)	20 (25%)
Group 2: Ventriculomegaly +	9 (30%)	18 (60%)	3 (10%)	30 (38%)
Group 3: Intraparenchymal damage	1 (14%)	0 (0%)	6 (86%)	7 (9%)
TOTAL	41 (52%)	29 (37%)	9 (11%)	79 (100%)

Two children were so severely disabled that the HOME Inventory was an inappropriate instrument. Of the remaining 77 children the mean total score of the HOME Inventory at age 1 was 35 (SD = 7), the mean total score at age 3.6 was 44 (SD = 8). The correlation between the total score at age 1 and 3.6 years was very high (Spearman rank correlation coefficient .77, $p < 0.0001$) and a summary score was made. The total scores of the HOME Inventory at 1 and 3.6 years were standardized (M = 0, SD = 1) and summed. A summary score more than the 75th percentile was considered as a high, between the 25th and the 75th percentile as an intermediate and less than the 25th percentile as a low stimulating home environment. The prevalence of socio-demographic risk factors in relation to the home environment is presented in Table 4.4.

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Table 4.4. Socio-demografic risk and home environment.

SOCIO-DEMOGRAPHIC RISK		HOME ENVIRONMENT		
Factors	High Risk	High n (%)	Medium n (%)	Low n (%)
1.Occupational status	Unemployed/Manual Employes	1 (5%)	6 (30%)	13 (65%)
2.Education of mother	Special education/Primary school finished	0 (0%)	2 (20%)	8 (80%)
3.Family support	Father absent	0 (0%)	5 (42%)	7 (58%)
4.Ethnic background	Non Dutch	0 (0%)	4 (25%)	12 (75%)

The socio-demographic risk score and the home environment were significantly correlated (Spearman rank correlation coefficient .68, $p < 0.0001$). Of the 20 children from a high stimulating home environment 19 (95%) had a socio-demographic risk score of 0 and only one (5%) a score of 1. Of the 37 children from an intermediate stimulating home environment 28 (76%) had a socio-demographic risk score of 0, 4 (11%) a score of 1, 2 (5%) a score of 2 and 3 (8%) a score of 3. Of the 20 children from a low stimulating home environment 4 (20%) had a socio-demographic risk score of 0, 3 (15%) a score of 1, 4 (20%) a score of 2, 7 (35%) a score of 3 and 2 (10%) a score of 4.

There was no significant correlation between biological (neonatal cerebral ultrasound and neurological score) and social factors (socio-demographic risk score and home environment). Correlations of biological and social factors versus cognitive development are presented in Table 4.5. Biological factors and cognitive development were significantly correlated at all ages. However at age 3.6 there was only a significant correlation with intelligence and not with achievement. Social factors were significantly correlated with cognitive development from 2 years onward. Mental development at 1 year of age correlated highest with biological factors and was not related to social factors. Achievement at 3.6 years of age correlated highest with social factors and was not related to biological factors. All subscales of the HOME Inventory at both ages, except acceptance of the child at age 3.6, were significantly correlated with achievement.

In a stepwise multiple regression analysis of the neonatal predictors (neonatal cerebral ultrasound and socio-demographic risk score) versus cognitive development, neonatal cerebral ultrasound alone best predicted the mental developmental index at age 1. Neonatal cerebral ultrasound and socio-demographic risk together best predicted

Table 4.5 Correlations of biological and social factors versus cognitive development.

COGNITIVE DEVELOPMENT		BIOLOGICAL FACTORS		SOCIAL FACTORS	
		Neonatal Cerebral Ultrasound	Neurological Score	Social Risk Score	Home Environment
1 Year	Mental Developmental Index	-.37**	-.63***	-.07	-.12
2 Years	Mental Developmental Index	-.32**	-.39***	-.39***	.52***
3.6 Years	Intelligence	-.24*	-.39***	-.24*	.35**
	Achievement	.02	-.01	-.54***	.79***

Spearman rank correlation coeficient, *=p<0.05, **=p<0.01, ***=p<0.001

the mental developmental index at age 2 and intelligence at age 3.6. The socio-demographic risk alone best predicted achievement at age 3.6. In a stepwise multiple regression analysis of both biological (neonatal cerebral ultrasound and neurological score) as well as both social factors (socio-demographic risk score and home environment), the neurological score alone best predicted the mental index at age 1. The neurological score together with the home environment best predicted the mental index at age 2 as well as intelligence and achievement at age 3.6 (Table 4.6).

Table 4.6 Stepwise multiple regression analyses of biological and social factors as predictors of cognitive development.

COGNITIVE DEVELOPMENT	NEONATAL BIOLOGICAL AND SOCIAL FACTORS (eg. cerebral ultrasound and socio-demografic risk)			BIOLOGICAL AND SOCIAL FACTORS (eg. cerebral ultrasound, neurology, socio-demographic risk and home environment)		
	SIGNIFICANT PREDICTORS	ADJ-R^2	p	SIGNIFICANT PREDICTORS	ADJ-R^2	p
1 Year						
MDI	Cerebral ultrasound	.16	0.0002	Neurology	.46	<0.0001
2 Years						
MDI	Socio-demographic risk	.15	<0.0001	Home environment	.24	<0.0001
	Cerebral ultrasound	.28	0.0004	Neurology	.47	<0.0001
3.6 Years						
MPC	Cerebral ultrasound	.07	0.003	Neurology	.16	<0.0001
	Socio-demographic risk	.13	0.02	Home environment	.34	<0.0001
ACH	Socio-demographic risk	.13	<0.0001	Home environment	.53	<0.0001
				Neurology	.56	0.02

The interaction between biological and social factors in cognitive development is presented in Figure 1. At age 1 neurologically at risk as well as neurologically abnormal children in a high and intermediate stimulating home environment had a significantly lower mean mental developmental index compared to neurologically normal children (Mann-Whitney test). At age 2 and 3.6 there were only significant differences in mean indices between neurologically abnormal and normal children in an intermediate stimulating home environment. The lowest mean index at age 3.6 (72) was found for achievement in neurologically normal children in a low stimulating home environment. These children lost 20 (Intelligence) to 32 (Achievement) index points from 1 to 3.6 years. Low mean indices at 3.6 years of age (<85) were also found in neurologically abnormal children in an intermediate stimulating home environment (intelligence 71, achievement 74) and in children at neurological risk in a low stimulating home environment (intelligence 81, achievement 78). The mean indices of the other groups of children at age 3.6 were all within the normal range (>85).
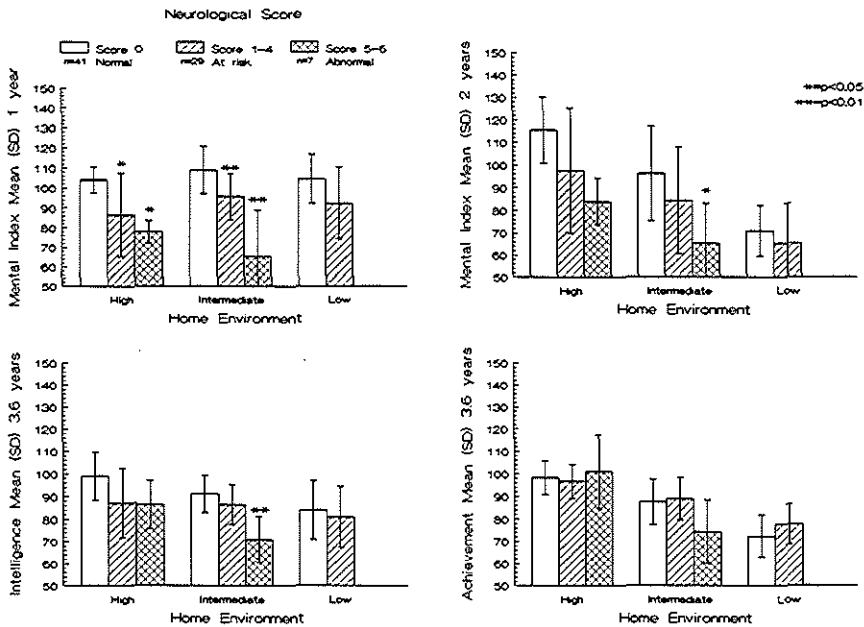

Figure 4.1 Neurological score, home environment and cognitive development.

4.5 DISCUSSION

In our study biological factors were significant predictors of cognitive development at 1 year of age whereas social factors were not. In his theory of the development of intelligence Piaget[26] describes intelligence in infancy as sensory-motor. Accordingly biological factors play a primary role in the manifestation of intelligence during infancy[27] and the mental scale of the Bayley test of infant development at age 1 mainly consists of sensori-motor tasks. With increasing age, more complex functions such as language and mental processing become more important in cognitive development. Consequently, correlation coefficients between biological factors and cognitive development decreased with an increasing age. At age 3.6 biological factors correlated with intelligence, while achievement only correlated with social and not with biological factors. In the multiple regression analysis the neurological score was a better predictor for cognitive outcome than neonatal cerebral ultrasound and was still a significant predictor of achievement at 3.6 years of age. The neurological score, however, only contributed 3 % of the explained variance in achievement.

In medical practice, prevention of cognitive delay has been traditionally defined primarily as prevention of biological abnormalities. However social factors play a major role. The socio-demographic risk score used in this study was composed of simple items which can be asked at delivery. Unfortunately, the majority of these factors are rather stable in time and not susceptible to intervention. Moreover the predictive value was low. The home environment of the child was a better predictor for cognitive outcome than the socio-demographic risk score. The HOME Inventory was designed to reflect parental support of early cognitive and socio-emotional development and consists of items more amenable to intervention. The HOME Inventory thus proved to be a better instrument to identify children at risk for a cognitive decline.

A high stimulating home environment resulted in a normal cognitive outcome at 3.6 years of age. For neurologically normal children in a high stimulating home environment developmental indices remained relatively stable and for neurologically at risk or abnormal children developmental indices improved between 1 and 3.6 years of age. Epidemiological studies[28] as well as studies of preterm infants [29-30] found that favorable early environmental circumstances can compensate for prenatal and perinatal insults. However in these studies no data were given about neonatal cerebral damage

and neurological follow-up. New in our study is the suggestion that even neurologically at risk or neurologically abnormal VLBW children are able to catch up on their cognitive delay in high stimulating home environments. In intermediate stimulating home environments the mean developmental indices for neurologically abnormal children remained below -1 SD from ages 1 to 3.6. In a low stimulating home environment the mean indices for intelligence and achievement at age 3.6 were below -1SD for children at neurological risk as well as for neurologically normal children. In these normal children the decline of developmental indices from age 1 to 3.6 years was most dramatic. These children lost 20 (1.3 SD) index points for intelligence from 1 to 3.6 years. A decline of 7 to 20 index points from 1 to 3 years has also been described in a literature study on full term children at high social risk[13]. The so-called downward slump in cognitive development in preschool VLBW children might therefore be the result of social factors and not be due to cerebral damage.

Early intervention can result in a better cognitive outcome. However most intervention studies concentrated on the socially disadvantaged families[13,31]. The Infant Health and Development Program, a comprehensive investigation on the effectiveness of developmental interventions for biologically vulnerable infants and toddlers[32], have recently demonstrated that early intervention was also effective in LBW children but was questionable in VLBW infants. Our results suggest that even in VLBW children, except in extreme conditions, a high stimulating home environment can overcome the biologic adversity of premature birth. Consequently early intervention programs might be effective. But which help at what age is important? Since different environmental variables may influence the child at different points in time, we examined the home environment of the child at two different ages. The home environment from 1 to 3.6 years was stable and at both ages the total score as well as all subscales of the HOME Inventory (except the subscale acceptance of the child) were significantly correlated with achievement at age 3.6 years. These results support a general model of early intervention. Studies on the effectiveness of early intervention programs have already shown that comprehensive early intervention programs focused on child development and family support in the first years of life [31-32], as well as more specific programs like the Mother-Infant Transaction Program in the first 3 months of life[33] are effective. Which program is most effective for what parents and children should be subject to further study.

Whether to correct or not to correct for prematurity, especially for extremely low birthweight infants (<1000 grams), is a controversial issue[34]. Some studies[35] found an overcorrection while others[36-37] concluded that (psycho-)motor development in preterm infants was not accelerated but guided by maturation of the central nervous system. Since we wanted to study the effects of biological as well as social factors on cognitive development and since most of the infants in our study group had gestational ages above 28 weeks and birthweights more than 1000 grams, we choose to correct for preterm birth.

There are some complicating factors in our study design. Biological and social factors were studied in a cohort of high risk VLBW infants. In contrast to other studies, children with neurodevelopmental disabilities were intentionally included in our study group. For these children standardized tests of general development may be less sensitive, as most of these tests were not designed for children with mental retardation. Development is a process of continuous change and there is a difference in what infants tests and tests for older children actually assess. However, by calculating developmental indices for the assessments at 1, 2 and 3.6 years of age, we compared our study group with the norm for healthy full term Dutch children. Moreover, in our study there was a significant correlation between all cognitive assessments at different ages. Whatever the inadequacies, these tests are the only developmental measures allowing direct comparison of cognitive outcome across different ages.

In conclusion our study is in strong support of the role of the home environment in understanding the cognitive development in VLBW children. When the VLBW infant at biological risk is born and raised within a stimulating home environment, the home environment might compensate for perinatal damage. When the VLBW infant at low or high biological risk is born and raised in a less stimulating home environment early intervention programs might constitute important efforts to prevent or minimize cognitive disabilities. It is evident that primary preventive activities must consist of the prevention of neonatal cerebral damage. However, unless comprehensive early intervention programs are provided, a large proportion of VLBW children are likely to be trapped in a cycle of events during their preschool years that can be counterproductive to their later cognitive development. Future research should concentrate on the development of instruments that can select infants in need of early intervention and that can demonstrate what help is effective for which parent and which child.

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CHAPTER 5

BEHAVIORAL PROBLEMS IN VERY LOW BIRTHWEIGHT CHILDREN

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5.1 SUMMARY

Parent (CBCL/2-3) and clinician reports of behavioral problems in very low birthweight (VLBW) children at 3.6 years of age were studied in relation to indicators of neonatal cerebral damage, cognition and social factors. On the CBCL/2-3 VLBW children had more depressed behavior and more internalizing problems by parent report and scored significantly more within the clinical range of the Total Problem Score (22%) than children in the comparison group (10%). The clinician reported 29% of behavioral problems. Neither neonatal cerebral ultrasound nor neurological examinations directly influenced behavioral outcome in VLBW children. Cerebral damage was related to cognitive development. Cognition directly influenced behavioral problems by clinician report while the home environment directly influenced problem behavior by parent report. We conclude that, in preschool VLBW children, depressed behavior might be associated with parental reactions to the birth of a VLBW child and that attention problems might be linked indirectly to brain damage via cognitive impairments.

5.2 INTRODUCTION

Numerous studies have been done about the neurological and cognitive development of infants born with birthweights less than 1500 grams (VLBW). Only recently more attention has been given to the behavioral issues surrounding VLBW. Some studies have reported an increase in behavioral problems in boys but not in girls (Breslau et al. 1988, Ross et al. 1990). Others found an increased risk specific for attention problems (Klein 1988, Minde et al. 1989, Szatmari et al. 1990). Only one study reported no increased risk for behavioral problems in VLBW children (Portnoy et al. 1988).

There are different ways in which VLBW might adversely affect behavioral outcome:

- Cerebral damage is known to increase the risk of behavioral problems in the population at large (Rutter 1984) and VLBW infants are frequently exposed to neonatal cerebral damage. There is some evidence that behavioral problems in VLBW infants might be linked to perinatal difficulties or to early neurological dysfunction (Drillien 1980, Herzig 1981, Escalona 1982, Minde *et al.* 1989). However, in none of these studies neonatal cerebral ultrasound findings were available. The child's behavior could be directly influenced by cerebral damage but also indirectly by subsequent cognitive deficits (Breslau 1990, Fernell *et al.* 1991). No study has been done about the relative contribution of neonatal cerebral damage and subsequent cognitive deficits to behavioral problems in VLBW children.

- Social factors which in themselves may be related with less favorable outcome are also associated with VLBW (Escalona 1982, Sameroff *et al.* 1987, Larson *et al.* 1988). In addition, by disruption of normal parental care and a high level of family stress, VLBW may also predispose towards less optimal parental care, which may in turn lead to long term behavioral difficulties.

Studying VLBW children provides an opportunity to assess the potential role of these different factors in the behavior of the child. In this paper we describe a prospective follow-up study in a cohort of VLBW children, treated by neonatal intensive care, from birth to 3.6 years of age at which time both parent and clinician reports of behavioral problems were collected. Indicators of cerebral damage (e.g., neonatal cerebral ultrasound and neurological examinations), cognitive development and social factors (e.g., socio-demographic risk and home environment) were considered as factors contributing to behavioral problems. The aims of our study were:

1. To establish the prevalence of behavioral problems in a cohort of VLBW children as measured by parental and clinician's reports.

2. To estimate the relative contributions of cerebral damage, cognition and social factors to behavioral outcome at 3.6 years of age.

Our hypothesis was that VLBW children would have higher rates of behavioral problems than non-VLBW children and that cerebral damage would be associated with higher rates of behavioral problems. This might occur as a direct consequence of the cerebral damage but also indirectly by their being more vulnerable for cognitive deficits as well as social risk factors. Figure 5.1 shows the preliminary model.
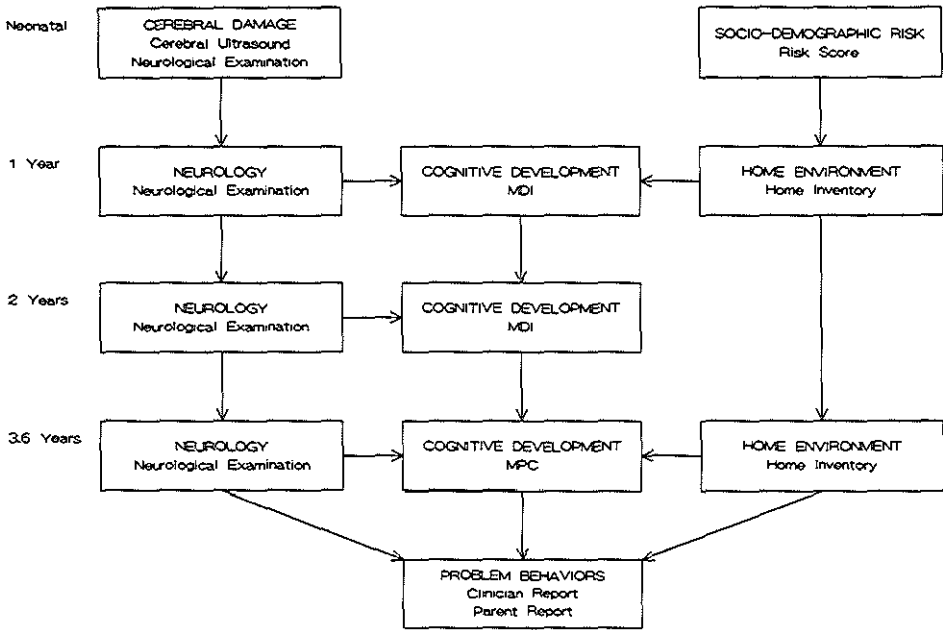
Figure 5.1 Preliminary model.

5.3 PATIENTS AND METHODS

Study group

This study is part of a larger longitudinal study on VLBW infants (Weisglas-Kuperus 1992). The total study group consisted of all preterm VLBW children (birthweight < 1500 grams, gestational age < 36 weeks), admitted to the Neonatal Intensive Care Unit of the Sophia Children's Hospital in Rotterdam (a regional tertiary intensive-care unit for the Dutch provinces of Zuid-Holland, Zeeland and West-Brabant) between August 1, 1985 and August 1, 1986 within 48 hours after birth (N = 114). Twenty-three infants (20%) died in the neonatal period or in the first year of life. Twelve children (10%) were not available for the whole follow-up period because of migration (N = 6), lack of interest (N = 3) or inability (N = 3) to cooperate. There were no children with major congenital anomalies. Two children were so severely handicapped that an evaluation of behavioral outcome was inappropriate. Of the remaining 77 children, there were thirty-three boys and forty-four girls. Birthweights ranged from 690

to 1495 grams (M = 1136, SD = 213). Gestational ages ranged from 25 to 35 weeks (M = 30.4, SD = 2.3). Obstetrical and neonatal conditions were recorded on a neonatal and obstetrical scale and are described in detail elsewhere (Weisglas-Kuperus *et al.* 1992). The mean occupational level of the fathers was 3.0 (SD = 1.9) on a standard Dutch 6-step scale (Van Westerlaak *et al.* 1975).

Behavioral Outcome

1. Parent report: Parents were asked to complete the Dutch version of the Child Behavior Checklist for ages 2-3 (CBCL/2-3) (Achenbach *et al.* 1987). The questionnaire contains 99 items for problem behavior, scored 0 (not true), 1 (somewhat true), or 2 (very true or often true) and has recently been standardized for the Netherlands. Six syndromes, i.e., Social Withdrawal, Depressed, Sleep Problems, Somatic Problems, Aggressive, and Destructive Behavior were recorded. In addition, Internalizing Scores and Externalizing Scores were calculated, according to the guidelines provided by Achenbach *et al.* (1987). The Total Problem Score (TPS) is obtained by summing up all items. The comparison group consisted of 192 healthy 3-year-old children (M = 3.6 years, SD = 3 months) belonging to a random sample of virtually all 2-3 years olds living in the Dutch province of Zuid Holland, used for the standardization of the CBCL/2-3 (Koot and Verhulst 1991). Parents of 91.5% of the children in the sample completed the CBCL/2-3. The mean occupational level of fathers was 3.7 (SD = 1.4) on a standard Dutch 6-step scale (Van Westerlaak *et al.* 1975). There were 103 boys and 89 girls.

2. Clinician report: In VLBW children, behavior was also observed and recorded during the neurodevelopmental assessment. At the end of the assessment, based on all available information of the child in interaction with the parents, a global rating of the child's behavior was given on a 4 point scale; i.e., none, mild, moderate or severe behavioral problems. Children with moderate to severe behavioral problems were grouped together according to 3 main categories; i.e., emotional, conduct and attention problems. Multiple diagnoses were allowed.

Indicators of cerebral damage

1. Neonatal cerebral damage: Neonatal cerebral ultrasound findings were classified as follows: Normal (score 0); abnormal without ventriculomegaly (score 1); abnormal with

ventriculomegaly (score 2); and abnormal with intraparenchymal damage (score 3). A standardized neonatal neurological examination was done weekly until discharge (Prechtl 1977). Results were classified as follows: Normal (score 0); mildly abnormal (score 1); and definitely abnormal (score 2). Neonatal cerebral ultrasound and neonatal examination scores were transformed into standardized z-scores and summed up to a score for neonatal cerebral damage.

2. Neurological development: A standardized neurological examination (Touwen 1976, Touwen 1979) was done at the corrected ages of 1, 2 and 3.6 years (± 2 weeks). The findings were classified as normal (score 0); mildly abnormal (score 1); and definitely abnormal (score 2). A child was considered definitely abnormal when a neurological disorder, such as cerebral palsy, was diagnosed. A child was considered mildly abnormal when minor neurological signs, such as minor left-right differences or mild hypertonia, were present but could not be attributed to a traditional neurological diagnosis.

Cognitive development

At a corrected age of 1 and 2 years cognition was assessed by the mental scale of the Dutch version of the Bayley Scales of Infant Development (van der Meulen and Smrkovsky 1983). At a corrected age of 3.6 years the Dutch adaptation of the Kaufman Assessment Battery for Children (Kaufman and Kaufman 1983, Neutel *et al.* 1989) was used. This cognitive battery measures Intelligence (the Mental Processing Composite, MPC) and Achievement (the Achievement Scale). For the present analysis only the MPC was used.

Social factors

1. Socio-demographic variables were grouped together in a cumulative socio-demographic risk score of four variables known to be important in cognitive development: the occupational status of the family, the mother's educational status, family support and ethnic background (Weisglas-Kuperus 1992).

2. The child's home environment was assessed by the Dutch version of the Home Observation for the Measurement of the Environment (Caldwell and Bradley 1984, de Jong and Meier 1985) at 1 and 3.6 years. For both ages a total score was computed. A high total score indicates a high, a low score a low stimulating home environment.

Data analysis

The statistical package Statgraphics 4.0 was used for univariate analysis, SPSS for multivariate analysis. A *p*-value of <.05 was considered significant. For the analysis of the relation between cerebral damage, cognitive development, social factors and behavioral outcome 3 types of analysis were done:

1. Preliminary correlations to select variables for subsequent analysis.

2. Regression analysis to determine how well the measures in the three domains related to the two outcome variables (parent and clinician reports of behavioral problems).

3. The model presented in Figure 5.1 was analyzed using path-analysis (Biddle and Marlin 1987) following the model of Goldberg et al. (1990).

5.4 RESULTS

Behavioral outcome at 3.6 years of age

Seventy-three CBCL/2-3 questionnaires could be used for analysis, 4 questionnaires were not returned by the parents. The prevalence of problem behavior as reported by the parents is presented in Table 5.1. Table 5.1 also compares the results on the CBCL/2-3 in VLBW children and children in the comparison group. When corrected for chance findings significantly more VLBW children than children in the comparison group scored above the 90th percentile for depressed behavior (*p*<0.004) on the behavior problem scales. Furthermore, VLBW children had more internalizing problems than children in the comparison group (*p*<0.0001). On the Total Problem Scale 22% of the scores were in the clinical range for VLBW children versus 10% in the comparison group (*p*<0.001).

Twenty-two of the 77 children (29%) had behavioral problems as reported by the clinician; 12 children (15%) had emotional, 5 (6%) had conduct and 11 (14%) had attention problems. There were no children with pervasive developmental disorders. Three children had emotional as well as conduct problems, 2 had conduct as well as attention problems and 1 had emotional and attention problems.

65

Table 5.1 Parent report of problem behavior (CBCL/2-3) of VLBW children versus comparison group.

PROBLEM BEHAVIOR PARENT REPORT (CBCL/2-3)	VERY LOW BIRTHWEIGHT (n=73)		COMPARISON GROUP (n=192)		Fisher's exact test
	Median (Range)	Prevalence* n (%)	Median (Range)	Prevalence* n (%)	p
Behavior Problem Scales:					
Social Withdrawal	4 (24)	3 (4.1%)	4 (20)	4 (2.1%)	ns.
Depressed	6 (18)	8 (11.0%)	2 (14)	4 (2.1%)	0.004
Sleep problems	2 (12)	1 (1.4%)	1 (15)	6 (3.1%)	ns.
Somatic problems	4 (13)	8 (11.0%)	2 (14)	6 (3.1%)	0.01[1]
Agressive	10 (52)	2 (2.7%)	18 (46)	6 (3.1%)	ns.
Destructive	5 (23)	5 (6.8%)	3 (17)	2 (1.0%)	0.02[1]
Any one or more		13 (17.8%)		19 (9.9%)	ns.
Total Behavior Problem Score	35 (145)	16 (21.9%)	32 (106)	19 (9.9%)	0.01
Internalizing Syndrome Score	9 (37)	25 (34.2%)	6 (27)	24 (12.5%)	0.0001
Externalizing Syndrome Score	14 (65)	2 (2.7%)	19 (54)	20 (10.4%)	0.03[1]

*Score above 98th percentile for syndrome score and above 90th percentile for Total Problem, Internalizing or Externalizing Scores.
[1] Not significant when corrected for the number of analysis using Bonferroni correction.

Parent and clinician reports are compared in Table 5.2. VLBW children with emotional problems had significantly higher Internalizing and Total Problem Scores than children without behavioral problems. Furthermore, significantly more VLBW children with behavioral problems according to clinician report had a score above the clinical cutoff point for syndrome scores (above the 98th percentile) than VLBW children without behavioral problems (65% vs. 26%, $p = 0.01$). When corrected for chance findings there were no significant differences on CBCL/2-3 syndrome scores between children with conduct or attention problems and children without behavioral problems

Table 5.2 Parent report in relation to clinician report.

PROBLEM BEHAVIOR CLINICIAN REPORT	PARENT REPORT (CBCL/2-3)		
	Internalizing Syndrome Score Median (Range)	Externalizing Syndrome Score Median (Range)	Total Behavior Problem Score Median (Range)
Behavioral Problems:			
Absent (n=51)	8 (26)	13 (29)	32 (72)
Present (n=22)	15 (35)**	22 (63)**	54 (140)**
- Emotional Problems (n=12)	16 (33)**	22 (61)*[1]	57 (129)**
- Conduct Problems (n= 5)	20 (26)*[1]	23 (57)	71 (121)*[1]
- Attention Problems (n=11)	15 (28)	19 (30)	53 (74)

U Mann Whitney *=p≤0.05,**=p≤0.01,***=p≤0.001
[1] Not significant when corrected for the number of analysis using Bonferroni correction.

by clinician report. There was also no significant difference in behavioral outcome for boys and girls by parent as well as clinician report.

Table 5.3 summarizes the correlations of the parent report of problem behavior in relation to indicators of cerebral damage, cognitive development and social factors. When corrected for chance findings, the total behavior problem score correlated significantly with the home environment at age 3.6 years. Correlations were somewhat, higher for Externalizing than for Internalizing Syndrome Scores. Table 5.4 summarizes the correlations of the clinician report of behavioral problems in relation to indicators of cerebral damage, cognition and social factors. When corrected for chance findings behavioral problems correlated significantly with cognitive development as well as the home environment at 3.6 years, conduct problems correlated significantly with the home environment at age 3.6 years and attention problems with cognition at age 3.6 years.

For both parent and clinician reports we conducted a series of independent regression analyses to examine what measures related best to behavioral outcome: in the neonatal period (i.e., neonatal cerebral damage, socio-demographic risk), at age 1 (i.e., neurology, cognition and home environment), at age 2 (i.e., neurology and cognition) and at age 3.6 (i.e., neurology, cognition and home environment). Two children with extremely high problem scores (> 4 *SD*) were influential outliers and therefore excluded from the regression analyses. Table 5.5 summarizes the results for the parent report. In the neonatal period the socio-demographic risk score was the only significant predictor. At 1 year of age there were no variables that contributed significantly to the equation. At age 2 cognition was the only significant variable. At age 3.6 the home environment had a significant contribution. The remaining variables did not contribute significantly to the equation at different ages. Table 5.6 summarizes the results for the clinician report of behavioral problems. At all ages cognition was significantly related to behavioral outcome. At 1 year of age the home environment also contributed to the regression of behavioral problems by clinician report.

Table 5.3 Correlations of cerebral damage, cognition, social factors and parent report of problem behavior.

		PARENT REPORT OF PROBLEM BEHAVIOR (CBCL/2-3)		
		Internalizing Syndrome Score	Externalizing Syndrome Score	Total Behavior Problem Score
INDICATORS OF CEREBRAL DAMAGE	- Cerebral Ultrasound - Neonatal Neurology - Neurology 1 year - Neurology 2 years - Neurology 3.6 years	.06 .19 -.10 .08 .02	-.03 .00 -.11 .01 -.07	-.01 .12 -.08 .06 -.02
COGNITIVE DEVELOPMENT	- Mental Developmental Index 1 year - Mental Developmental Index 2 years - Intelligence 3.6 years	-.15 -.21 -.09	-.04 -.23*[1] -.19	-.15 -.30*[1] -.22
SOCIAL FACTORS	- Socio-demographic Risk Score - HOME Inventory 1 year - HOME Inventory 3.6 years	.22 -.03 -.25*[1]	.27*[1] -.13 -.33**	.30*[1] -.16 -.37**

Spearman Rank correlation coefficient *=p≤0.05,**=p≤0.01,***=p≤0.001
[1] Not significant when corrected for the number of analysis using Bonferroni correction.

Table 5.4 Correlations of cerebral damage, cognition, social factors and clinician report of behavioral problems.

		CLINICIAN REPORT OF BEHAVIORAL PROBLEMS			
		Emotional Problems	Conduct Problems	Attention Problems	All Behavioral Problems
INDICATORS OF CEREBRAL DAMAGE	- Cerebral Ultrasound - Neonatal Neurology - Neurology 1 year - Neurology 2 years - Neurology 3.6 years	.15 .11 .09 .26*[1] .20	-.01 -.07 .00 .14 -.10	-.07 .03 .06 .01 .03	.08 .14 .14 .23*[1] .20
COGNITIVE DEVELOPMENT	- Mental Developmental Index 1 year - Mental Developmental Index 2 years - Intelligence 3.6 years	-.17 -.08 -.20	-.10 -.16 -.07	-.12 -.30**[1] -.42***	-.27*[1] -.31**[1] -.47***
SOCIAL FACTORS	- Socio-demographic Risk Score - HOME Inventory 1 year - HOME Inventory 3.6 years	.08 -.10 -.25*[1]	.28*[1] -.28*[1] -.35**	.11 -.21 -.27*[1]	.17 -.24*[1] -.40***

Spearman Rank correlation coefficient *=p≤0.05,**=p≤0.01,***=p≤0.001
[1] Not significant when corrected for the number of analysis using Bonferroni correction.

Table 5.5 Multiple regression analyses of parent report of problem behavior (CBCL/2-3)

| | | PARENT REPORT OF PROBLEM BEHAVIOR (CBCL/2-3) | | | | | |
		Coeff B	SE B	ADJ-R^2	F-change	p	df
Neonatal	Socio-demographic risk	4.50	1.96	.07	5.30	.02	1,69
	Remaining variables (forced)	-	-	.08	1.07	ns	2,68
1 Year	All variables (forced)	-	-	.04	.84	ns	3,65
2 Years	Mental Developmental Index	-.20	.09	.08	5.39	.02	1,65
	Remaining variables (forced)	-	-	.08	.00	ns	2,64
3.6 Years	HOME Inventory	-.73	.28	.10	6.90	.01	1,61
	Remaining variables (forced)	-	-	.11	.43	ns	3,59

Table 5.6 Multiple regression analyses of clinician report of behavioral problems

| | | CLINICIAN REPORT OF BEHAVIORAL PROBLEMS | | | | | |
		Coeff B	SE B	ADJ-R^2	F-change	p	df
Neonatal	All variables (forced)	-	-	.03	1.24	ns	2,68
1 Year	Mental Developmental Index	-.02	.00	.10	7.86	.006	1,67
	HOME Inventory	-.04	.02	.18	5.80	.02	2,66
	Remaining variables (forced)	-	-	.19	1.36	ns	3,65
2 Years	Mental Developmental Index	-.02	.00	.13	9.56	.003	1,65
	Remaining variables (forced)	-	-	.14	.98	ns	2,64
3.6 Years	Intelligence	-.04	.00	.35	35.75	.000	1,65
	Remaining variables (forced)	-	-	.38	1.26	ns	3,63

To analyze the model in Figure 5.1 several assumptions were made and set out in advance as formal criteria (Goldberg *et al.* 1990). First, direct pathways from early measures were included only if they were not explained via temporally intervening measures. Second, where there was continuity in measures from the same domain (e.g., cognitive development at age 1 correlating with cognitive development at age 3.6) the path of influence from year 0 was assumed to be via continuity with year 1, 2 and 3.6. Third, continuity within a domain (auto-correlation) was given priority over correlations across time and domain, i.e., paths across time and domain were considered only if they significantly added to the variance. Finally, where domains were interrelated and both predicted outcome, they were entered in a stepwise regression to determine which ordering yielded the strongest prediction of outcome. Figure 5.2 shows the final model and the beta weights ($p < .05$) for both parent and clinician reports of problem behaviors. The initial model was only partially confirmed. Unexpected findings may be summarized as follows: cerebral damage had a moderate direct influence on cognitive development at Year 1; Year 1 cognitive development had

a small but significant influence on Year 2 neurology; home environment had an influence on cognitive development, but only across time; we found no relation between neurology or cognitive development and parent report of problem behavior; we found no relation between home environment or neurology and clinician's report.
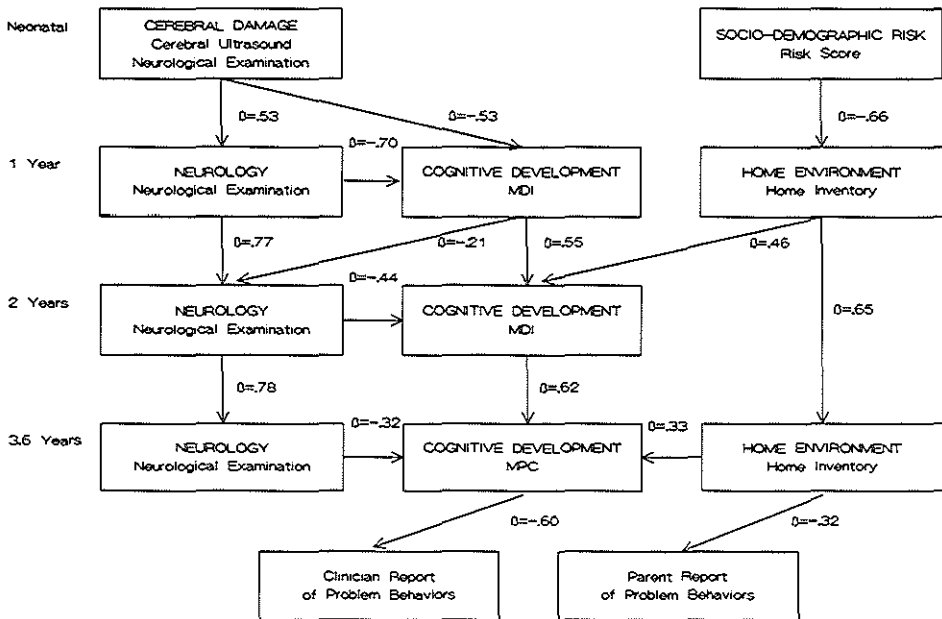

Figure 5.2 Prediction of parent and clinician reports of problem behavior.

5.6 DISCUSSION

In our study 22% of the VLBW children and 10% of the comparison group scored within the clinical range of problem behavior by parent report. Parents of VLBW children reported significantly more depressed behavior and internalizing problems than parents of children in the comparison group. In VLBW children there was also a significant relationship between emotional problems by clinician report and internalizing problems by parent report. This was not the case for conduct or attention problems by clinician report.

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Assessment of problem behavior in the preschool years poses a particularly difficult research task. In this study we therefore used parental as well as clinician reports to establish the behavioral outcome of VLBW children at 3.6 years of age. However, both measures of behavioral outcome have some limitations. Most problem behaviors in preschool children do not result in diagnoses like those included in the DSM-III-R (Koot and Verhulst 1991). For this reason we only described behavioral problems according to main categories using the clinician report. The clinician scored the child's behavior at the end of the neurodevelopmental assessment and was consequently influenced by the neurological and cognitive status of the child. The CBCL/2-3 is a broad band scale and there is no specific behavior problem scale for attentional problems. There is also a bias using parent reports. All children in our study experienced a high number of adverse perinatal conditions. These children are likely to be overprotected by their parents. Parents, anxious about their children's health, may therefore be more inclined to report internalizing problems. Possibly these parents less readily report externalizing problems in their children. Parents and clinicians see children in a different context, rate different samples of behavior and possibly use different standards in rating the same child. In our study group these differences were found not only for conduct problems, but also for attention problems as reported by the clinician. The prevalence of 14% of attention problems found in this study is in agreement with the 16% found by Szatmari *et al.* (1990) in VLBW children at 5 years of age. Because parents and clinician have different views of the same child both parent and clinician report are important in the assessment of preschool problem behavior. Whatever the inadequacies in the preschool assessment of behavior, early detection of behavioral problems is vital. Children with behavioral problems in preschool are likely to have later learning and psychiatric disorders (Lerner *et al.* 1985, Egeland *et al.* 1990).

The preliminary model, as proposed in our study, was only partially confirmed. Contrary to the expectation, neither neonatal cerebral ultrasound nor neurological examinations had a direct influence on behavioral outcome. Neonatal cerebral damage, however, had a direct influence on cognitive development and cognition had a direct influence on behavioral problems by clinician report. The home environment had a direct influence on problem behavior by parent report and was also significantly related to cognitive development across time. Allthough the explained variances found in this study were small, other authors (Campbell 1987) also found that a poor behavioral

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outcome seems to be mediated by an unsupportive home environment. In studies of non-VLBW infants (Breslau 1990, Gould *et al.* 1988) significant correlations of attention problems and cognition also have been found.

The conclusion of this study is that VLBW children are at risk for a wide range of behavioral problems. An assessment of these problems becomes feasible well before these children can be diagnosed as learning disabled or psychiatrically disordered by DSM-III categories. The excess of behavioral sequelae in VLBW children might be of two types:

- Depressed behavior might be associated with parental reactions to the birth of a VLBW child and to neonatal intensive care treatment in general. It is difficult for these parents to establish a good relationship with their infants, possibly due to some of the infant's characteristics as well. Modulation of arousal and difficulties in responsivity have been documented in VLBW infants. In addition, it is understandable that parents' awareness of their child's potential handicap may interfere with processes related to the formation of secure attachments, leading to behavioral problems. If we accept the notion that development is a transactional process, our findings indicate the need for early intervention programs focused on changing parents' interaction with their young children. Recent evidence suggests that comprehensive early intervention programs might not only be effective for cognitive but also for behavioral outcome (The Infants Health and Development Program 1990).

- Attention problems might be linked indirectly to brain abnormalities as well as to the home environment via cognitive impairments. Attention problems in VLBW children therefore present a specific problem and should be subject to more detailed studies.

This study does not answer the question to what extent our findings have implications for other groups of high risk children. An increase in depressive symptoms and inattention has also been found in children with brain disorders of different etiology (Breslau 1990). Our study is in support of these findings. Breslau concluded that family environment had a significant effect on depressive symptoms and not on symptoms of inattention. Our study suggests that the quality of the home environment may be directly or indirectly (via cognition) influential in both types of behavioral outcome.

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CHAPTER 6

INATTENTION AND ACTIVITY IN VERY LOW BIRTHWEIGHT CHILDREN

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CHAPTER 6

INATTENTION AND ACTIVITY IN VERY LOW BIRTHWEIGHT CHILDREN

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6.1 SUMMARY

Inattention and activity were assessed in 63 very low birthweight (VLBW) and 63 full term children at 3.6 years of age. In VLBW children the relation of inattention and activity with neonatal cerebral ultrasound, neurodevelopmental outcome (eg. neurology, intelligence and achievement (K-ABC), language comprehension and expression) and the home environment (Caldwell & Bradley) was studied. VLBW children were less attentive but not more active than full term children. The simultaneous subscale of the Kaufman Assessment Battery for children (p = 0.02) together with language expression (p = 0.03) best predicted inattention, explaining 22% of the variance. The home environment of the child alone best predicted activity (p = 0.01) explaining 10% of the variance. Neonatal cerebral ultrasound and neurological examinations were no significant predictors for inattention and activity. We conclude that inattention and hyperactivity in preschool VLBW children are etiologically separated and that a cognitive impairment in simultaneous processing is at the root of attention deficits in VLBW children.

6.2 INTRODUCTION

Infants born with birthweights less than 1500 grams (VLBW) have a higher incidence of handicaps than full term infants (Veen et al., 1991). There is also evidence that VLBW children are more at risk for impairments such as attention problems and subsequent learning deficits (Astburry, Orgill & Bajuk, 1987; Breslau, Klein & Allen, 1988; Klein, 1988; MacCormick, Gortmaker & Sobol, 1990; Minde et al., 1989; Ross, Lipper & Auld, 1991; Szatmari, Saigal, Rosenbaum, Campbell & King, 1990). In children with attention-deficit hyperactivity disorder (ADHD), regional cerebral blood flow measured by PET scanning showed regions of hypoperfusion in striatal and posterior

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periventricular areas (Lou, Hendriksen & Bruhn, 1990). These findings could represent sequelae of hypoxic ischemic lesions, a frequent complication in VLBW infants. Recent advances in technology have made neonatal cerebral ultrasound in high risk VLBW infants a routine matter. This offers an opportunity for documenting neonatal cerebral damage in children at risk for attention problems. However, to our knowledge, problems of attention and activity have not been studied systematically in children in whom neonatal cerebral damage has been identified by routine neonatal cerebral ultrasound.

According to the DSM-III-R the essential features of ADHD are developmentally inappropriate degrees of inattention, impulsiveness and hyperactivity. In approximately half of the cases, onset of the disorder is before the age of four (American Psychiatric Association, 1987). However, the diagnosis of ADHD according to DSM-III-R criteria is not appropriate in preschool children and there is a lack of (neuro)psychological procedures for the assessment of inattention and activity in preschool age.

Academic underachievement is a characteristic of most children with ADHD. Whether this is solely due to inattention or results from other neurodevelopmental deficits is uncertain (Normile, Altman & Gershon, 1989). Family adversities and maladaptive patterns of parent-child interaction play an important role in the course of ADHD. The role of the home environment in the aetiology of inattention and hyperactivity, however, remains obscure (Rutter, 1989; Shaywitz & Shaywitz, 1989).

In this study inattention and activity were assessed in high risk VLBW and healthy full term children at 3.6 years of age. We wanted to find an answer to the following questions:

1. Are VLBW children more hyperactive and inattentive than healthy full term children?

2. Is inattention and hyperactivity in VLBW children associated with neonatal cerebral damage?

3. What are the neurodevelopmental correlates of inattention and hyperactivity in VLBW children at 3.6 years of age?

4. What is the influence of the home environment on inattention and hyperactivity in VLBW children?

6.3 PATIENTS AND METHODS

Study group

This study is part of a longitudinal study on VLBW infants (Weisglas-Kuperus, 1992a). The total study group consisted of all preterm VLBW children (n = 114, birthweight < 1500 grams, gestational age < 36 weeks), admitted to the Neonatal Intensive Care Unit of the Sophia Children's Hospital in Rotterdam (a regional tertiary intensive-care unit) between August 1, 1985 and August 1, 1986 within 48 hours after birth. Twenty-three infants (20%) died in the neonatal period or in the first year of life. Twelve children (10%) were not available for the whole follow-up period because of migration (n = 6), lack of interest (n = 3) or inability (n = 3) to cooperate. Birthweight ranged from 690 to 1495 grams (M = 1136, SD = 213). Gestational age ranged from 25 to 35 weeks (M = 30.4, SD = 2.3). A handicap was diagnosed if one of the following conditions was found at 3.6 years of age: a neurological disorder, a mental handicap, a severe visual or hearing impairment. Thirteen of the 79 children had a handicap and were excluded from further analysis.

Inattention and Activity

At the age of 3.6 years parents were asked to complete the Parent Version of the Groninger Behavior Observation Scale (GBO Parent), a questionnaire for assessing inattention and hyperactivity in school children (Vaessen & Van der Meere, 1990). The GBO Parent consists of 15 questions and is scored on a 4 point scale (1 = does not apply, 2 = more "no" than "yes", 3 = more "yes" than "no", 4 = yes, this does apply). Of the original version one of these 15 questions (Is always occupied by other things when having to prepare for school) was not appropriate for preschool children, the remaining 14 items were used in this study (Table 6.1). According to the original version, a sumscore of all 14 items, and subscores for activity (item 3,4,7,10,14) and inattention (item 1,2,5,8,11,13) were computed. Item 6, 9 and 12 were eliminated because of equal loadings on the two factors. A higher score is associated with more inattention and hyperactivity.

Table 6.1 The 14 (out of 15) items of the Groninger Behavior Observation Scale, parent version, used for preschool children.

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  1.   Is very impulsive; starts immediately without thinking first.
  2.   Has more trouble concentrating at the end of the day.
  3.   Is very talkative during meals, spends more time talking than eating.
  4.   Is constantly moving his/her legs or tilting his/her chair during meals.
  5.   Easily gives up, sometimes irritated when doing something he/she finds hard to accomplish.
  6.   Often doesn't think before talking, blurts out all kind of remarks.
  7.   Wants to continue talking even after having been asked to be quiet.
  8.   Is easily distracted, even when engaged in something he/she finds interesting
  9.   Repeatedly leaves the table during meals.
 10.   Talks whenever possible.
 11.   Is unable to be engaged in the same activity for longer periods of time, for instance
       changes toys every 5 minutes or wants to play outdoors.
 12.   Always touches everything.
 13.   Is very playful for his/her age.
 14.   Is constantly fidgeting.
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Three questionnaires were not returned by the parents. Of the remaining 63 children 35 were girls and 28 boys. The comparison group consisted of 63 healthy full term children, born without complications, matched for sex and social class. The 90th percentile of the sumscore in the comparison group was chosen as a cut-off point, above which children were considered to show significant problems in attention and activity.

Neonatal cerebral damage

Neonatal cerebral ultrasound findings were classified as follows (Weisglas-Kuperus, Baerts, Fetter & Sauer, 1992b): Normal (score 0); abnormal without ventriculomegaly or intraparenchymal damage (score 1); abnormal with ventriculomegaly and/or intraparenchymal damage (score 2).

Neurodevelopmental assessment at 3.6 years of age

At a corrected age of 3.6 years (± 2 weeks) a neurodevelopmental assessment was performed by an experienced developmental pediatrician who did not know the perinatal history.

1. Neurology: A standardized neurological examination (adapted from Touwen, 1979) was done. Findings were classified as normal, minor neurological dysfunction (MND) or abnormal. A child was called abnormal when a neurological disorder, such as cerebral palsy was diagnosed, these children were excluded from further analysis. Minor neurological dysfunction was diagnosed if minor neurological signs, such as minor left-right differences or mild hypertonia, were present.

Table 6.2 Subtests of the K-ABC administered at 3.6 years of age in the order of testing.

I	INTELLIGENCE (MENTAL PROCESSING COMPOSITE)
1.	Magic Window (Simultaneous Processing Scale); the child's ability to identify and name an object whose picture is rotated behind a narrow slit, so that the picture is partially exposed at any point in time.
2.	Face Recognition (Simultaneous Processing Scale); the child's ability to attend closely to one or two faces whose photographs are exposed briefly, and then to select the correct face(s), shown in a different pose, from a group photograph.
3.	Hand Movements (Sequential Processing Scale); the child's ability to copy the precise sequence of taps on the table with fist, palm, or side of the hand performed by the examiner.
4.	Gestalt Closure (Simultaneous Processing Scale); the child's ability to mentally "fill in the gaps" in a partially completed inkblot drawing, and name or describe that drawing.
5.	Number Recall (Sequential Processing Scale); the child's ability to repeat in a sequence a series of numbers spoken by the examiner.
II	ACHIEVEMENT SCALE
6.	Expressive Vocabulary; the child's ability to state the correct name for objects pictured in photographs.
7.	Faces and Places; the child's ability to name the fictional, famous persons, or well-known places pictured.
8.	Arithmetic; the child's ability to identify numbers, counts, compute, and demonstrate understanding of mathematical concepts.
9.	Riddles; the child's ability to infer the name of a concrete or abstract verbal concept when given several of its characteristics.

2. Cognition: The Dutch adaptation of the Kaufman Assessment Battery for Children (Kaufman & Kaufman, 1983; Neutel, Eldik & Van der Meulen, 1989) was used. The K-ABC measures intelligence (the Mental Processing Composite, MPC) and achievement (the Achievement Scale). At 3.6 years of age 9 subtests are administrated in a fixed order (Table 6.2). The Intelligence Scales consist of 5 subtests that are combined to form Sequential Processing and Simultaneous Processing subscales. On the Achievement Scale 4 subtests are combined to form a global achievement score. All scales have a mean value of 100 and a SD of 15.

3. Language: To assess language comprehension the Dutch version of the Reynell Developmental Language Scale B revised (Reynell, 1969; Boomers & Muggen 1982) was used. Expressive language was scored on an 8 points scale representing 8 features of language structure with increasing complexity (Goorhuis-Brouwer, 1985).

Home Environment

The child's home environment was assessed by the Dutch version of the Home Observation for the Measurement of the Environment (Caldwell & Bradley, 1984; De Jong & Meier, 1985) at 1 and 3.6 years of age. The Home Inventory at age 1 consists of 45 items (maximal total score 45) representing six categories of social stimulation

important in infant development (eg responsivity of the mother, acceptance of behavior, organization of the environment, provision of play material, maternal involvement and variety of stimulation). The Home Inventory at age 3.6 consists of 55 items (maximal total score 55) representing seven categories of social stimulation important in toddler development (eg learning stimulation, language stimulation, physical environment, warmth and affection, academic stimulation, modeling, variety in experience and acceptance). The total scores of the Home Inventory at 1 and 3.6 years were standardized (M = 0, SD = 1) and summed up. A summary score of more than the 75th percentile was considered as a high, of the 25th to 75th percentile as an intermediate and of less than the 25th percentile as a low stimulating home environment.

Data analysis

The statistical package Statgraphics 4.0 was used. Univariate statistical analysis was performed to study associations between separate items. Stepwise multiple regression analysis was used to determine how well neonatal cerebral ultrasound findings, the neurodevelopmental assessment and the home environment predicted inattention and activity at age 3.6 years. A p value of <0.05 was considered to be significant.

6.4 RESULTS

Inattention and activity in VLBW and healthy full term children

The sumscores of the Groninger Behavior Observation Scale in VLBW and full term children are presented in Figure 6.1. The sumscore ranged from 17 to 45 in healthy full term (90th percentile = 39) and from 17 to 50 in VLBW children. Six of the fullterm (2 girls and 4 boys) and 13 (6 girls and 7 boys) of the VLBW children scored above the 90th percentile (Fisher's exact test, p = 0.07).

Mean values for the sumscore, the activity and inattention subscales in VLBW and full term children are presented in Table 6.3. VLBW children had a higher mean value on the sumscore and inattention subscale and not on the activity subscale than full term children. There were no significant differences for boys and girls in mean values on the sumscore, activity and inattention subscores in VLBW as well as in fullterm children.
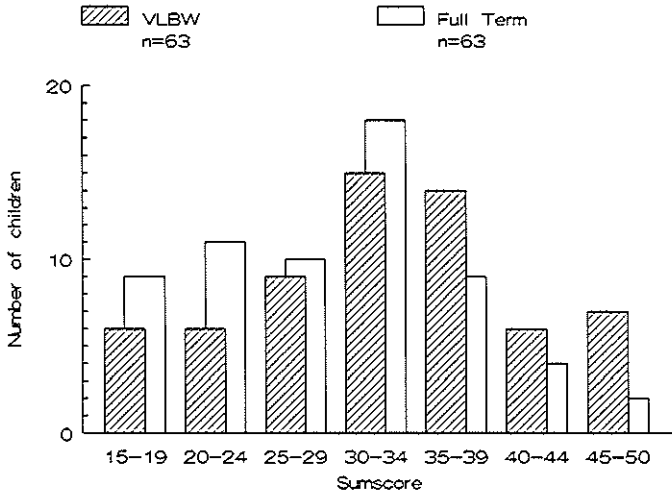
Figure 6.1 Groninger Behavior Observation Scale, sumscore in VLBW and healthy full term children.

Table 6.3 Activity and inattention in full term controls and VLBW children.

SUBJECTS	GRONINGER BEHAVIOR OBSERVATION SCALE			
	n	Sumscore Mean (SD)	Activity Subscale Mean (SD)	Inattention Subscale Mean (SD)
FULL TERM CONTROLS	63	29.0 (7.7)	9.7 (2.9)	11.9 (4.2)
VERY LOW BIRTHWEIGHT	63	32.6 (9.0)*	10.8 (3.4)	13.8 (4.3)*

*=p<0.05

Neonatal cerebral damage

Inattention and activity in VLBW children in relation to the severity of neonatal cerebral damage is given in Table 6.4. When corrected for chance findings there were no significant differences in mean values on the sumscore, activity and inattention subscale comparing children with normal neonatal cerebral ultrasound to children with abnormal cerebral ultrasound.

Table 6.4 Activity and inattention in VLBW children in relation to the severity of neonatal cerebral damage.

NEONATAL CEREBRAL ULTRASOUND	GRONINGER BEHAVIOR OBSERVATION SCALE			
	n	Sumscore Mean (SD)	Activity Subscale Mean (SD)	Inattention Subscale Mean (SD)
Normal	18	35.5 (9.5)	12.3 (3.0)	14.4 (4.5)
Ventriculomegaly -	19	32.8 (8.6)	9.8 (3.2)*[1]	14.5 (4.7)
Ventriculomegaly + and/or Intraparenchymal Damage	26	30.5 (8.6)	10.5 (3.6)	12.8 (3.9)

*=p<0.05
[1]Not significant when corrected for chance findings, using Bonferroni correction.

Neurodevelopmental outcome

Inattention and activity in VLBW children in relation to neurodevelopmental outcome at 3.6 years of age is given in Table 6.5. When corrected for chance findings two significant subscale differences were found. Children with a score <85 on the simultaneous scale had a higher mean value on the inattention subscale than children with a score >85 on the simultaneous scale. Children with a score <85 on the achievement scale had a higher mean value for the activity subscale than children with a score >85 on the achievement scale. Children with minor neurological dysfunction were not more active or inattentive than those with normal neurology. Although not significant, the total pattern in all other comparisons (sequential scale, language comprehension and expression) was that children with better test results (>mean-1SD) were rated as less active and more attentive than those with lower test results (<mean-1SD). The sumscore reflected the differences found in the subscales.

Home environment

Activity and inattention in VLBW children in relation to the home environment is given in Table 6.6. Children from an intermediate or low stimulating home environment had higher mean values for the sumscore, the activity as well as the inattention subscale than children from a high stimulating home environment.

Table 6.5 Activity and inattention in VLBW children in relation to the neurodevelopmental assessments at 3.6 years of age.

NEURODEVELOPMENTAL ASSESSMENT		GRONINGER BEHAVIOR OBSERVATION SCALE			
		n 63	Sumscore Mean (SD)	Activity Subscale Mean (SD)	Inattention Subscale Mean (SD)
Neurology	Normal	44	33.4 (8.9)	11.2 (3.5)	14.0 (4.3)
	Minor Neurological Dysfunction	19	30.7 (8.9)	9.8 (3.1)	13.3 (4.5)
Intelligence (K-ABC)	Sequential >85	54	32.3 (9.0)	10.6 (3.4)	13.7 (4.5)
	Sequential <85	9	34.7 (8.7)	11.7 (3.4)	14.4 (3.6)
	Simultaneous >85	36	29.8 (7.8)	10.1 (3.5)	12.6 (4.2)
	Simultaneous <85	27	36.4 (9.1)**	11.7 (3.1)	15.4 (4.1)**
Achievement (K-ABC)	>85	38	29.9 (8.7)	9.7 (3.3)	13.0 (4.6)
	<85	25	36.8 (7.8)**	12.4 (2.8)**	15.7 (3.7)
Language	Comprehension >-1SD	40	30.7 (8.7)	10.2 (3.5)	13.0 (4.4)
	Comprehension <-1SD	23	36.0 (8.6)*[1]	11.8 (3.1)	15.2 (3.9)*[1]
	Expression >-1SD	43	30.6 (9.0)	10.4 (3.4)	12.9 (4.5)
	Expression <-1SD	20	36.5 (7.6)*[1]	11.6 (3.3)	15.7 (3.3)*[1]

*=p<0.05, **=p<0.01, ***=p<0.001
[1] Not significant when corrected for chance findings, using Bonferroni correction.

Table 6.6 Activity and inattention in VLBW children in relation to the home environment.

HOME ENVIRONMENT	GRONINGER BEHAVIOR OBSERVATION SCALE			
	n 63	Sumscore Mean (SD)	Activity Subscale Mean (SD)	Inattention Subscale Mean (SD)
High	17	26.8 (8.2)	9.1 (3.1)	11.3 (3.8)
Intermediate	29	33.9 (8.3)**	11.2 (3.3)*	14.3 (4.4)*
Low	17	36.4 (8.3)**	11.6 (3.4)*	15.4 (3.7)**

*=p<0.05, **=p<0.01

Prediction of activity and inattention

In a stepwise multiple regression analysis of neonatal cerebral ultrasound, the neurodevelopmental assessments at 3.6 years of age (eg neurology, sequential and simultaneous processing, achievement, language comprehension and expression) and the home environment as predictors for the activity subscore, the home environment alone was the best predictor for activity (p = 0.01) explaining 10% of the variance. In a stepwise multiple regression analysis of neonatal cerebral ultrasound, the neurodevelopmental assessments at 3.6 years of age and the home environment as predictors for the inattention subscore, the simultaneous scale of the K-ABC (p = 0.02) and language expression (p = 0.03) together best predicted inattention explaining 22% of the variance.

6.5 DISCUSSION

In our study of preschool children, inattention and activity were assessed by parent questionnaire. Parents of VLBW children rated their children as significantly more inattentive but not more active than parents of full term children. Inattention in VLBW children was, however, not related to neonatal cerebral damage as detected by cerebral ultrasound. As in other studies (Vaessen *et al.*, 1990) there was also no difference either in inattention or activity in neurologically normal children and children with minor neurological dysfunction at 3.6 years of age. Neonatal cerebral ultrasound can demonstrate structural brain damage and is a good predictor of neurological outcome (Weisglas-Kuperus *et al.*, 1992b). It is not predictive, however, of more subtle impairments like attention problems. Regional cerebral blood flow measured by PET scanning probably is of more importance in the differentiation between ADHD and non-ADHD children (Lou *et al.*, 1990) than neonatal cerebral ultrasound findings.

Children with a score less than 85 on the simultaneous scale of the K-ABC scored significantly higher on the inattention subscale than children with a score more than 85 on the simultaneous scale. No significant differences were found for the sequential scale. The K-ABC intelligence scales are based on a neuropsychological model of sequential and simultaneous processing confirmed by factor analysis (Kaufman *et al.*, 1983; Neutel *et al.*, 1989). Our results suggest that cognitive deficits in simultaneous problem solving are at the root of attention problems in VLBW children. These divided attention deficits have also been reported in children who were classified as neurologically suboptimal at birth (De Sonneville, 1988) and in learning disabled children (Van der Meere, Van Baal & Sergeant, 1989). Children with a score < mean-1SD for language comprehension and expression were also more inattentive than children with a score > mean-1SD for language comprehension and expression. These results were not significant however when corrected for chance findings. Nevertheless expressive language together with the simultaneous scale best predicted inattention. This is in agreement with Rapin (1988) who also described that disorders of higher cerebral function in preschoolers are likely to present as inadequate language development.

Children with a score less than 85 on the achievement scale scored significantly higher on the activity subscale and not on the inattention subscale than children with a

score more than 85 on the achievement scale. In a previous study (Weisglas-Kuperus 1992) we described a close relationship of the home environment with achievement as well as with emotional and conduct problems. In the present study the home environment was the only independent predictor for the activity subscale. Achenbach, Verhulst, Baron & Althaus (1987) found that hyperactivity in Dutch elementary school boys, measured by the Child Behavior Checklist was not associated with inattentive but with aggressive behavior. As in other studies of problem behavior in preschool children (Koot & Verhulst, 1991), there were no significant differences between boys and girls in our study. Nonetheless, preschool hyperactivity, especially in boys, might be a marker for long term aggressive problems and maladjustment at a later age (Koot & Verhulst, 1992).

In mentally retarded children many of the features of ADHD may be present because of the generalized delay in intellectual development. In children with cerebral palsy the measurement of activity is inappropriate. It could also be that psychological sequelae stem from the physical handicap and not from cerebral damage. Children with a handicap were therefore excluded from this study. Populations of the most vulnerable intensive care survivors are small, and matched controls do not exist. Nevertheless our study demonstrates that high risk samples are useful in studying which aspects of behavior are influenced by the central nervous system and how these interact with the child's home environment. It is obvious that additional parameters for inattention and activity may be found with other tools of assessment like rating scales based on direct clinical observation or more objective measures like those based on ethological observations. The usefulness of such parameters in the preschool assessment of inattention and activity is subject to further study.

We conclude that VLBW children are less attentive than full term children. Inattention in preschool VLBW children is associated with simultaneous processing and language development. At preschool age neuropsychological assessment is more sensitive to the measurement of these higher cerebral functions than is neonatal cerebral ultrasound or preschool neurological examinations. Activity is associated with the home environment and may thus etiologically be separated of inattention. Whether neonatal cerebral damage, preschool minor neurological dysfunction, inattention or activity will predict future learning disabilities and behavioral problems at school age is subject to further study.

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CHAPTER 7

MINOR NEUROLOGICAL DYSFUNCTION AND QUALITY OF MOVEMENT
IN RELATION WITH NEONATAL CEREBRAL DAMAGE AND DEVELOPMENT
IN PRESCHOOL VERY LOW BIRTHWEIGHT CHILDREN

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CHAPTER 7

MINOR NEUROLOGICAL DYSFUNCTION AND QUALITY OF MOVEMENT
IN RELATION WITH NEONATAL CEREBRAL DAMAGE AND DEVELOPMENT
IN PRESCHOOL VERY LOW BIRTHWEIGHT CHILDREN

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7.1 SUMMARY

Minor neurological dysfunction and the quality of movement were studied in relation to neonatal cerebral damage (eg. neonatal neurology and cerebral ultrasound) and developmental assessments at 3.6 years of age (eg. Mc Carthy motor scale, Kaufman intelligence and achievement scale, receptive and expressive language) in 66 non-handicapped VLBW children. Minor neurological dysfunction was found in 19 of the 66 (29%) children and was significantly related to the quality of movement. The results demonstrate that at preschool age, minor neurological dysfunction is associated with neonatal cerebral damage, but that the assessment of the quality of movements is associated with more complex sensory motor tasks and simultaneous processing. At preschool age, the quality of movement might therefore be a better marker of later learning problems than traditional signs of minor neurological dysfunction.

7.2 INTRODUCTION

Infants born with birthweights less than 1500 grams (VLBW) are at high risk for neonatal cerebral damage. Abnormal neonatal cerebral ultrasound findings are present in up to 72% of VLBW infants. Intraparenchymal damage is associated with cerebral palsy. Less severe neonatal cerebral lesions are associated with minor neurological dysfunction (MND) (Weisglas-Kuperus et al. 1992). The prevalence of minor neurological dysfunction is higher in preterm than in full term children (Forslund and Bjerre 1989, Hadders-Algra et al. 1988a, Marlow et al. 1989). In addition preterm children

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perform significantly lower on tests of motor performance (Elleman *et al.* 1990, Marlow *et al.* 1989).

Minor neurological and motor impairments are of interest, because they seem to be associated with learning difficulties, school failure and behavioral problems at school age (Losse *et al.* 1991, Drillien 1983, Herzig 1981, Wolff *et al.* 1985, Hadders-Algra *et al.* 1988b). Identification of children with minor impairments at preschool age is important, in order to organize timely intervention. However, this presumes the presence of diagnostic tools.

One of these tools is a developmental assessment. In standardized developmental tests, the child's performance is compared to the performance of the population of children of the same age. Developmental tests measure performance level quantitatively. They cannot lead to conclusions about the reasons of the deficient performance, which is required for proper treatment. Developmental assessments in preschool children are also time consuming. Tests proposed for the early identification of children suspected of having later learning difficulties therefore often contained a mixture of sensory-motor, language and other cognitive tasks (Bax 1987). The use of such tests makes it difficult to study the independent contribution of sensory-motor, cognitive and language development to later learning problems.

Another tool is the neurological examination. A standardized age appropriate method, for the assessment of minor neurological dysfunction in preschool years, is not yet available. Preschool children can be difficult to handle and being stubborn is almost part of their usual behavioral repertoire. This makes a standardized neurological examination difficult. A neurological examination in preschool children should therefore contain specific observation of the motor behavior of the child (Touwen *et al.* 1992).

Variability of posture and motility is characteristic for the normal nervous system and dysfunction of the brain will lead to a loss of variability (Touwen 1992a,b, 1991, 1989, 1984, 1978, 1976). In preterm infants, the qualitative assessment of general movements has been shown a promising method for the early detection of motor impairment (Touwen 1990, Ferrarri *et al.* 1990). At preschool age, the significance of the quality of movement, as compared to more traditional signs of minor neurological dysfunction, is not known.

In this paper the results of a standardized neurological examination at 3.6 years of age will be described. The following questions will be addressed:

1. What is the relation between neonatal cerebral damage on the one hand, and minor neurological dysfunction and the quality of movement at 3.6 years of age on the other hand?

2. What is the relation between minor neurological dysfunction and the quality of movement on the one hand, and sensory-motor, cognitive and language development at 3.6 years of age on the other hand?

7.3 PATIENTS AND METHODS

Study group

This study is part of a longitudinal study on VLBW infants (Weisglas-Kuperus 1992). The total study group consisted of all preterm VLBW children (n = 114, birthweight < 1500 grams, gestational age < 36 weeks), admitted to the Neonatal Intensive Care Unit of the Sophia Children's Hospital in Rotterdam (a regional tertiary intensive-care unit) between August 1, 1985 and August 1, 1986 within 48 hours after birth. Twenty-three infants (20%) died in the neonatal period or in the first year of life. Twelve children (10%) were not available for the whole follow-up period because of migration (n = 6), lack of interest (n = 3) or inability (n = 3) to cooperate. Birthweight ranged from 690 to 1495 grams (M = 1136, SD = 213). Gestational age ranged from 25 to 35 weeks (M = 30.4, SD = 2.3).

Neonatal cerebral ultrasound findings were classified as normal (score 0); abnormal without ventriculomegaly (PIVH I-II, periventricular flaring and/or other lesions, score 1); abnormal with ventriculomegaly (PIVH III, periventricular flaring and/or other lesions, score 2); and abnormal with intraparenchymal damage (PIVH IV and/or PVL, score 3).

A standardized neonatal neurological examination was done weekly until discharge (Prechtl 1977). Results were classified as normal (score 0); mildly abnormal (score 1); and definitely abnormal (score 2).

At a corrected age of 3.6 years (± 2 weeks) a neurodevelopmental assessment was performed by an experienced developmental pediatrician (NW) who did not know the perinatal history. A handicap was diagnosed if one of the following conditions was found: a neurological disorder, a mental handicap, a severe visual or hearing

impairment. Thirteen of the 79 children had a handicap and were excluded from further analysis. The remaining 66 children form the study group of this paper.

Neurological examination

The neurological assessment was based on the standardized neurological examination by Touwen (1979). It consisted of an evaluation of posture, tone, reflexes, trunk coordination, gross and fine motor functions. Children were examined in sitting, standing, walking and lying positions. Results were summarized in a neurological profile (Table 7.1). A child was classified as having minor neurological dysfunction (MND) if more than one minor neurological sign, such as minor left-right differences or mild hypertonia, was present.

The quality of movement was assessed by means of visual Gestalt perception. Normal movements are performed fluently and are variable in speed, intensity and force. Abnormal movements lack one or more of these characteristics. Spontaneous motility was observed in gross and fine motor functions. During the assessment the quality of gross and fine motor movement was recorded according to three categories: speed, smoothness and adequacy (Table 7.2). A subscore for the quality of gross and fine movement (min 0, max 5) and a total score (min 0, max 10) were calculated.

Developmental assessment

1. The Dutch version of the Motor Scale of the Mc Carthy Scales of Children's Abilities (Mc Carthy 1972, Van der Meulen and Smrkovsky 1985) was used to assess motor performance. This scale consists of more complex sensory-motor tasks, requiring instruction and demonstration.

2. Cognition was assessed by the Dutch adaptation of the Kaufman Assessment Battery for Children (K-ABC) (Kaufman and Kaufman 1983, Neutel *et al.* 1989). The K-ABC measures Intelligence (the Mental Processing Composite, MPC) and Achievement (the Achievement Scale). The Intelligence scale is based on neuropsychological theories of mental processing and consists of 2 subscales of Sequential and Simultaneous Processing.

3. Receptive language was assessed by the Dutch version of the Reynell Developmental Language Scale B revised (Reynell, 1969; Boomers & Muggen 1982). Expressive language was scored on an 8 points scale representing 8 features of language structure with increasing complexity (Goorhuis-Brouwer, 1985).

Table 7.1 Neurological profile

CLUSTERS	CONTENT		CRITERIA FOR MND
1. Posture L+R	- posture during sitting, walking and lying		- minor postural deviations such as collapse, asymmetries, hyperextension
2. Muscle Tone L+R	- muscle tone of arms and legs		- minor changes of muscle tone
3. Reflexes L+R	- biceps - knee - ankle - footsole response		- increased or decreased intensities/thresholds - asymmetries - Babinski sign
4. Trunk Coordination L+R	- trunk rotation sitting and standing - reaction to push sitting - reaction to push standing	3=cannot without support 2=no differentiation sh. hip 1=some rotation <30° 0=good rotation 3=falls aside 2=uses arms lateral support 1=lift hands from knees 0= balance, no arm mvts 2=falls, must be caught 1=uses arms/feet for support 0= balance, no support	- total score >90th percentile
5. Gross Motor Function	- sitting up from supine - standing up from sitting on the floor - running - turning	2=cannot without hands 1=can, but lifts legs 0=can, without lifting legs 3=cannot 2=with help 1=no help, with rotation 0=no help, without rotation 2=cannot 1=runs, can't make speed 0=runs well, good speed 3=cannot 2=no differentiation neck, shoulder 1=no differentiation shoulder, leg 0=good rotation of hips and legs	- total score >90th percentile
6. Fine Motor Function L+R	- type of grasping - number of objects - finger movements - hand coordination - arm coordination	5=no grasping 4=palmar 3=radial palmar 2=scissor 1=inferior pincer 0=pincer 3=unable to hold 2=1 objects one hand 1=1 objects two hands 0=2 objects one hand 2=marked overshoot 1=some overshoot 0=adequate 3=dyskinesia 2=marked tremor 1=slight tremor 0=no tremor 2=marked overshoot 1=some overshoot 0=adequate	- total score >90th percentile

Table 7.2 Criteria for the quality of gross and fine motor movement

QUALITY OF MOVEMENTS	CRITERIA
Speed	0=Movements are performed at a variable tempo. 1=Movements are invariably performed very rapidly or very slowly.
Smoothness	0=Movements are smooth and supple. 1=Movements are sometimes abrupt or jerky. 2=Movements are very awkward abrupt and jerky.
Adequacy	0=Movements are adequate and easily goal directed. 1=Movements are sometimes inadequate. 2=Movements are mainly inadequate.

Data analysis

The statistical package Statgraphics 4.0 was used. Univariate statistical analysis was performed to study associations between separate items. To examine the significance of minor neurological dysfunction and the quality of movement to neonatal cerebral damage and developmental outcome, stepwise multiple regression analyses were done. A p value of <0.05 was considered to be significant.

6.4 RESULTS

Neurological examination

Nineteen (29%) of the 66 children were classified as having minor neurological dysfunction. Results are presented in detail in Table 7.3. The mean total score for the quality of movement was 0.8 (SD 1.3); 0.4 (SD 0.8) for the gross motor and 0.4 (SD 0.9) for the fine motor subscale. The quality of movement in relation to minor neurological dysfunction is presented in Table 7.4. The quality of gross as well as fine movement was significantly lower in children with minor neurological dysfunction.

Neonatal cerebral damage

Twenty of the 66 children (30%) had normal neonatal cerebral ultrasound; 19 (29%) abnormal without ventriculomegaly; 26 (39%) abnormal with ventriculomegaly; and 1 (2%) abnormal with intraparenchymal damage. Thirty-four of the 66 children (52%) had normal neonatal neurological examinations; 26 (39%) mildly; and 6 (9%) definitely abnormal neurological examinations.

Table 7.3 Signs of minor neurological dysfunction

NEUROLOGICAL PROFILE	SIGNS OF MINOR NEUROLOGICAL DYSFUNCTION	
	Absent	Present
1. Posture	44 (67%)	22 (33%)
2. Muscle Tone	56 (85%)	10 (15%)
3. Reflexes	56 (85%)	10 (15%)
4. Trunk Coordination	61 (92%)	5 (8%)
5. Gross Motor Function	61 (92%)	5 (8%)
6. Fine Motor Function	59 (88%)	7 (12%)
Minor Neurological Dysfunction (More than 1 sign)	47 (71%)	19 (29%)

Table 7.4 The quality of movement in relation to minor neurological dysfunction

NEUROLOGICAL EXAMINATION			
Quality of Movement	Minor Neurological Dysfunction		
	Absent(n=47)	Present(n=19)	Total
Gross Movement Mean (SD)	0.2 (0.6)	0.9 (1.1)**	0.4 (0.8)
Fine Movement Mean (SD)	0.2 (0.5)	1.2 (1.2)***	0.4 (0.9)
Total Score Mean (SD)	0.3 (0.8)	2.1 (1.6)***	0.8 (1.3)

Student T, **=p<0.01, ***=p<0.001

Table 7.5 Developmental assessments at 3.6 years of age

DEVELOPMENTAL ASSESSMENTS		
Type of assessment	Mild Delay (<-1SD)	
	Absent	Present
Mc Carthy -Motor Scale	52 (84%)	10 (16%)
K-ABC -Sequential Subscale	57 (86%)	9 (14%)
-Simultaneous Subscale	38 (58%)	28 (42%)
-Achievement Scale	39 (59%)	27 (41%)
Language -Comprehension	40 (62%)	24 (38%)
-Expression	44 (67%)	22 (33%)

Developmental assessments

Results of the developmental assessments are summarized in Table 7.5. Of the 66 children 52 were assessed on the Mc Carthy motor scale and 4 refused to cooperate. On the K-ABC all children could be assessed. Language comprehension could be assessed in 64 children, language expression was assessed in all children.

MND and the quality of movement in relation to neonatal cerebral damage

Correlations of minor neurological dysfunction and the quality of movement in relation with neonatal cerebral damage are presented in Table 7.6. There was a significant correlation of both abnormal neonatal cerebral ultrasound and abnormal neonatal neurological findings to minor neurological dysfunction. Of the individual items of the neurological profile, the results were significant for posture and reflexes in relation to neonatal cerebral ultrasound and for posture in relation to neonatal neurology. Cerebral ultrasound findings were significantly correlated to the quality of movement, but neonatal neurological findings were not.

Table 7.6 Correlations of the neurological examination at age 3.6 and neonatal cerebral damage

NEUROLOGICAL EXAMINATION	INDICATORS OF NEONATAL CEREBRAL DAMAGE	
	Cerebral Ultrasound	Neonatal Neurology
A Neurological Profile		
1. Posture	.25*	.28*
2. Tone	.19	.20
3. Reflexes	.29*	.20
4. Trunk coordination	.23	.19
5. Gross Motor Function	.16	.03
6. Fine Motor Function	.12	.07
Minor Neurological Dysfunction	.38**	.32**
B Quality of Movement		
Gross Movement	.20	.12
Fine Movement	.29*	.03
Total Score	.32**	.06

Spearman rank correlation coefficient, *=p<0.05, **=p<0.01,

MND and the quality of movement in relation to the developmental assessments
Correlations of minor neurological dysfunction and the quality of movement in relation to the developmental assessments are presented in Table 7.7. The Mc Carthy motor scale was significantly correlated with signs of minor neurological dysfunction (eg. posture, tone, reflexes and fine motor function) as well as with the quality of gross and fine movement. Simultaneous processing was significantly correlated with the quality of gross movement. Receptive and expressive language was significantly correlated with the quality of fine movement.

Table 7.7 Correlations of the neurological examination and the developmental assessments at age 3.6

NEUROLOGICAL EXAMINATION	DEVELOPMENTAL ASSESSMENTS					
	Mc Carthy	Kaufman Assessment Battery for Children			Language	
	Motor	Sequential	Simultaneous	Achievement	Comprehension	Expression
A Neurological Profile						
1. Posture	-.28*	-.16	-.03	.18	-.10	-.05
2. Tone	-.33**	-.05	-.09	-.02	-.18	-.12
3. Reflexes	-.39**	.04	-.06	.12	-.19	-.20
4. Trunk Coordination	-.21	.03	-.06	.12	.11	-.03
5. Gross Motor Function	-.22	.05	-.10	.16	-.09	-.11
6. Fine Motor Function	-.34**	-.10	-.19	.14	-.05	-.13
Minor Neurological Dysfunction	-.51***	-.15	-.24	.09	-.21	-.20
B Quality of Movement						
Gross Movement	-.57***	-.13	-.35**	-.05	-.12	-.07
Fine Movement	-.34**	-.03	-.19	-.12	-.28*	-.29*
Total Score	-.61***	-.16	-.34**	-.12	-.26*	-.21

Spearman rank correlation coefficient, *=p<0.05, **=p<0.01, ***=p<0.001

Table 7.8 Minor neurological dysfunction and the quality of movement in relation to neonatal cerebral damage and the developmental assessment, stepwise multiple regression analysis

	MINOR NEUROLOGICAL DYSFUNCTION AND QUALITY OF MOVEMENT		
	Significant Independent Variables	ADJ-R^2	p
NEONATAL CEREBRAL DAMAGE			
Cerebral Ultrasound	Minor Neurological Dysfunction	.13	0.002
Neonatal Neurology	Minor Neurological Dysfunction	.08	0.01
DEVELOPMENTAL ASSESSMENTS			
Mc Carthy – Motor Scale	Quality of Movements Minor Neurological Dysfunction	.31 .34	0.001 0.04

K-ABC   – Sequential Subscale
   – Simultaneous Subscale
   – Achievement Scale
	-
	Quality of Movements
	-
		-
		.07
		-
			ns
			0.02
			ns

Language – Comprehension – Expression	- -	- -	ns ns

Multiple regression analyses

To determine the significance of minor neurological dysfunction and the quality of movement for neonatal cerebral damage and development at age 3.6, stepwise multiple regression analyses were done. For neonatal cerebral damage, minor neurological dysfunction was the best independent variable explaining 13% of the variance in neonatal cerebral ultrasound findings and 8% of the variance in neonatal neurology. The quality of movement (p = 0.001) together with minor neurological dysfunction (p = 0.04) explained 34% of the variance of the motor scale. The quality of movement alone explained 7% of the variance of the simultaneous subscale of the Kaufman Assessment Battery for children (Table 7.8).

7.5 DISCUSSION

Preschool VLBW children are not only at risk for handicaps, but have also a wide range of minor impairments (Veen *et al.* 1991). In our study group of VLBW children, all treated by neonatal intensive care, 13 of the 79 (16%) children had a handicap at 3.6 years of age. Of the remaining 66 non-handicapped children 19 (29%) were classified as having minor neurological dysfunction at 3.6 years of age. Minor neurological dysfunction was significantly related to the quality of movement. They related differently to neonatal cerebral damage and developmental outcome, however.

Minor neurological dysfunction at preschool age significantly related to neonatal cerebral damage. In the neurological profile the traditional neurological items such as

posture and reflexes were significantly related to neonatal cerebral ultrasound. Muscle tone was of limited value possibly due to difficulties in reliable assessment because of lack of cooperation of children at this age.

The quality of movement was the best independent variable for more complex sensory motor tasks, explaining 31% of the variance, while the assessment of more traditional signs of minor neurological dysfunction contributed an additional 3% to the explained variance only. Huttenlocher et al. (1992) suggested that a small battery of tests such as walking on toes, walking on heels, tandem gait and touch localization are often more useful in the detection of children with learning difficulties than the more traditional items of the neurological examination. This proposed battery is based on motor tasks, for which task-oriented cooperation of the child is a prerequisite. At pre-school age, observation of the quality of movement appears to be a better method. In premature infants, the quality of general movements, analyzed from video recordings during neonatal intensive care treatment, has been shown a promising method for the prediction of outcome at 2 years of age (Ferrari *et al.*1990). Whether there is any relationship between the neonatal quality of movement and at 3,6 years of age, and whether the quality of movement at 3.6 years of age is also a good predictor for later outcome is not yet known. Nevertheless, research should concentrate on the further development of an instrument for the assessment of the quality of movement in preschool children. Such research is in progress in the Institute for Developmental Neurology in Groningen by one of us (M.S.H.). Part of it has been described (Touwen *et al.* 1992).

In our study of preschool children the quality of movement was related to cognitive and language development, whereas minor neurological dysfunction was not. In older children a relation between minor neurological dysfunction and learning and behavioral problems has been described (Hadders-Algra *et al.* 1988b). At preschool age, many more complex items for the assessment of minor neurological dysfunction, such as for discoordination, cannot be used yet. At that age the quality of movement might be a better reflection of higher cortical functions than signs of minor neurological dysfunction. Obviously follow-up into school age is essential.

We conclude that the assessment of age related signs of minor neurological dysfunction and of the quality of movement are both important in the neurological examination at preschool age. The assessment of signs of minor neurological dysfunction is useful in the evaluation of sequelae of cerebral damage, as detected by neonatal

cerebral ultrasound. The quality of movement might be predictive of later learning prob-
lems. The design of a more detailed instrument for the assessment of the quality of
movement is in progress (M.S.H.). Such an instrument might become a diagnostic tool
to aid early identification of children at risk for later learning problems.

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CHAPTER 8

HEARING AND LANGUAGE

IN PRESCHOOL VERY LOW BIRTHWEIGHT CHILDREN

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8.1 SUMMARY

To get more insight into preschool language and hearing in high risk VLBW children, we conducted a prospective study in a cohort of 79 children. The prevalence of language impairment and hearing loss at age 3-4 years, their relationship to each other as well as to perinatal conditions, neurodevelopmental outcome and the home environment are described. Mild hearing loss was found in 26%, moderate hearing loss in 13% and severe hearing loss in 3% of the children. None of the children was deaf. Abnormal tympanometry was found in 57% of the children. Hearing loss at age 4 years was related to a less optimal neonatal condition and was not related to the obstetrical condition or to neonatal cerebral ultrasound findings. Language impairment was found in 21% of the children at age 3.6 years. Receptive and expressive language were not related to perinatal conditions. There was no relation between the language assessments and the audiological assessments. Cognition and the home environment of the child were the only independent variables in the prediction of language in preschool VLBW children.

8.2 INTRODUCTION

Infants born with birthweights less than 1500 grams (VLBW) are exposed to numerous potentially damaging events in the neonatal period which may result in an increased risk of sensorineural hearing loss. In addition VLBW infants, who are often ventilatory dependent with nasogastric tubes, are particularly prone to otitis media with effusion (OME) and associated conductive hearing losses (1,8,15,28,33). VLBW children are known to have an increased prevalence of language delay (16,22). Perinatal risk factors

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(22,18) and neonatal cerebral damage (2,5,17) have been associated with early language delay in VLBW infants. At 3 years of age VLBW children do not appear to have overcome this language delay (14). Language delay might be associated with hearing loss, but is also common in children with mental retardation (32). Moreover social factors play an important role in preschool language development (9,29).

VLBW children are at multiple risk for language delay, due to hearing loss, mental retardation and social risk. Elucidating the relationship between hearing loss and later language development in VLBW children is complicated by this multiplicity of factors which co-determine outcome. For this reason we undertook a prospective follow-up study in a cohort of high risk VLBW children. The aims of our study were:

1.   To establish the prevalence of hearing loss and language impairment in preschool high risk VLBW children.
2.   To examine whether perinatal conditions have an influence on hearing and language in preschool years.
3.   To determine the relationship of receptive and expressive language with hearing, neurodevelopmental outcome and the home environment of the child.

8.3 PATIENTS AND METHODS

Study group

This study is part of a larger longitudinal study on VLBW infants. Part of the data have been described elsewhere (39). The total study group consisted of all preterm VLBW children (birthweight <1500 grams, gestational age <36 weeks), who were admitted to the Neonatal Intensive Care Unit of the Sophia Children's Hospital in Rotterdam (a regional tertiary intensive-care unit) between August 1, 1985 and August 1, 1986 within 48 hours after birth (n=114). Twenty-three infants (20%) died in the neonatal period or in the first year of life. Twelve children (10%) were not available for the whole follow-up period because of migration (n=6), lack of interest (n=3) or inability (n=3) to cooperate on the part of the parents. Of the remaining 79 children there were 34 boys and 45 girls. Birthweights ranged from 690 to 1495 grams (M=1136, SD 213). Gestational ages ranged from 25 to 35 weeks (M=30.4, SD 2.3). Obstetrical and neonatal conditions were recorded in a modified version of the Prechtl list of obstetrical and neonatal optimality (39).

Neonatal cerebral ultrasound findings were classified as follows:

- Group 0: Normal.

- Group 1: Abnormal without ventriculomegaly.

- Group 2: Abnormal with ventriculomegaly.

- Group 3: Abnormal with intraparenchymal damage.

Audiological examination

Systematic hearing assessment by pure tone audiometry and tympanometry was carried out at the age of 4 years by a specially trained assistant. In a subgroup, brainstem electric response audiometry (BERA) had been performed at a younger age when indicated by clinical symptoms of hearing loss. To maximize cooperation, the audiometric assessment at four years was done at home. The examination consisted of:

1. Pure tone audiometry at the frequencies 0.5, 1, 2, and 4 kHz with air-conducted stimulation only (Madsen, DSA 84). Pure hearing loss was classified according to the Fletcher-Index (the mean of the losses at 0.5, 1, and 2 kHz) for the most abnormal ear:

- No hearing loss   :Fletcher-Index < 20

- Mild loss   :Fletcher-Index 20-35

- Moderate loss   :Fletcher-Index 35-60

- Severe loss   :Fletcher-Index 60-85

- Deaf   :Fletcher-Index > 85

2. Tympanometry was done with a screening-tympanometer (Welch Allyn, MicroTymp). Tympanograms were typed as A, B, or C according to the conventional criteria (10). Type A tympanograms are normal, type B indicates a fluid filled middle ear, and type C indicates abnormally low pressure in the middle ear cavity, perhaps with partial fillings with fluid. Children were considered to be free of middle ear problems only if a normal tympanogram was found for both ears.

3. ENT-history was recorded as to ear disorders, treatment, and audiological examinations. The placement of ventilation tubes was considered proof for persistent middle ear disorders.

Language development

At a corrected age of 3.6 years (± 2 weeks) language was assessed by an experienced developmental pediatrician who did not know the perinatal history. To assess language

comprehension the Dutch version of the Reynell Developmental Language Scale B revised (4,26) was used. Bilingual children were assessed in Dutch. In case of doubt the mother was asked to translate. Children with a score <-2SD were considered to have a receptive language impairment. Expressive language was scored on an 8 points scale representing 8 features of language structure of increasing complexity (12). Children who were unable to speak in 3 word sentences by the age of 3.6 years (score 5) were considered to have an expressive language impairment. A general language impairment was defined as an expressive as well as a receptive impairment.

Neurodevelopmental assessment

At age 3.6 years, cognition was assessed by the Dutch adaptation of the Kaufman Assessment Battery for Children (20,24). This cognitive battery measures Intelligence (the Mental Processing Composite, MPC) and Achievement (the Achievement Scale). Both scales have a mean value of 100 and a SD of 15. Children with a score <70 on both scales were considered to be mentally handicapped.

A standardized neurological examination adapted from Touwen (36) was done. Findings were classified as normal (score 0), minor neurological dysfunction (score 1), or abnormal (score 2). A child was called abnormal when a neurological disorder, resulting in a handicap such as cerebral palsy, was diagnosed.

Home Environment

The home environment of the child was assessed by the Dutch version of the Home Observation for the Measurement of the Environment (6,19). At age 3.6 years the Home Inventory consists of 55 items (maximal total score = 55) and seven categories of social stimulation important in toddler development. A total score and seven subscores were computed. A total score less than the 25th percentile was considered as a low stimulating home environment.

Data analysis

The statistical package Statgraphics 4.0 was used. Univariate statistical analysis was performed to study associations between separate items. A stepwise multiple regression analysis was used to determine how well perinatal factors (obstetrical and neonatal optimality score, neonatal cerebral ultrasound) predicted the two outcome variables (audiological and language assessments) and to determine how well the

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preschool assessment (hearing, cognition, neurology, home environment) predicted receptive and expressive language. A p-value of <.05 was considered significant.

8.4 RESULTS

In 54 of the 79 children audiometry resulted in a reliable audiogram at 4 years of age. In another 7 children hearing had been assessed by brainstem electric response audiometry at an earlier age. The prevalence of hearing loss is given in Table 8.1. The hearing loss was bilateral in 14 of the 16 children with mild, 3 of the 8 children with moderate and 1 of the 2 children with severe hearing loss. None of the children used a hearing aid. Tympanometry was available in 63 of the 79 children. The results are presented in Figure 8.1. Nine of the 79 children (11%) had one (n=6) or more (n=3) ventilation tube placements before 4 years of age. There was a significant correlation between the audiometric and the tympanometric results (correlation coefficient .48).

Table 8.1 Prevalence of hearing loss in VLBW children

HEARING LOSS	AUDIOLOGICAL EXAMINATION		
	Audiometry n (%)	Bera n (%)	Total n (%)
Absent (FI <20)	32 (59%)	3 (42%)	35 (58%)
Mild (FI 20-35)	14 (26%)	2 (29%)	16 (26%)
Moderate (FI 35-60)	8 (15%)	0 (0%)	8 (13%)
Severe (FI 60-85)	0 (0%)	2 (29%)	2 (3%)
Deaf (FI >85)	0 (0%)	0 (0%)	0 (0%)
Total	54 (88%)	7 (12%)	61 (100%)

In 75 of the 79 children receptive language could be assessed (mean 38.7, SD 8.8). Two children (one with a mild and one with a severe hearing loss) were so severely handicapped that the Reynell was an inappropriate instrument, two children refused to cooperate. Expressive language could be evaluated in all cases (mean 6.6, SD 1.1). There was a significant correlation between receptive and expressive language (correlation coefficient .73). Seventeen of the 79 children had a language impairment. The prevalence of receptive, expressive as well as general language impairments is presented in Figure 8.2.

Mean values of the receptive and expressive language assessments in relation to the audiological assessments are presented in Table 8.2. There were no significant relations between the audiological and language assessments.
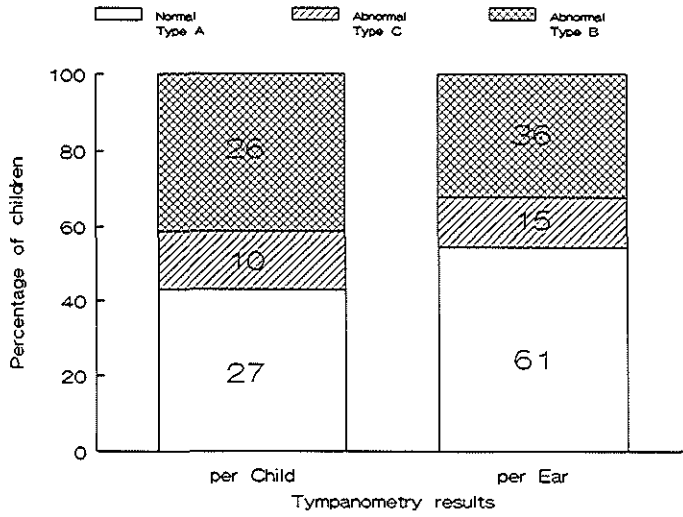
**Figure 8.1** Tympanogram in VLBW children at 4 years of age.
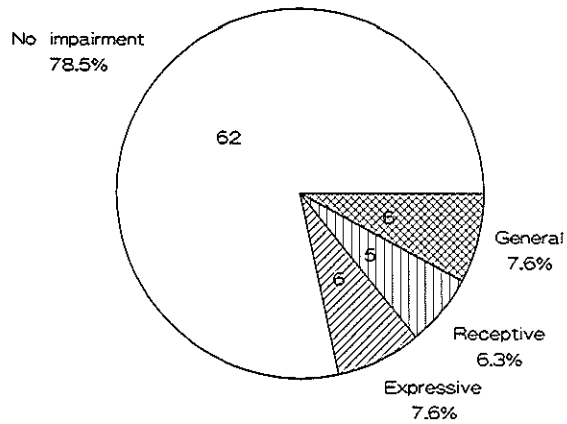
Figure 8.2 Prevalence of language impairment in VLBW children

Table 8.2 Language assessments in relation to the audiological assessments

| | | LANGUAGE | | | |
| | | Comprehension | | Expression | |
	n	Mean (SD)	T-test	Mean (SD)	T-test
HEARING LOSS					
absent	35	38.0 (9.3)	-	6.8 (1.2)	-
mild	15	38.3 (6.2)	ns	6.2 (1.1)	ns
moderate/severe	9	42.0 (7.2)	ns	7.2 (0.8)	ns
TYMPANOMETRY					
normal	27	36.3 (9.1)	-	6.6 (0.9)	-
abnormal	35	41.6 (6.7)	ns	7.0 (0.9)	ns
VENTILATION TUBE PLACEMENT					
absent	68	38.8 (8.5)	-	6.6 (1.1)	-
present	9	38.3 (11.1)	ns	6.9 (0.9)	ns

In a stepwise multiple regression analysis of perinatal factors (obstetrical and neonatal optimality score, neonatal cerebral ultrasound) as predictors to hearing (score 0 = no hearing loss, score 1 = mild hearing loss, score 2 = moderate to severe hearing loss), hearing was best predicted by the neonatal optimality score alone (p = 0.02) which accounted for 16% of the variance. Children with normal hearing had a higher optimality score in the neonatal period. The relation of neonatal optimality to hearing loss is presented in Figure 8.3. Hearing in relation to the individual items of the neonatal scale is presented in Table 8.3. Infants with hypocalcaemia and anaemia at admission had significantly more hearing loss than infants without these neonatal conditions. Hearing in relation to neonatal cerebral ultrasound is presented in Table 8.4. Comparing the children with children with and without hearing loss there were no significant differences between children with normal and abnormal neonatal cerebral ultrasound findings (group 1, group 2 and group 3).

In a stepwise multiple regression analysis of perinatal factors (obstetrical and neonatal optimality score, neonatal cerebral ultrasound) as predictors to receptive and expressive language, perinatal factors were not significant predictors of language.

In a stepwise multiple regression analysis of hearing, cognition, neurology and home environment as predictors to receptive and expressive language, receptive language was predicted best by cognition (p < 0.001) together with the home environment (p < 0.001) explaining 58% of the variance. As well expressive language was predicted best by cognition (p < 0.001) together with the home environment (p = 0.006) explaining 42% of the variance. Seven of the 17 children with a language impairment and none of the 62 non-language impaired children had a mental handicap.

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Table 8.3 Hearing at age 4 in relation to neonatal conditions

NEONATAL CONDITIONS	HEARING LOSS	
	Absent (n=35)	Present (n=26)
1.Ventilatory assistance	21 (60%)	21 (81%)
2.IRDS (clinical and X ray)	12 (34%)	15 (58%)
3.BPD (oxygen treatment > 28 days)	12 (34%)	12 (46%)
4.Apnoea	19 (54%)	19 (73%)
5.PDA (confirmed by ultrasound)	7 (20%)	7 (27%)
6.Pneumothorax	3 (6%)	0 (0%)
7.Hyperbilirubinemia (150umol/l)	19 (54%)	16 (61%)
8.Sepsis/meningitis (bloodcult +)	4 (11%)	6 (23%)
9.Seizures	1 (3%)	1 (4%)
10.Shock	2 (6%)	3 (11%)
11.Hypoglycemia (Gluc<2.0)	13 (37%)	12 (46%)
12.Hypocalcaemia (Ca <1.75)	5 (14%)	10 (38%)*
13.Anaemia at admission (Ht <0.5)	4 (11%)	10 (38%)*

IRDS=Idiopathic Respiratory Distress Syndrome, BPD=Broncho Pulmonary Dysplasia, PDA=Persistent Ductus Arteriosus
Fisher's Exact   *=p<0.05

Table 8.4 Hearing at age 4 in relation to neonatal cerebral ultrasound findings

| NEONATAL CEREBRAL ULTRASOUND	HEARING LOSS	
	Absent (n=35)	Present (n=26)
Group 0 (Normal)	12 (34%)	4 (15%)
Group 1 (Abnormal, ventriculomegaly -)	9 (26%)	8 (31%)
Group 2 (Abnormal, ventriculomegaly +)	10 (29%)	11 (42%)
Group 3 (Abnormal, intraparenchymal damage)	4 (12%)	3 (11%)

Fisher's Exact, ns.
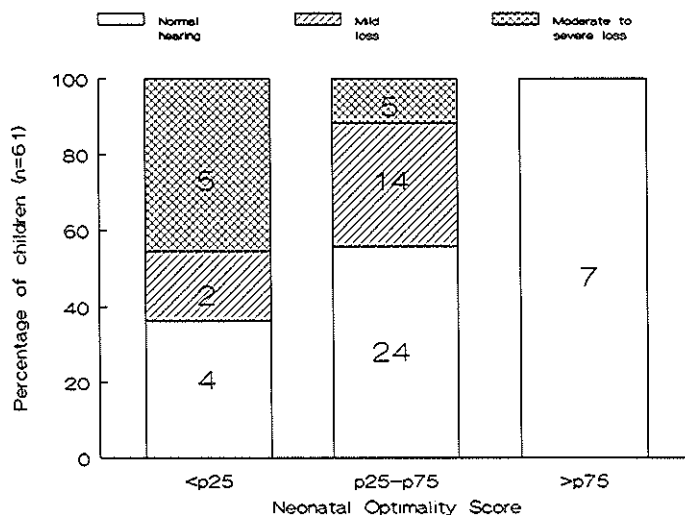
Figure 8.3 Neonatal optimality score and hearing at 4 years of age.

Table 8.3 Correlations of the subscales of the Home Inventory and Language at 3.6 years of age

HOME INVENTORY	LANGUAGE	
	Comprehension	Expression
Subscales		
I Learning Stimulation	.60***	.39***
II Language Stimulation	.43***	.40***
III Physical Environment	.42***	.37**
IV Warmth and Affection	.29**	.10
V Academic Stimulation	.51***	.43***
VI Modeling	.48**	.34**
VII Variety in Experience	.49***	.43***
VIII Acceptance	.18	.06
TOTAL	.66***	.47***

Spearman rank correlation coefficient, *=p<0.05, **p=<0.01, ***p=<0.001

Nine of the 17 language impaired children and 11 of the 62 non-language impaired children came from a low stimulating home environment. Only 4 of the 17 children had a language impairment without mental retardation or a low stimulating home environment. Correlation coefficients of the different subcategories of the Home Inventory with receptive and expressive language are presented in Table 8.5. Language was correlated to all subscales of the Home Inventory except acceptance of the child and warmth and affection.

8.5 DISCUSSION

In our cohort of high risk VLBW children the prevalence of hearing loss was 42%. Mild hearing loss (26%) was more frequent than moderate (13%) to severe (3%) hearing loss and none of the children was deaf. In other studies of LBW infants a prevalence of 14 to 23% of hearing loss was found (1,11). These different percentages may be explained by differences in neonatal risk but also by different definitions of hearing loss. Recent evidence suggests that children with unilateral as well as bilateral minimal hearing loss can experience significant communication and educational difficulties at school age (35). Therefore we deliberately included unilateral as well as bilateral hearing loss. The prevalence of 46% abnormal tympanography curves found in our study group is comparable to the 46% found in another study of LBW infants (37). The percentage of 32% type B tympanograms found in our study is much higher than the 22% type B tympanograms found in an epidemiological study of the Dutch population at 4 years of age (40).

The prevalence of language impairment in our study group was 22%. Neither expression nor receptive language was related to hearing loss, tympanometry results or ventilation tube placement. In studies of non-VLBW children sensorineural hearing loss as well as persistent OME has a negative effect on preschool expressive language development and learning at school age (3,21,25,27,30,38). That we did not found this relation in our study group may be explained by the fact that systematic tympanometry and audiometry was only done once at the age of 4. An adequate auditory input is of particular importance in early language development and the critical period for language development is before the age of 3 (13,25). Despite the high percentage of abnormal tympanometry at age 4, only 9 children had ventilation tube placements during the first 4 years of life. Our study group might thus be considered undertreated. Lack of appropriate treatment during the critical period may have resulted in language impairment, even though language ability was not related to hearing loss, measured at the age of 4.

Of the perinatal conditions, the neonatal optimality score alone best predicted hearing at age 4. Allthough hyperbilirubinaemia was treated promptly with phototherapy and aminoglycoside antibiotics were not used, neonatal conditions still constitute a significant cause of hearing loss in VLBW children. As in other studies (7), the total neonatal score was found to be a better predictor for hearing loss than any single neonatal condition or neonatal cerebral ultrasound.

There was no relationship between perinatal factors and receptive and expressive language. Other studies (2,5,17) found a direct relation between neonatal cerebral damage and language. However, in these studies language was assessed during the second year. Largo et al. (22) found that language development became increasingly dependent on social class after 14 months of age. In a previous paper we described that neonatal cerebral damage was a good predictor for cognition (39). In the present study cognition and the home environment of the child were good predictors of preschool language. These results suggest that at 3.6 years of age the direct relation between neonatal cerebral damage and language is probably washed out by the influence of the home environment. Preschool language impairment has been implicated as an indicator for learning problems at school age (22,31). Early identification of language delayed children and timely intervention might well ameliorate some of these long-term problems.

In conclusion the present study supports previous observations concerning the high prevalence of hearing loss and language impairment in high risk VLBW infants. There was no direct relation between the audiological and language assessment in the preschool years. The hearing impairment seen in this population is serious enough, however, to produce problems with sound localization, speech recognition in the presence of background noise, and academic progress (35). Audiological assessments must be made earlier in order to identify these problems. Systematic brain stem electric response audiometry at the age of 3 to 6 months (34) and regular audiological monitoring for progressive sensorineural hearing loss and/or possible conductive hearing loss from OME might have resulted in the placement of more ventilation tubes. In addition, prescription of hearing aids should be considered in cases with persistent hearing loss (23). Our results demonstrates that preschool language impairment in VLBW children is associated with cognition and the child's home environment rather than with hearing loss at age 4. Regular monitoring of language skills and early intervention programs to stimulate the development of the child are indicated. The effect of such a follow-up regime on hearing and language development in high risk VLBW children is subject to further study.

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CHAPTER 9

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CHAPTER 9

VISUAL FUNCTIONS IN RELATION WITH
NEONATAL CEREBRAL ULTRASOUND, NEUROLOGY AND COGNITIVE DEVELOPMENT
IN VERY LOW BIRTHWEIGHT CHILDREN.

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9.1 SUMMARY

In order to determine the relationship between visual functions and neonatal cerebral ultrasound, neurological examinations and cognitive development, a prospective longitudinal study was conducted in 69 high risk very low birthweight children. Visual development was studied at 1 and 2.6 years of corrected age by assessment of visual acuity, binocular visual fields, optokinetic nystagmus and strabismus. Visual impairments were found in 33% at age 1 and in 28% at age 2.6. Visual impairments were related to intraparenchymal damage, as detected by neonatal cerebral ultrasound, as well as to abnormal neurological examinations and lower mean developmental indices. A stepwise multiple regression analysis with neonatal cerebral ultrasound as the dependent variable and visual functions at ages 1 and 2.6 and neurological examinations at ages 1 and 2 as independent variables, however, demonstrated that standardized neurological examinations were better markers of neonatal cerebral damage than visual functions. In cognitive development at ages 1 and 2, the neurological examination at age 1 was the most important variable. In cognitive development at age 3.6, visual functions at age 2.6 were more important. Early visual impairments might thus influence later cognitive development. The effectiveness of appropriate early intervention strategies to stimulate visual and cognitive development in infants with less severe visual impairments should be subject to further study.

9.2 INTRODUCTION

Very low birthweight (VLBW) infants are at risk for mental, motor and sensory abnormalities including the visual system (20). Visual impairments are found in up to 73% of high risk VLBW infants at 6 months of age, with a gradual improvement of visual functions thereafter. Nevertheless in 29% of high risk VLBW infants, visual impairments are still present at 1 year of age (19). Ophthalmological problems like retinopathy of prematurity, severe myopia and astigmatism have been found frequently (3). However, most visual impairments seem to be of cerebral rather than of ophthalmological origin. Perinatal hypoxia, a frequent complication in VLBW infants, is a risk factor for visual impairments (2,4). A high prevalence of visual impairments has also been found in VLBW infants with abnormal neonatal cerebral ultrasound and neurological abnormalities (19,21) and in older children with motor and mental handicaps (8,12). Visual impairments might thus be a marker for cerebral damage and consequently might be predictive of later neurodevelopmental outcome.

Severe visual impairments can also affect development by a different process of information gathering (6). In addition, the development of children with visual impairments may be influenced by associated motor or mental deficits. Early detection of visual impairment is important for early treatment of ophthalmological abnormalities and for counseling parents in case of severe visual impairment. The significance of less severe visual impairments at an early age for later cognitive development is, however, unknown.

In this paper a prospective longitudinal study in a cohort of 69 high risk VLBW children from birth to 3.6 years of age is described. Visual development was studied at 1 and 2.6 years of age in relation to neonatal cerebral ultrasound, neurology and cognitive development. The aim of this study was to investigate:
1. Whether visual impairments at 1 and 2.6 years of age are markers of neonatal cerebral damage.
2. Whether visual impairments at 1 and 2.6 years of age can influence cognitive development.

9.3 PATIENTS AND METHODS

Study group

This study is part of a longitudinal study on VLBW infants (22). The total study group consisted of all preterm VLBW children (birthweight < 1500 grams, gestational age < 36 weeks), admitted to the Neonatal Intensive Care Unit of the Sophia Children's Hospital in Rotterdam (a regional tertiary intensive-care unit) between August 1, 1985 and August 1, 1986 within 48 hours after births (n = 114). Twenty-three infants (20%) died in the neonatal period or in the first year of life. Twenty-two children (19%) were not available for the whole follow-up because of migration (N = 6), lack of interest (N = 6) or inability (N = 10) to cooperate on the part of the parents. Of the remaining 69 children 30 were boys and 39 girls. Gestational age ranged from 25 to 35 weeks (M = 30, SD = 2). Birthweight ranged from 690 to 1495 grams (M = 1142, SD = 215). Obstetrical and neonatal conditions were recorded on an obstetrical and neonatal scale.

Neonatal cerebral ultrasound findings were classified as follows: Normal (score 0), abnormal without ventriculomegaly (PIVH I-II, periventricular flaring and/or other lesions, score 1), abnormal with ventriculomegaly (PIVH III, periventricular flaring and/or other lesions, score 2) and abnormal with intraparenchymal damage (PIVH IV and/or PVL, score 3) (23).

Visual development

Visual functions were assessed at 1 and 2.6 years of corrected age, by experienced examiners who were blind as to the neonatal findings.

- Binocular visual acuity was assessed with a modified version (7) of the acuity card procedure (10). This method is based on the preference of the infant for patterns in a uniform stimulus field, when both are presented simultaneously. Acuity was taken as the finest grating for which the observer made a significant proportion of correct judgments. Results of visual acuity were compared with normal values obtained in earlier studies (11). Values below the 5th percentile were considered as abnormal.

- Binocular visual fields were assessed using kinetic perimetry with an arc perimeter along horizontal and vertical meridians (12). Field asymmetries of ≥ 13 degrees and values below the 2.5th percentile per meridian were considered as abnormal.

- Binocular optokinetic nystagmus (OKN) was tested by observing eye movements in response to movement of a large piece of paper, covered with randomly spaced dots

(dot size 1 square cm), about 25 cm in front of the child's head, in the right or left direction (velocity about 30°/sec). Asymmetrical optokinetic nystagmus and spontaneous nystagmus were considered as abnormal.

- For the detection of strabismic deviations reflex images, the cover/uncover test, eye motility and the prisms fusion test were used.

Ophthalmological examination

Screening for retinopathy of prematurity was performed at regular intervals in all infants and was started as soon as the clinical condition allowed, if possible 8 weeks before term until a corrected age of 8 weeks after term (1). The retinal findings were staged according to the international classification (15). In addition children were seen for objective refraction when indicated by clinical symptoms of vision loss.

Neurodevelopmental assessment

Independent of the visual assessment, a neurodevelopmental assessment took place at a corrected age of 1, 2 and 3.6 years of age by an examiner who was blind as to the neonatal findings (NW).

- A standardized neurological examination (16,17) was done at the corrected ages of 1, 2 and 3.6 years. Findings were classified as normal, (score 0), mildly abnormal (score 1) and definitely abnormal (score 2). A child was classified as definitely abnormal when a neurological disorder, such as cerebral palsy, was diagnosed. A child was classified as mildly abnormal when more than one minor neurological sign, such as minor left-right differences or mild hypertonia, was present but could not be attributed to a traditional neurological diagnosis.

- At a corrected age of 1 and 2 years cognition was assessed with the mental scale of the Dutch version of the Bayley Scales of Infant Development (18). At a corrected age of 3.6 years the Dutch adaptation of the Kaufman Assessment Battery for Children (K-ABC) (9,13) was used. The K-ABC measures Intelligence (the Mental Processing Composite, MPC) and Achievement (the Achievement Scale). The Intelligence scale is based on neuropsychological theories of mental processing and consists of 2 subscales of Sequential and Simultaneous Processing. An index of more than -2SD (< 70) below the mean on both the Intelligence and the Achievement scale was considered as a mental handicap.

Data analysis

The statistical package Statgraphics 4.0 was used. Univariate statistical analysis was performed to study associations between separate items. In addition stepwise multiple regression analyses were performed to determine whether neurological and visual assessments were independent markers of neonatal cerebral damage and to determine the best predictors (eg. visual functions at ages 1 and 2.6 and or neurological assessments at ages 1 and 2) to cognitive development at 1, 2 and 3.6 years of age. A p value of < .05 was considered as significant.

9.5 RESULTS

Visual functions

At 1 year of age visual acuity could be reliably assessed in 61, visual fields in 58, optokinetic nystagmus in 57 and strabismus in 61 of the 69 children. At 2.6 years of age visual acuity could be reliably assessed in 62, visual fields in 61, optokinetic nystagmus in 65 and strabismus in 65 of the 69 children. In the remaining children visual functions could not be reliably assessed due to lack of cooperation on the part of the child. Twenty of the 61 children (33%) at age 1 and 18 of the 65 children (28%) at age 2.6 had one or more visual impairments. The prevalence of visual impairments at age 1 and 2.6 is presented in detail in Table 9.1. Of the 20 children with visual impairments at age 1, 13 still had visual impairments at age 2.6, in 5 visual functions were normalized and in 2 visual functions could not reliably assessed. Three of the remaining 5 children with visual impairments at age 2.6 had no visual impairments at age 1 and 2 could not be reliably assessed.

Visual functions and ophthalmological problems

Retinopathy of prematurity (ROP) was seen in 10 of the 69 (15%) infants. ROP stage 3 was found in 3 (4%) and ROP stage 4 in 4 (6%) infants. Visual impairment in relation to ROP is presented in detail in Table 9.2.

Objective refraction demonstrated myopia and/or astigmatism in 5 (7%) of the 69 children, 2 of them were corrected in the first year and 3 thereafter.

Severe visual impairments, interfering with normal function, were found in 5 of the 69 children (7%). These 5 children were considered as visually handicapped. All 4 children with ROP stage 4 were visually handicapped and 1 child was cortically blind.

Four of the 5 children with a visual handicap had multiple handicaps (2 children with cerebral palsy, a mental and a visual handicap, 1 child with cerebral palsy, a mental handicap, severe bilateral hearing loss and a visual handicap, 1 child with cerebral palsy and a visual handicap). All 5 visually handicapped children were referred to a specialized early intervention program in the first year of life.

Table 9.1 Prevalence of visual impairments in VLBW children at 1 and 2.6 years of age

	1 Year			2.6 Years		
	Normal n (%)	Impaired n (%)	Total	Normal n (%)	Impaired n (%)	Total
Visual Acuity	48 (79%)	13 (21%)	61	51 (82%)	11 (18%)	62
Visual Fields	48 (83%)	10 (17%)	58	57 (93%)	4 (7%)	61
Opto Kinetic Nystagmus	49 (86%)	8 (14%)	57	57 (88%)	8 (12%)	65
Strabismus	49 (80%)	12 (20%)	61	53 (82%)	12 (18%)	65
TOTAL	41 (67%)	20 (33%)	61	47 (72%)	18 (28%)	65

Table 9.2 Visual functions at ages 1 and 2.6 in relation to rethinopathy of prematurity

RETHINOPATHY OF PREMATURITY (ROP)	VISUAL FUNCTIONS					
	1 Year			2.6 Years		
	Normal	Impaired	TOTAL	Normal	Impaired	TOTAL
ROP Stage 0	36	15	51	43	12	55
ROP Stage 1	2	0	2	2	0	2
ROP Stage 2	1	0	1	1	0	1
ROP Stage 3	2	1	3	1	2	3
ROP Stage 4	0	4*	4	0	4**	4
TOTAL	41	20	61	47	18	65

Fisher's Exact   *=p<0.05, **=p<0.01

Visual functions, neonatal cerebral damage and neurology

Visual functions in relation to neonatal cerebral ultrasound are presented in Table 9.3. There was a significant relation of visual impairments at both ages and intraparenchymal damage, as detected by neonatal cerebral ultrasound.

Visual functions in relation to the neurological examinations at 1, 2 and 3.6 years of age are presented in Table 9.4. There was a significant relation between visual impairments at age 1 and a definitely abnormal neurological examination at ages 1, 2 and 3.6. Visual impairments at age 2.6 were only significantly related to a definitely abnormal neurological examination at age 2 and 3.6. The neurological classification changed over time and is presented in detail elsewhere (22).

Stepwise multiple regression analyses of neonatal cerebral ultrasound as dependent variable and the visual functions at ages 1 and 2.6 as well as the neurological examinations at ages 1 and 2 as independent variables are presented in Table 9.5.

Table 9.3 Visual functions at ages 1 and 2.6 in relation to neonatal cerebral ultrasound

NEONATAL CEREBRAL ULTRASOUND	VISUAL FUNCTIONS					
	1 Year			2.6 Years		
	Normal	Impaired	TOTAL	Normal	Impaired	TOTAL
Normal	15	2	17	15	3	18
Ventriculomegaly -	10	3	13	13	3	16
Ventriculomegaly +	16	10*[1]	26	18	8	26
Intraparenchymal damage	0	5***	5	1	4**	5
TOTAL	41	20	61	47	18	65

Fisher's Exact *=p<0.05, **=p<0.01,***=p<0.001
[1] Not significant when corrected for the number of analyses using Bonferroni correction

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Table 9.4 Visual functions at ages 1 and 2.6 in relation to neurology

NEUROLOGY	VISUAL FUNCTIONS					
	1 Year			2.6 Years		
	Normal	Impaired	TOTAL	Normal	Impaired	TOTAL
1 Year						
Normal	33	6	39	33	7	40
Mildly Abnormal	7	7*[1]	14	11	6	17
Definitely Abnormal	1	7***	8	3	5*[1]	8
2 Years						
Normal	35	7	42	37	7	44
Mildly Abnormal	6	5	11	9	4	13
Definitely Abnormal	0	8***	8	1	7***	8
3.6 Years						
Normal	33	5	38	35	5	40
Mildly Abnormal	8	7*[1]	15	11	6	17
Definitely Abnormal	0	8***	8	1	7***	8
TOTAL	41	20	61	47	18	65

Fisher's Exact *=p<0.05, **=p<0.01,***=p<0.001
[1] Not significant when corrected for the number of analyses using Bonferroni correction

Table 9.5 Visual functions at ages 1 and 2.6 and neurology at ages 1 and 2 as markers of neonatal cerebral ultrasound

Dependent Variable		VISUAL FUNCTIONS ALONE			VISUAL FUNCTIONS AND NEUROLOGY		
		Independent Variables	Explained Variance (ADJ-R^2)	p	Independent Variables	Explained Variance (ADJ-R^2)	p
NEONATAL CEREBRAL ULTRASOUND	Age 1 (n=61)	Visual functions	17%	0.0006	Neurology Visual functions	33% -	0.0001 ns.
	Age 2 to 2.6 (n=65)	Visual functions	7%	0.02	Neurology Visual functions	35% -	0.0001 ns.

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Visual functions and cognitive development

Two of the 5 visually handicapped children were so severely impaired (neurologically, mentally as well as visually) that developmental testing was inappropriate and an arbitrary score of -3SD was given. The other 3 visually handicapped children had residual visual function and developmental testing was adapted to minimize the effects of their visual handicap on developmental test results (24).

Visual functions at ages 1 and 2.6 in relation to cognitive development are presented in Figure 9.1 and 9.2. At both ages children with a visual impairment had a significantly lower mean mental developmental index at ages 1 and 2 and lower mean score at the simultaneous subscale and the achievement scale of the K-ABC at age 3.6.

Stepwise multiple regression analyses of the visual functions at ages 1 and 2.6 and the neurological examinations at ages 1 and 2 as independent variables and cognitive development at ages 1, 2 and 3.6 as dependent variable is presented in Table 9.6.

Table 9.6 Neurological examinations, visual functions and cognitive development, stepwise multiple regression analyses.

COGNITIVE DEVELOPMENT	SIGNIFICANT	All children		Handicaps excluded*	
Dependent Variables	Independent Variables	Explained Variance (ADJ-R^2)	p	Explained Variance (ADJ-R^2)	p
1 YEAR (Bayley)					
Mental Developmental Index	Neurology 1 Year Vision 2.6 Years	61% 74%	0.0001 0.0001	32% 41%	0.0001 0.008
2 YEARS (Bayley)					
Mental Developmental Index	Vision 2.6 Years Neurology 1 Year	23% 31%	0.003 0.007	8% -	0.03 ns
3.6 YEARS (K-ABC)					
Sequential Subscale	Neurology 1 Year	16%	0.001	- -	ns ns
Simultaneous Subscale	Vision 2.6 Years Neurology 1 Year	35% 48%	0.0001 0.0005	18% 35%	0.0002 0.001
Achievement	Vision 2.6 Years	17%	0.001	9% -	0.03 ns

* Children with cerebral palsy, mental handicap, severe visual and/or hearing impairment excluded (n=12).

VISUAL FUNCTIONS
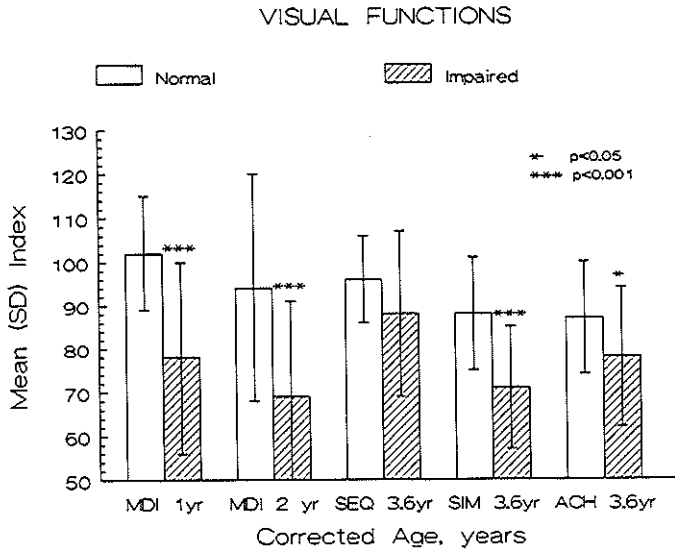
Figure 9.1 Mean developmental indices at ages 1, 2 and 3.6 in normal and visually impaired children at age 1 (n=61).

VISUAL FUNCTIONS
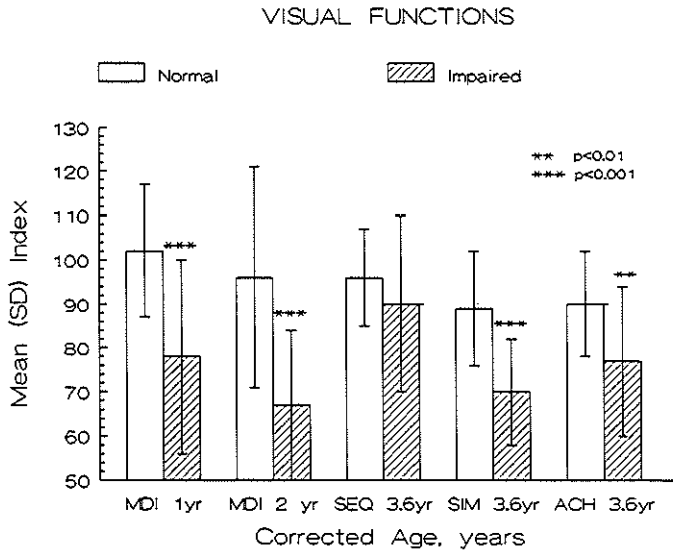
Figure 9.2 Mean developmental indices at ages 1, 2 and 3.6 in normal and visually impaired children at age 2.6 (n=65)
(MDI=mental developmental index, SEQ=sequential processing, SIM=simultaneous processing,ACH=achievement)

9.5 DISCUSSION

In this prospective longitudinal study of high risk VLBW infants, the prevalence of 33% of visual impairments found at 1 year of age and of 28% at 2.6 years of age is comparable to the 29% found at age 1 in a previous retrospective study (19). Visual functions were, however, not stable in time. In addition, due to lack of cooperation on the part of the child, 7 children could not be reliably assessed at both ages. In 5 of the 20 (25%) children with visual impairments at age 1, visual functions were normalized and 13 (65%) still had visual impairments at age 2.6, while 3 of the 18 (17%) children with visual impairments at age 2.6 had no visual impairments at age 1. These results demonstrate that repeated assessment of visual functions after the first year of life is indicated in high risk VLBW children.

As in previous studies (8,11), there was a close relationship between neurological as well as mental handicaps and visual functions. All children with cerebral palsy and 6 of the 7 with a mental handicap were visually impaired. As in other studies (19,21), there was also a significant relationship between visual impairment and intraparenchymal damage as detected by neonatal cerebral ultrasound. In a regression analysis with neonatal cerebral ultrasound as the dependent variable, visual functions at 1 year of age explained 17% and at 2.6 years of age 7% of the variance. Visual functions, particularly at age 1, could thus be considered as a marker of neonatal cerebral damage. The standardized neurological examination at age 1 as well as at age 2, however, explained 33 to 35% of the variance. Our results suggest that, although cerebral damage can result in neurological abnormalities as well as visual impairments, neurological examinations in the first years of life are better markers of neonatal cerebral damage than visual functions.

Visual impairments at ages 1 and 2.6 resulted in significantly lower mean mental developmental indices at ages 1 and 2, as well as in lower mean scores on the simultaneous subscale and the achievement scale at age 3.6. Stepwise multiple regression analyses demonstrated, however, that in cognitive development at ages 1 and 2, the neurological examination at age 1 was the most important variable. In cognitive development at age 3.6, visual functions at age 2.6 are more important. Sensory-motor abilities are vital in the cognitive development of the infant. With increasing age, more sophisticated processing, integration and feedback between visual and cognitive abilities are demanded of the child. Severely visually impaired children

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have to rely on sequential observations and relations with other objects are frequently lost (6). Our results demonstrate that simultaneous information processing is, in particularly, also hampered in the less severe visually impaired child, who has access to visual images and visualization. Even less severe visual impairments might thus affect cognitive development.

Recent evidence (5) suggests that the visual system of children who had suffered from perinatal hypoxia can retain some degree of plasticity for many years after the occurrence of structural damage. Other authors recently demonstrated that in severely visually impaired infants, visual development can be favorably influenced by an early intervention program based on visual and general developmental principles (14). Whether early intervention programs can also stimulate a better visual outcome in high risk infants with less severe visual impairments is not known.

We conclude that VLBW children are at high risk for visual impairments. Neonatal cerebral damage is related to neurological abnormalities as well as to visual impairments. Hence, in infants with visual impairments, without ophthalmological abnormalities, a neurodevelopmental examination is indicated, while in infants with neurodevelopmental abnormalities an assessment of visual functions is indicated. Visual impairments can affect cognitive development. Therefore early visual assessment is not only important to detect ophthalmological problems, but also as an incentive for an early intervention program to stimulate visual and cognitive development. The effectiveness of such a program in less severely visually impaired children should be subject to further study.

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CHAPTER 10

SUMMARY AND CONCLUSIONS

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10.1 SUMMARY

In this thesis a prospective longitudinal follow-up study has been described from birth to 3.6 years of age in a cohort of 79 high risk VLBW children. The predictive value of standardized assessments during neonatal intensive care treatment and at 1 and 2 years of corrected age, for neurodevelopmental outcome at 3.6 years of age was established. The effect of biological and social factors on development was studied, as well as the relation between biological and social factors and specific impairments.

Chapter 2 gives an overview of the follow-up results and describes which assessments are useful in pediatric practice at what age. Neonatal cerebral ultrasound findings, neurological examinations and mental development at 1 and 2 years of age were examined in relation to neurodevelopmental outcome at 3.6 years of age. At age 3.6 the prevalence of minor handicaps was 11% (n=9) and of major handicaps 5 % (n=4). The neurological classification changed in time. Cerebral palsy was found in 9 (11%) children at 3.6 years of age and could reliably be diagnosed at age 2. For short term follow-up, as feedback to the neonatologist, the positive predictive value of intraparenchymal damage as detected by neonatal cerebral ultrasound was better than the positive predictive value of a definitely abnormal neurological examination at age 1. Visual handicaps (n=4, 5%) and severe bilateral hearing loss (n=1, 1%) were all detected in the first year of life. A mental handicap was found in 7 (9%) children at 3.6 years of age. It was impossible to predict mental handicaps for the individual child. Only 35% of the children with a mental delay at age 2 had a mental handicap at age 3.6, and 35% of the children with a mental delay at age 2 had normal cognitive outcome. Pediatricians therefore should be cautious in the interpretation of developmental test results in infancy. Long-term follow-up is essential for the child and its parents.

Chapter 3 describes in detail which assessments will predict outcome most accurately before discharge from the neonatal intensive care. Birthweight, gestational age, obstetrical and neonatal optimality, neonatal neurological examinations and neonatal cerebral ultrasound were studied in relation to outcome. The best predictor for outcome was a simple cerebral ultrasound classification according to the presence or

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absence of ventriculomegaly and intraparenchymal damage of any cause. Infants with normal neonatal cerebral scans or abnormal scans without ventriculomegaly almost invariably had a normal neurological outcome. In infants with cerebral lesions with ventriculomegaly the prevalence of normal neurological outcome decreased to 43% (minor neurological dysfunction in 14 (47%) and cerebral palsy in 3 (10%) of the 30 children). Intraparenchymal damage was associated with cerebral palsy as well as other (mental and sensory) handicaps in 6 of the 7 (86%) children. Neonatal neurological examinations at preterm age had additional value in predicting neurological outcome especially in the group with ventriculomegaly. In stepwise multiple regression analysis, neither birthweight nor gestational age, obstetrical nor neonatal optimality independently predicted outcome in high risk VLBW children at 3.6 years of age.

Chapter 4 describes the effects of biological and social factors on cognitive development. Neonatal cerebral ultrasound and a neurological score were used as indicators of biological risk. A socio-demographic risk score and the HOME Inventory were used as indicators of social risk. The mean mental index at 1 year of age was 96 (SD 19), at 2 years of age 86 (SD 26) and at 3.6 years of age for intelligence 87 (SD 13) and for achievement 86 (SD 14). In a stepwise multiple regression analysis of biological as well as social factors, the neurological score alone was the best predictor for cognitive development at age 1, explaining 46% of the variance. From 2 years onward the best predictors for cognitive development were the neurological score together with the home environment explaining 46% of the variance for the mental developmental index at age 2, 34% for intelligence and 56% for achievement at age 3.6. Children at high biological risk were able to catch up on their cognitive delay in a highly stimulating home environment. Children at low as well as high biological risk in a less stimulating home environment showed a decline in cognitive development. For these children early intervention programs might be important in the prevention of cognitive disabilities.

Chapter 5 describes parent (CBCL/2-3) and clinician reports of behavioral problems at age 3.6 in relation to neonatal cerebral damage, neurology, cognition and social factors. On the parent's questionnaire, VLBW children had more depressed behavior and scored significantly more within the clinical range of the Total Problem Score (22%) than full term children (10%). The clinician reported 29% of behavioral problems. Neither neonatal cerebral ultrasound nor neurological examinations directly

influenced behavioral outcome in VLBW children. Cerebral damage, however, was related to cognitive development. Cognition directly influenced behavioral problems by clinician report while the home environment directly influenced problem behavior by parent report. There was a significant correlation between emotional problems as reported by the clinician, and problem behavior as reported by the parents. Conduct and attention problems by clinician report were not significantly related to problem behavior by parent report. Our results suggest that, in preschool VLBW children, depressed behavior might be associated with parental reactions to the birth of a VLBW child. Attention problems might be linked indirectly to brain damage via cognitive impairments.

Chapter 6 describes inattention and activity at age 3.6 in relation to neonatal cerebral ultrasound, neurodevelopmental outcome (eg. neurology, intelligence and achievement, receptive and expressive language) and the home environment in more detail. In this study concentrating on minor impairments, children with a handicap were excluded. VLBW children were less attentive but not more active than full term children. Neither neonatal cerebral ultrasound nor neurological examinations did significantly predict inattention or activity in VLBW children. The simultaneous subscale of the Kaufman Assessment Battery for children ($p = 0.02$) together with language expression ($p = 0.03$) best predicted inattention, explaining 22% of the variance. The home environment alone best predicted activity ($p = 0.01$) explaining 10% of the variance. Inattention and activity in preschool VLBW children are thus etiologically separated.

Chapter 7 describes in detail the neurological examination at age 3.6. In this study concentrating on minor impairments, children with a handicap were excluded. Traditional signs of minor neurological dysfunction and the quality of movement were assessed and studied in relation to neonatal cerebral damage (eg. neonatal neurology and cerebral ultrasound) and developmental assessment at age 3.6 (eg. motor scale, intelligence and achievement, receptive and expressive language). Minor neurological dysfunction was significantly related to the quality of movement. Their significance in relation to neonatal cerebral damage and developmental outcome was different however. Minor neurological dysfunction was associated with neonatal cerebral damage, while the quality of movement was associated with more complex sensory motor tasks and simultaneous processing. At preschool age, the quality of movement

might therefore be a better marker of later learning problems than traditional signs of minor neurological dysfunction.

Chapter 8 describes the prevalence of preschool language impairments and hearing loss, their relationship to each other as well as to perinatal conditions, neurodevelopmental outcome and the home environment. Mild unilateral or bilateral hearing loss was found in 26%, moderate hearing loss in 13% and severe hearing loss in 3% of the children. None of the children were deaf. Abnormal tympanometry was found in 57% of the children. Preschool hearing loss was related to a less optimal neonatal condition and not to the obstetrical condition nor to neonatal cerebral ultrasound findings. Language impairments were found in 21% of the children at age 3.6 years. Receptive and expressive language were not related to perinatal conditions. There was no relation between language and audiological assessments. In a stepwise multiple regression analysis, cognition and the child's home environment were the only significant variables in the prediction of language abilities in preschool VLBW children, explaining 58% of the variance in receptive and 42% of the variance in expressive language.

Chapter 9 describes the relation between visual functions and neonatal cerebral ultrasound, neurological and cognitive development. Visual impairments were found in 33% at age 1 and in 28% at age 2.6. Visual impairments were related to intraparenchymal damage, as detected by neonatal cerebral ultrasound, as well as to abnormal neurological examinations at all ages. Stepwise multiple regression analyses with visual functions at ages 1 and 2.6 and neurological examinations at ages 1 and 2 as independent variables, however, demonstrated that at both ages standardized neurological examinations were better markers of neonatal cerebral damage than visual functions. In cognitive development at 1 and 2 years of age, the neurological examination at age 1 was the most important variable. In cognitive development at age 3.6 visual functions at age 2.6 were more important. Early visual impairments might thus influence later cognitive development. The effectiveness of appropriate early intervention strategies to stimulate visual and cognitive development in infants with less severe visual impairments should be subject to further study.

10.2 CONCLUSIONS

In this longitudinal study of VLBW infants, all treated by neonatal intensive care, the prevalence of minor handicaps was 11% and of major handicaps 5 %. These results are comparable to the prevalence of handicaps at age 5 (minor handicaps 8%, major handicaps 6,5%) found in the POPS study. In this epidemiological study, all VLBW infants in the Netherlands, treated in regional hospitals as well as by neonatal intensive care, are included. The mortality rate in our study was 20% which is 8% lower than found in the POPS study. Our results suggest that neonatal intensive care can increase the survival rate of VLBW infants with a stable handicap rate. These results are promising, since the likelihood of a handicap is greater in VLBW infants requiring intensive care. However, a handicap rate of 16%, even in severely ill VLBW infants, is still a cause of great concern. In the past neonatal intensive care has greatly improved the infant's chance of survival. In the future efforts should be directed towards diminishing the handicap rate and improving the quality of later life in VLBW infants.

In our study neonatal complications resulted in more neonatal cerebral damage as detected by neonatal cerebral ultrasound and neonatal neurological examinations. Children with neonatal cerebral damage were at high risk for cerebral palsy and other handicaps as well as minor neurological dysfunction. Neonatal cerebral ultrasound can thus be used as an instrument for the evaluation of intensive care treatment. Unfortunately serial scanning is mandatory, since the maximum extent of hemorrhagic lesions may not develop until after the first week of life and ischemic lesions may not become visible only after the first two weeks of life. At that time, the most critical period of the infant's illness could be over. This limits the value of the technique as a reliable method for recognizing the infant for whom selective withdrawal of intensive care is a realistic and honest option. New techniques such as near infra-red spectroscopy, that can directly provide information about cerebral oxygenation and perfusion during neonatal intensive care treatment, may be of more help in the search for causes of neonatal cerebral damage that may be prevented.

Some of the abnormal neonatal cerebral ultrasound findings, however, were present from birth or appeared in the first week of life suggesting a prenatal or perinatal origin. Prenatal factors may be of great importance in the aetiology of cerebral palsy. Primary prevention of handicaps should also consist of optimal pre- and perinatal care

and prevention of premature birth. Unfortunately in the Netherlands, the number of premature and low birthweight children is rising, due to an increased age of mothers in pregnancy and due to assisted reproduction techniques such as induced ovulation and in vitro fertilization.

In the individual child the predictive value of the assessments in the neonatal period and at 1 and 2 years of age, for outcome at 3.6 years of age remained low. The neurological classification changed in time and it was impossible to predict mental handicaps. This is not surprising since growing up is a process of continuous change. Mean cognitive indices from the second year onwards were below -1SD. In addition VLBW children had more problem behavior than children in a comparison group. Growing older, the home environment became increasingly important in cognitive development. Our study clearly demonstrated that, except in extreme cases, even for VLBW children at high biological risk, social factors were more important than biological ones for developmental outcome. Government, politicians and managers, deciding about financial resources, should pay more attention to these considerations. It is unacceptable that neonatal intensive care stops when the baby goes home. Intensive care for VLBW children has to include long-term care for the child and its parents. Unless this long-term care is provided, a large proportion of VLBW children are likely to be trapped in a cycle of events during preschool years that can be counterproductive to their cognitive as well as to their behavioral development.

Repeated assessments are also necessary to detect minor impairments. In our study we found a significant relationship between early visual functions and cognitive development. Such a relationship was not found between audiological assessments and language development. Visual functions however were assessed at age 1 and 2.6 and hearing at the end of our study at age 4. In the first years of life sensory-motor functions are essential in development. Therefore, during this critical period, minor visual and hearing impairments should be diagnosed and treated. The effectiveness of appropriate early intervention strategies to stimulate visual and language development in infants with visual and/or hearing impairments should be subject to further study.

Long-term follow-up is essential to increase our knowledge of the effects of improved survival among a new generation of VLBW infants. In this thesis, follow-up of high-risk VLBW infants could only be described until 3.6 years of age. Follow-up until school age is essential to detect learning problems. In order to organize timely

intervention, identification of these children at preschool age is important. In our study minor neurological dysfunction was associated with neonatal cerebral damage, while the quality of movement as well as inattention were both associated with simultaneous processing and might be predictive of later learning problems. Future research should concentrate on the design of instruments that can assess precursors of learning problems in preschool children more accurately.

The main conclusion of this thesis is that whether the brain is damaged or not, many high-risk VLBW infants do end up with developmental problems. All efforts should be directed towards preventing these disabilities in the future. It is evident that primary preventive activities must concentrate on the prevention of cerebral damage by optimal pre-, peri- and neonatal care. But the home environment, except in case of extreme cerebral damage, is of more importance to the ultimate developmental outcome for the individual child. Child and parents should be viewed as an interdependent system. To stimulate the development of the child and to prevent behavioral problems, early intervention programs therefore should take care of the child as well as its parents. Studies in the United States have already demonstrated that comprehensive early intervention programs focussing on child development and family support in the first years of life are effective, as well as more specific programs focussed on the mother-infant interaction in the first 3 months of life. Future research should concentrate on the development of instruments able to select parents and infants in need of early intervention and able to demonstrate what help is effective for which parent and which child. In order to develop early intervention programs for high-risk VLBW children a good cooperation between obstetricians, pediatricians, child psychiatrists and psychologists, educators and many allied disciplines is essential. In the development of effective early intervention programs the parents' involvement is of even more importance. Learning from the problems they experience in the care of their VLBW child is the most important contribution, regardless of improvements in neonatal intensive care, to the chance of a better quality of life of future VLBW infants.

SAMENVATTING EN CONCLUSIES

SAMENVATTING

In dit proefschrift wordt een vervolgonderzoek beschreven van 79 kinderen met een zeer laag geboortegewicht (minder dan 1500 gram). Doel van het onderzoek was om de voorspellende waarde van vroegtijdig onderzoek (in de neonatale periode en op de gecorrigeerde leeftijd van 1 en 2 jaar) voor de ontwikkeling op 3 1/2 jaar vast te stellen. De invloed van biologische en sociale factoren op de ontwikkelingsmogelijkheden van het kind is bestudeerd, evenals de relatie tussen biologische en sociale factoren en specifieke ontwikkelingsstoornissen.

Hoofdstuk 2 geeft een eerste overzicht van de resultaten en beschrijft welke methoden van onderzoek, tijdens opname op de afdeling intensieve zorg voor pasgeborenen, op 1 en op 2 jaar, voor de uitkomst op 3 1/2 jaar van belang zijn. Echografisch onderzoek van de hersenen, neurologisch onderzoek en de mentale ontwikkeling op 1 en 2 jaar werden onderzocht in relatie tot handicaps op de leeftijd van 3 1/2 jaar. Negen kinderen (11%) hadden op 3 1/2 jaar een lichte en 4 kinderen (5%) een ernstige handicap. Bij 9 kinderen (11%) was sprake van spasticiteit. Deze diagnose kon in alle gevallen op de leeftijd van 2 jaar worden gesteld. Voor korte termijn evaluatie van de neonatale intensieve zorg, bleek de voorspellende waarde van beschadiging van het hersenweefsel (vastgesteld m.b.v. echografisch onderzoek tijdens de opname) beter dan de voorspellende waarde van een duidelijk afwijkend neurologisch onderzoek op de leeftijd van 1 jaar. Vier kinderen (5%) hadden een visuele handicap en 1 (1%) een ernstige bilaterale gehoorstoornis. Al deze zintuiglijke afwijkingen werden in het eerste levensjaar gediagnostiseerd. Zeven kinderen (9%) hadden een geestelijke handicap op 3 1/2 jaar. Het bleek onmogelijk om een geestelijke handicap op basis van het onderzoek op 1 en 2 jaar voor het individuele kind te voorspellen. Slechts 35% van de kinderen met een duidelijke mentale achterstand op de leeftijd van 2 jaar waren geestelijk gehandicapt en 35% hadden een normale mentale ontwikkeling op 3 1/2 jaar. Ontwikkelingstests in de eerste levensjaren moeten daarom met de grootste voorzichtigheid worden geïnterpreteerd. Voor het individuele kind en de ouders is het vervolgen van de ontwikkeling op lange termijn noodzakelijk.

Hoofdstuk 3 beschrijft in detail welke methoden van onderzoek, tijdens opname op de afdeling intensieve zorg voor pasgeborenen, de beste voorspellende waarde hebben. Geboortegewicht, zwangerschapsduur, condities in de zwangerschap, tijdens de geboorte en tijdens de opname als pasgeborene (obstetrische en neonatale optimaleit), neurologisch onderzoek en echografisch onderzoek van de hersenen werden bestudeerd in relatie tot de uitkomst op 3 1/2 jaar. Een eenvoudige indeling van echografisch onderzoek (normaal, ventrikeldilatatie afwezig, ventrikeldilatatie aanwezig, beschadiging van het hersenweefsel) bleek de beste voorspellende waarde te hebben. De ontwikkeling van kinderen met een normale echografie of met afwijkingen zonder ventrikeldilatatie was in vrijwel alle gevallen normaal. Slechts 13 van de 30 (43%) kinderen met ventrikeldilatatie waren neurologisch normaal, bij 14 (47%) was sprake van lichte neurologische functiestoornissen en bij 3 (10%) van spasticiteit. Zes van de 7 kinderen (86%) met beschadiging van het hersenweefsel waren spastisch, al dan niet in combinatie met geestelijke en/of zintuiglijke handicaps. Neonataal neurologisch onderzoek was van additionele waarde in de voorspelling van neurologische afwijkingen, met name in de groep kinderen met ventrikeldilatatie bij echografisch onderzoek. Geboortegewicht, zwangerschapsduur, obstetrische en neonatale optimaliteit waren geen significante onafhankelijke variabelen voor de uitkomst op 3 1/2 jaar.

Hoofdstuk 4 beschrijft de invloed van biologische en sociale factoren op de mentale ontwikkeling van het kind. Echografie van de hersenen en een neurologische score werden gebruikt als maten voor biologisch risico. Een socio-demografische risico score en een opvoedingsklimaatschaal werden gebruikt als maten voor sociaal risico. De gemiddelde mentale ontwikkelingsindex van kinderen met een zeer laag geboortegewicht bleek na het eerste levensjaar te dalen van 96 (SD 19) op 1 naar 86 (SD 26) op 2 jaar. Op 3 1/2 jaar was de gemiddelde score voor intelligentie 87 (SD 13) en voor verworven kennis 86 (SD 14). In een stapsgewijze multipele regressie analyse met de biologische en sociale factoren als onafhankelijke variabelen, werd op 1 jaar voor de mentale ontwikkelingsindex 46% van de variantie verklaard door de neurologische score. Vanaf 2 jaar werd de mentale ontwikkeling het beste verklaard door de neurologische score en het opvoedingsklimaat tezamen; op 2 jaar verklaarde dit 46% van de variantie voor de mentale ontwikkelingsindex; en op 3 1/2 jaar 34% van de intelligentie score en 56% van de verworven kennis score. In neurologisch opzicht afwijkende kinderen hadden op 1 jaar gemiddeld een lagere mentale ontwikkelingsindex dan in

neurologisch opzicht normale kinderen. In een goed opvoedingsklimaat kon deze achterstand worden ingehaald. In een weinig stimulerend opvoedingsklimaat daalde de ontwikkelingsindex van zowel de in neurologisch opzicht normale als abnormale kinderen. Systematisch onderzoek naar de preventieve werking van vroegtijdige interventie programma's om ontwikkelingsstoornissen bij kinderen met een zeer laag geboortegewicht te voorkomen is noodzakelijk.

Hoofdstuk 5 beschrijft probleemgedrag (gerapporteerd door de ouders en onderzoekster) op de leeftijd van 3 1/2 jaar in relatie tot echografisch onderzoek van de hersenen, neurologisch onderzoek, mentale ontwikkeling en sociale factoren. Op de gedragsvragenlijst ingevuld door de ouders (CBCL/2-3), scoorden kinderen met een zeer laag geboortegewicht significant hoger voor depressief gedrag dan kinderen in de controle groep. Op de totale probleem score van de CBCL/2-3 hadden 22% van de kinderen met een zeer laag geboortegewicht en 10% van de kinderen in de controle groep probleemgedrag. De onderzoekster vond bij 29% van de kinderen met een zeer laag geboortegewicht probleemgedrag. Emotionele problemen, gerapporteerd door de onderzoekster, hadden een significante relatie met probleemgedrag, gerapporteerd door de ouders. Aandachts- en gedragsproblemen, gerapporteerd door de onderzoekster, hadden geen significante relatie met probleemgedrag, gerapporteerd door de ouders. Echografie van de hersenen en neurologisch onderzoek hadden geen directe relatie met probleemgedrag op 3 1/2 jaar, maar wel met de mentale ontwikkeling. Er was een direct verband tussen de mentale ontwikkeling en probleemgedrag, gerapporteerd door de onderzoekster en tussen het opvoedingsklimaat en probleemgedrag, gerapporteerd door de ouders. De reactie van de ouders op de spanningsvolle gebeurtenissen, rondom de geboorte van hun kind met een zeer laag geboortegewicht, kan een oorzaak zijn van emotionele stoornissen bij hun kind. Hersenbeschadiging zou indirect, via cognitieve stoornissen, een oorzaak kunnen zijn van aandachtsproblemen.

Hoofdstuk 6 gaat dieper in op deze mogelijke relatie tussen aandachtsproblemen en overbeweeglijkheid, hersenbeschadiging en cognitieve vaardigheden bij niet gehandicapte kinderen. Kinderen met een laag geboortegewicht bleken, volgens hun ouders, minder aandachtig maar niet meer beweeglijk te zijn dan kinderen uit een controle groep. Er was geen verband tussen echografie van de hersenen, neurologisch onderzoek en aandacht of activiteit bij kinderen met een zeer laag geboortegewicht. Simultane informatieverwerking (Kaufman Assessment Battery for Children) en expressieve taal

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verklaarden 22% van de variantie voor aandacht. Activiteit werd voor 10% verklaard door het opvoedingsklimaat. Aandachtsproblemen en overbeweeglijkheid bij kinderen met een zeer laag geboortegewicht hebben dus vermoedelijk een verschillende oorzaak.

Hoofdstuk 7 beschrijft het neurologisch onderzoek op de leeftijd van 3 1/2 jaar bij niet gehandicapte kinderen. Lichte neurologische functiestoornissen en de kwaliteit van bewegen werden bestudeerd in relatie tot neonatale hersenbeschadiging (echografie en neurologie) en in relatie tot de ontwikkeling op 3 1/2 jaar (motoriek, sequentiele en simultane informatieverwerking en verworven kennis, receptieve en expressieve taal). Er bestond een significante relatie tussen lichte neurologische functiestoornissen en de kwaliteit van bewegen. Hun betekenis in relatie tot neonatale hersenbeschadiging en de ontwikkeling op 3 1/2 jaar was echter verschillend. Lichte neurologische functiestoornissen correleerde het beste met neonatale hersenbeschadiging. De kwaliteit van bewegen correleerde het beste met de ontwikkeling (motoriek en simultane informatieverwerking). De kwaliteit van bewegen is op de peuterleeftijd vermoedelijk een betere maat voor latere leerproblemen dan meer traditionele symptomen van neurologische functiestoornissen.

Hoofdstuk 8 beschrijft het bestaan van gehoorsverlies en spraaktaal achterstand op de peuterleeftijd, hun onderlinge relatie, en hun relatie met condities rondom de geboorte, neurologie, ontwikkeling en het opvoedingsklimaat. Lichte unilaterale of bilaterale gehoorsverliezen werden bij 26%, matige gehoorsverliezen bij 13% en ernstige gehoorsverliezen bij 3% van de kinderen vastgesteld. Geen van de kinderen was doof. Bij 57% van de kinderen werd een abnormaal tympanogram gevonden. Er bestond een significant verband tussen gehoorsverlies en een minder optimale conditie van het kind tijdens de opname op de afdeling voor intensieve zorg. Er was geen significant verband tussen gehoorsverlies en zwangerschapscomplicaties of tekenen van neonatale hersenbeschadiging. Spraaktaal achterstand op de leeftijd van 3 1/2 jaar werd gevonden bij 21% van de kinderen en had geen verband met de conditie van het kind voor en na de geboorte, tekenen van neonatale hersenbeschadiging of gehoorsverlies. In een stapsgewijze multiple regressie analyse verklaarden de mentale ontwikkeling van het kind en het opvoedingsklimaat 58% van de variantie voor receptieve taal en 42% voor expressieve taal op 3 1/2 jaar.

Hoofdstuk 9 beschrijft de relatie tussen visuele functies, echografie van de hersenen, neurologische en cognitieve ontwikkeling van het kind. Op de leeftijd van 1

jaar werd bij 33% van de kinderen visuele stoornissen gevonden en op 2 1/2 jaar 28%. Er was een significant verband tussen visuele stoornissen, neonatale hersenbeschadiging en abnormale neurologie. In multiple regressie analyses met visuele functies en neurologisch onderzoek als onafhankelijke variabelen en echografie als afhankelijke variabelen, bleek het neurologisch onderzoek echter een betere onafhankelijke variabele dan de visuele functies. Ook voor de cognitieve ontwikkeling op 1 en 2 jaar bleek het neurologisch onderzoek op 1 jaar de beste onafhankelijke variabele. Voor de cognitieve ontwikkeling op de leeftijd van 3.6 jaar waren de visuele functies op 2 1/2 jaar echter de beste onafhankelijke variabele. Vroege visuele stoornissen zijn dus van invloed op de latere cognitieve ontwikkeling. De effectiviteit van vroegtijdige interventie programma's om de visuele ontwikkeling te stimuleren, zal in de toekomst verder bestudeerd worden.

CONCLUSIES

In dit onderzoek van kinderen met een zeer laag geboortegewicht, die allen intensieve zorg als pasgeborene nodig hadden, was op 3 1/2 jaar bij 11 % van de kinderen sprake van een lichte en bij 5% van een ernstige handicap. Deze resultaten zijn vergelijkbaar met het percentage handicaps op de leeftijd van 5 jaar (lichte handicaps 8%, ernstige handicaps 6,5 %) gevonden in de POPS studie. In deze epidemiologische studie waren alle pasgeborenen met een zeer laag geboortegewicht in Nederland, ongeacht of zij intensieve zorg nodig hadden of niet, opgenomen. De mortaliteit in onze onderzoeksgroep was 20%, dit is 8% lager dan in de POPS studie is gevonden. Uit deze resultaten zou men, met enig voorbehoud, de conclusie kunnen trekken dat door intensieve pasgeborenenzorg de overlevingskans van kinderen met een zeer laag geboortegewicht stijgt bij een gelijkblijvende kans op handicaps. Deze resultaten zijn bemoedigend omdat kinderen met een zeer laag geboortegewicht, die zo ernstig ziek zijn dat intensieve zorg nodig is, een grotere kans op handicaps hebben dan minder zieke pasgeborenen. Het gevonden percentage van 16% handicaps is echter, zelfs bij ernstig zieke pasgeborenen met een zeer laag geboortegewicht, reden voor grote ongerustheid. In het verleden is, dankzij de enorme verbeteringen in de intensieve zorg voor pasgeborenen, de overlevingskans aanzienlijk gestegen. In de toekomst moet de nadruk worden gelegd op het voorkomen van handicaps en het verbeteren van de kwaliteit van leven van kinderen met een zeer laag geboortegewicht.

In ons onderzoek hadden kinderen met meer complicaties op de afdeling intensieve zorg meer neonatale hersenbeschadiging, zoals gemeten met behulp van echografisch en neurologisch onderzoek. Deze kinderen met neonatale hersenbeschadiging hadden een verhoogde kans op spasticiteit, al dan niet in combinatie met andere handicaps, en op lichtere neurologische functiestoornissen. Echografie van de hersenen in de neonatale periode, bleek een goed instrument voor de korte termijn evaluatie van intensieve zorg in het algemeen. De uiteindelijke grootte van hersenafwijkingen kan soms echter pas na 14 dagen zichtbaar worden. Daarom is herhaald echografisch onderzoek in de eerste levensweken noodzakelijk. De kritische periode in de ziekte van het kind kan dan al voorbij zijn. Om die reden is echografisch onderzoek minder geschikt als evaluatie instrument bij beslissingen over de zinvolheid van het continueren van de intensieve behandeling van het individuele kind. Nieuwe technieken, zoals "near infrared spectroscopy", die directe informatie over de bloed- en zuurstofvoorziening in de hersenen kunnen geven, zijn in de toekomst hopelijk van meer waarde in het onderzoek naar oorzaken van vermijdbare hersenbeschadiging.

Een aantal van de gevonden hersenafwijkingen, vastgesteld m.b.v. echografie, waren al vlak na de geboorte of in de eerste levensweek aanwezig, duidend op het ontstaan van een hersenbeschadiging voor of tijdens de geboorte. Factoren tijdens de zwangerschap zijn belangrijk in het ontstaan van neurologische afwijkingen. Een optimale zorg voor en tijdens de geboorte en het voorkomen van vroeggeboorten is van het grootste belang in de primaire preventie van handicaps. Helaas stijgt op dit moment het aantal vroeggeboorten in ons land. Deze stijging is het gevolg van geavanceerde technieken toegepast bij ongewenste onvruchtbaarheid, zoals geïnduceerde ovulatie en in vitro fertilisate.

Voor het individuele kind bleek de voorspellende waarde van het onderzoek in de pasgeborenen periode, op 1 en op 2 jaar voor de uitkomst op 3 1/2 jaar laag. De neurologische classificatie wisselde met de leeftijd en het was onmogelijk om in de eerste levensjaren een geestelijke handicap te kunnen voorspellen. Dit is niet verbazingwekkend. De ontwikkeling van een kind is immers een proces van continue verandering. De gemiddelde mentale ontwikkelingsindex daalde van het eerste naar het tweede levensjaar tot beneden de -1SD. Bovendien hadden kinderen met een laag geboortegewicht meer probleemgedrag dan kinderen uit een controle groep. Naarmate het kind ouder werd, werd de invloed van het opvoedingsklimaat steeds belangrijker in

de mentale ontwikkeling. Onze studie toont duidelijk aan dat in de uiteindelijke ontwikkelingsmogelijkheden van het kind omgevingsfactoren van meer belang zijn dan biologische factoren, behalve in geval van extreem ernstige hersenbeschadiging. Beleidmakers en alle anderen die beslissen over de financiële middelen in de gezondheidszorg, zouden zich hiervan bewust moeten zijn. Op intensieve zorg voor pasgeborenen behoort intensieve nazorg voor het kind en zijn ouders te volgen. Alleen door deze intensieve nazorg kan worden voorkomen dat een onnodig groot aantal ouders en kinderen in de eerste levensjaren in een vicieuze cirkel terecht komen. Bij het kind kan dit leiden tot een achteruitgang van de mentale ontwikkeling en probleemgedrag.

Regelmatig onderzoek is ook nodig om kleinere afwijkingen tijdig te kunnen diagnostiseren en zo mogelijk te behandelen. In ons onderzoek vonden wij een verband tussen visuele stoornissen op 2 1/2 jaar en de mentale ontwikkeling op 3 1/2 jaar. Dit verband kon niet worden aangetoond voor gehoorsverlies en spraaktaal ontwikkeling. Het gehoorsonderzoek vond echter eenmalig plaats op de leeftijd van 4 jaar. In de eerste levensjaren zijn de zintuiglijke en motorische functies van groot belang voor de verdere ontwikkelingsmogelijkheden van het kind. Daarom is vroegtijdige onderkenning en behandeling van deze functiestoornissen in een vroeg stadium heel belangrijk. De effectiviteit van vroegtijdige interventie programma's, die de ontwikkeling van kinderen met functiestoornissen kunnen stimuleren, zal onderwerp zijn van verder onderzoek.

Om de consequenties van de sterke stijging van de overlevingskansen in deze nieuwe generatie van kinderen met een zeer laag geboortegewicht goed te kunnen overzien is onderzoek op latere leeftijd noodzakelijk. In dit proefschrift konden de kinderen slechts vervolgd worden tot de leeftijd van 3 1/2 jaar. Vervolgonderzoek op de schoolleeftijd is belangrijk om leerstoornissen te kunnen opsporen. Om tijdige hulp bij leerstoornissen te kunnen bieden, is het vroegtijdig onderkennen van deze stoornissen, liefst vóór de schoolleeftijd, van groot belang. In ons onderzoek op 3 1/2 jaar bleken lichte neurologische functiestoornissen niet, maar zowel de kwaliteit van het bewegingspatroon als ook gebrek aan aandacht wel samen te hangen met simultane informatieverwerking. Dit zouden vroege tekenen kunnen zijn van latere leerproblemen. Toekomstig onderzoek zal zich richten op het ontwikkelen van instrumenten die deze voorlopers van leerstoornissen nauwkeuriger kunnen meten dan in de huidige studie mogelijk was.

De belangrijkste conclusie van dit proefschrift is dat een groot aantal kinderen met een zeer laag geboorte gewicht problemen in hun ontwikkeling ondervinden, of zij nu hersenbeschadiging hebben of niet. In de toekomst zal alle inspanning uit moeten gaan naar het voorkomen van deze problemen. Het is evident dat primaire preventie van ontwikkelingsstoornissen nog steeds bestaat uit het voorkomen van hersenbeschadiging door een optimale zorg tijdens de zwangerschap, de bevalling en na de geboorte. Maar het opvoedingsklimaat is voor de uiteindelijke ontwikkelingsmogelijkheden van nog groter belang. Om een optimale ontwikkeling van kinderen met een laag geboortegewicht te realiseren moeten kinderen en ouders tezamen worden geholpen. In de Verenigde Staten is al aangetoond dat intensieve vroegtijdige interventieprogramma's de mentale ontwikkeling van kinderen met een laag geboortegewicht kunnen stimuleren en gedragsproblemen kunnen voorkomen. Toekomstig onderzoek zal moeten uitwijzen welke onderzoeks- en interventiemethoden geschikt zijn om binnen de Nederlandse situatie te kunnen aangeven welke hulp effectief is bij welk kind en welke ouders. Om vroegtijdige interventieprogramma's voor deze kinderen en ouders te kunnen ontwikkelen, is een goede samenwerking tussen obstetricus, kinderarts, kinderpsychiater en psycholoog, onderwijskundigen en vertegenwoordigers van vele andere disciplines van belang. Een actieve inbreng van de ouders in de ontwikkeling van dergelijke programma's is echter van nog groter belang. Door het kenbaar maken van de problemen die zij ondervinden bij de opvoeding van hun kind met een zeer laag geboortegewicht, kunnen ouders een belangrijke bijdrage leveren aan de verbetering in de kwaliteit van leven van toekomstige kinderen met een zeer laag geboortegewicht.

DANKWOORD

Het tot stand komen van dit proefschrift was niet mogelijk geweest zonder een bijdrage van velen.

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Rotterdam,
december 1992.

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Schrijven is verhuizen. schrijven is sjouwen met meubelstukken en draven met tierelan-
tijnen, zeulen met zware gevaarten en jongleren met klein grut. De verhuizers in het
hoofd sjouwen af en aan. In en uit. Van hot naar haar. Er zijn verhuizers bij die er gek
van worden.

Uit: De Paleizen van het geheugen. Gerrit Komrij en Willem van Malsen.