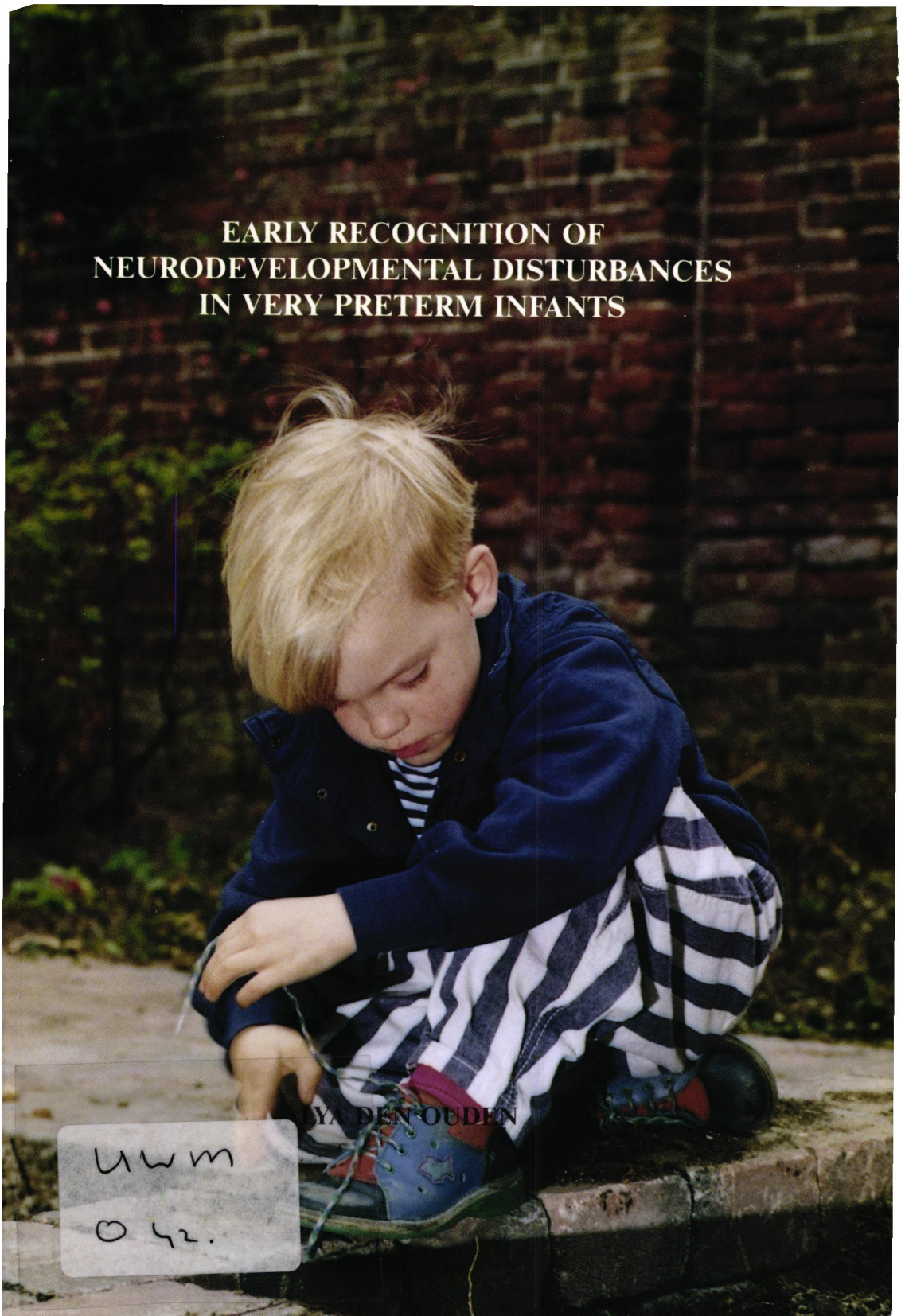
EARLY RECOGNITION OF NEURODEVELOPMENTAL DISTURBANCES IN VERY PRETERM INFANTS



LYA DEN OUDEN

EARLY RECOGNITION OF NEURODEVELOPMENTAL DISTURBANCES IN VERY PRETERM INFANTS

cover: Govert, 5 years old: can tie shoelaces.
photo: E.A.P. Koningsveld

EARLY RECOGNITION OF NEURODEVELOPMENTAL DISTURBANCES IN VERY PRETERM INFANTS

proefschrift

Ter verkrijging van de graad van Doctor
aan de Rijksuniversiteit te Leiden,
op gezag van de Rector Magnificus Dr. L. Leertouwer,
hoogleraar in de faculteit der Godgeleerdheid,
volgens besluit van het college van dekanen te verdedigen
op donderdag 27 juni 1991 te klokke 15.15 uur

door

ADRIANA LYSIA DEN OUDEN
geboren te Oegstgeest in 1950

DRUKKERIJ DE KEMPENAER, OEGSTGEEST - 1991

PROMOTIECOMMISSIE

Promotor	:	Prof.dr. J.H. Ruys
Co-promotor	:	Dr. S.P. Verloove-Vanhorick
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Overige leden	:	Prof.dr. J.J.P. van de Kamp
		Dr. H.M. Berger

ISBN: 90-9004309-8

STELLINGEN

behorend bij het proefschrift:

Early recognition of developmental disturbances in very preterm infants.

1 Developmental medicine is the basis of pediatrics.
Nelson's textbook of pediatrics

2 De sterk gedaalde mortaliteit met een nagenoeg gelijk gebleven handicap percentage bij zeer vroeg geboren kinderen in de laatste decennia maakt duidelijk dat de perinatologische behandeling zeer succesvol is.

3 De hoge frequentie van lichtere stoornissen op de kleuter- en school leeftijd bij zeer vroeg geboren kinderen maakt ook dat velen van hen in hun latere leven toch buitenbeentjes blijven.

4 Hoewel onderzoek in de neonatale periode kinderen met een verhoogd risico op (ernstige) ontwikkelingsstoornissen kan identificeren is het onmogelijk op basis van dergelijk onderzoek een normale ontwikkeling te voorspellen.

5 Ernstige ontwikkelingsstoornissen kunnen doorgaans vroeg in het leven worden vastgesteld. Lichtere stoornissen, die toch een onmiskenbare invloed op het leven hebben, zijn echter (nog) niet vroeg vast te stellen.

6 Bij de beoordeling van de psychomotore ontwikkeling van te vroeg geboren kinderen lijkt correctie voor de mate van prematuriteit in het eerste levensjaar een redelijk compromis. Na het eerste levensjaar moet correctie niet meer worden toegepast.

7 Onderzoek van gezond overlevende te vroeg geboren kinderen vormt de sleutel tot het vaststellen van mogelijk beschermende mechanismen, die hersenbeschadiging kunnen voorkomen.

8 Follow-up van te vroeg geboren kinderen blijft zowel uit wetenschappelijk oogpunt als vanuit het oogpunt van patientenzorg noodzakelijk en moet voldoende lang duren om ook stoornissen op de schoolleeftijd op te sporen.

9 De uitspraak 'hoe meer zielen, hoe meer vreugd' gaat bij in-vitro fertilisatie niet op. Gezien de ernstige medische en psychosociale complicaties bij drie- en grotere meerlingen zouden deze dan ook als een mislukking van de IVF beschouwd moeten worden.

10 De toegenomen frequentie van kinderen met ernstige respiratoire restverschijnselen (bronchopulmonale dysplasie) na neonatale intensive care is zorgwekkend.

11 Voor de emotionele ontwikkeling van kinderen met een bronchopulmonale dysplasie is het van groot belang dat zo vroeg mogelijk ontslag naar huis wordt nagestreefd. Een adequate multidisciplinaire poliklinische nazorg is hiervoor een conditio sine qua non.

12 Aangezien de definities van neonatale intensive care, high care en/of post-intensive care niet eenduidig zijn en deze definities nog frequent worden gewijzigd, verdient het aanbeveling een zodanig geautomatiseerde registratie van patientengegevens op te zetten dat niet alleen een kwantificering conform iedere redelijke definitie hieruit af te leiden is, maar ook de gegevens door de jaren heen onderling vergelijkbaar blijven.

13 De complexiteit van de medische problemen in de neonatologie maakt de registratie van een hoofddiagnose zoals voorgeschreven voor de landelijke medische registratie tot een zeer willekeurige aangelegenheid. Gegevens die hierop zijn gebaseerd moeten dan ook met een flinke dosis zout bekeken worden.

14 Dat de 'disutility' van kinderartsen groter is dan die van andere medische specialisten is waarschijnlijk het gevolg van de extreme 'disutility' in de neonatologie. Een voldoende bestaffing van neonatale intensive care centra zou dan ook de hoge prioriteit moeten krijgen. J.D. van Gool, R. de Groot. Med Contact 1991,46, 331-333.

15 De toename van prinsen in de verpleegkunde en assepoesters in de geneeskunde kan er toe leiden dat de ziekenhuislakens weldra vanuit een andere discipline worden uitgedeeld.

16 Een verplicht vaderschapsverlof zal veel vooroordelen tegen werkende moeders wegnemen.

A.L. den Ouden Leiden, 27 juni 1991

I, that am curtail'd of this fair proportion,
cheated of feature by dissembling nature,
deform'd, unfinish'd, sent before my time
into this breathing world scarce half made up,
and that so lamely and unfashionable
that dogs bark at me as I halt by them;

Shakespeare, King Richard III

Contents

INTRODUCTION

Neurodevelopmental disabilities occur in every population. In preterm infants they are more frequent and the frequency with which they occur is not stable over time. In a survey of the literature on the outcome for very low birth weight (VLBW) infants, Stewart et al (1981) found that before 1960 a decrease of mortality was accompanied by an increase of handicapped survival, but after 1960 the handicap rate stabilized at 6-8% of VLBW liveborn infants, while the mortality rate further decreased. Hagberg et al (1984) found that after 1975 the percentage of diplegia increased among preterm infants.

In addition to these neurological sequelae, less severe neurodevelopmental disabilities are diagnosed in older children. Minor neurological dysfunction, abnormal EEG tracings and perceptuo-motor difficulties were diagnosed in a relatively high proportion of preterm children, although the mean IQ was within the normal range (Fitzhardinge and Ramsay 1973). Vohr and Garcia Coll (1985) reported recently that over 50 % of their very low birthweight survivors needed special education services. Hertzig (1981) found neurological 'soft' signs in half of her population of 8-year-old preterm infants. Although IQ scores in children with or without these 'soft' signs did not differ, significantly more children with soft signs needed special education or had been referred for psychiatric consultation. Similar results were found in a small sample of children with birth weight between 1500 and 2000 grams in Amsterdam (Evers-Embden 1983).

The relatively high incidence of both major and minor disorders attests to the continuing high-risk status of the preterm infant. Follow-up of very preterm infants is therefore necessary; it should serve three main aims. In the first place, in each individual child, to identify developmental disturbances as early as possible in order to start interventional therapy to mitigate the effects of this disturbance on the child and its family. Secondly, to establish which developmental disabilities occur and with what frequency, in order to plan appropriate management and intervention strategies. Thirdly, to evaluate perinatal management in order to try to prevent possible causes of developmental disturbance.

Short-term follow-up has the advantage of early identification of severe neurodevelopmental disabilities. It is possible to relay information about infant morbidity at a time when it is most likely to have relevance to perinatal management. There are, however, concerns about the over-

emphasis on neurological impairments, some of which may lessen in severity or appear to be transient (Nelson and Ellenberg 1982). On the other hand, there is the likelihood of underestimation of subtle mental retardation and learning disorders that may not be apparent until a later age.

Long-term follow-up is difficult and expensive. It is essential, however, to know the later outcome of children who were born very preterm. It is therefore a challenge to learn which assessments in the first years of life are useful in order to identify children with neurodevelopmental disabilities.

The aim of the present study was to answer some questions about the value of investigations in the neonatal period and early childhood in very preterm infants for the identification of children with neurodevelopmental disorders. This concerned specific investigations in the neonatal period in hospital-bound populations, as well as routine clinical evaluations in the neonatal period and early childhood of a large geographically-defined population.

The questions concerning the neonatal period are:

1. Is it possible to identify children at risk for severe neurodevelopmental handicap in the perinatal period by biochemical or doppler-ultrasonographic parameters?

2. Is it possible to predict neurodevelopmental outcome from the staging of myelination by magnetic resonance imaging shortly after term?

3. Are neonatal seizures or neurological abnormalities as observed by routine paediatric examination in the neonatal period predictive of later neurodevelopmental problems?

The questions concerning early childhood are:

4. Are neurological abnormalities in infancy predictive of the neurodevelopmental outcome, even when they seem to be transient?

5. Is the neurodevelopmental assessment which is frequently used in this country capable of identifying children with neurodevelopmental problems; should correction for preterm birth be applied when this assessment is used in preterm infants?

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PART I

PREDICTIVE VALUE OF INVESTIGATIONS IN THE NEONATAL PERIOD

Chapter 1

THE RELATIONSHIP BETWEEN SERUM CK-BB ACTIVITY IN THE PRETERM INFANT AND OUTCOME AT TWO AND FOUR YEARS OF AGE

Lya den Ouden, Margot van de Bor, Frank van Bel,
Hans Janssen, Ronald Brand, Jan H.Ruys.

Developmental Medicine and Child Neurology, 1990, 32, 509-514.

Chapter 1

THE RELATIONSHIP BETWEEN SERUM CK-BB ACTIVITY IN THE PRETERM INFANT AND OUTCOME AT TWO AND FOUR YEARS OF AGE

Summary

The relationship between serum creatine kinase brain specific isoenzyme (CK-BB) activity immediately after birth and neurodevelopmental outcome at 2 and 4 years corrected age was studied prospectively in 45 preterm infants (< 34 weeks gestation). Nine infants died during the neonatal period and one was lost to follow-up. Of the 35 children available for follow-up, 7 had motor disabilities (4 severe diplegia, 2 mild to moderate diplegia, 1 hemiplegia). No relationship existed between these motor disabilities and serum CK-BB activity after birth. There seemed to be a relationship between increased serum CK-BB activity after birth and low scores on the Bayley scales of mental development, but this did not reach significance. At the age of 4 years 4 of the 5 survivors with high serum CK-BB activity after birth (> 25 U/L) needed special schooling due to mental retardation. Increased serum CK-BB activity after birth may be associated with delayed mental development, but further study is needed, especially in asphyxiated infants.

Introduction

Abnormal findings on neurological examination, ultrasound and magnetic resonance imaging of the brain during the neonatal period have been reported to be related to motor disabilities at later ages (Dubowitz et al. 1981,1984, De Vries and Dubowitz 1985). However, the prediction of mental delay, unlike motor disabilities, remains a problem. Motor defects are usually the result of local brain lesions, whereas mental delay may be mainly the result of more diffuse brain damage. Elevated serum CK-BB activity was reported in relation with brain injury in both adults (Somer et al. 1975) and neonates (Becker and Menzel 1978, Speer et al. 1983). Kaste et al (1977) found that high serum CK-BB activity was specifically associated with diffuse brain damage, whereas patients with localised brain damage had mostly low CK-BB activity. We undertook a prospective study to determine whether serum CK-BB activity in the newly born

preterm baby plays a prognostic role in the differentiation between motor and mental disabilities at a later age.

Patients and method

In the first nine months of 1984 forty-five consecutively admitted infants of less than 34 weeks gestation, determined by maternal dates or Ballard scores (Ballard et al. 1979) and consecutively admitted to our neonatal intensive care unit immediately after birth were enrolled in the study after informed parental consent was obtained. The study was approved by the scientific committee of the Department of Pediatrics.

Blood samples for CK-BB measurements were taken from an indwelling umbilical artery catheter shortly after birth (within eight hours), between 8 and 16 hours later, and daily thereafter until day seven. Three hundred microliter samples were instantly centrifuged (10 min; 3500 rpm). After separation of the serum, mercaptoethanol was added, in a final concentration of 15 mmol/l (Cho and Meltzer 1979). The sera were stored at -20·C until batch analysis was performed within two weeks. Serum CK activity was determined automatically (Oliver 1955), using the RA-1000 (Technicon instruments, Tarrytown, NY). Reference values used for adult males range from 5 to 50 U/L. The CK isoenzymes were separated electrophoretically, using the Corning CK isoenzyme substrate set (Corning Medical, Palo Alto, CA). For quantitative results the percentage CK-BB isoenzyme was multiplied with the total CK activity to get the isoenzyme concentration in U/L.

Perinatal data included gestational age, birthweight, and Apgar scores at 1 and 5 minutes. Using an Advanced Technology Laboratory mechanical sector scanner (ATL Mark 300C) with a 5 MHz transducer, we performed ultrasound examination of the brain daily during the first week of life and twice weekly thereafter until discharge. Periventricular-intraventricular haemorrhages (PIVH) were graded according to the classification of Papile et al (1978).

Neurodevelopmental outcome was assessed at the corrected ages of 2 years and 4 years by means of a paediatric examination,a neurological examination based on the method of Touwen (1976), and visual and hearing screening. The developmental level was assessed at 2 years of age by a paediatrician, using the Gesell test adapted for Dutch children (Schlesinger-Was 1982), and by a psychologist, who was unaware of the neonatal status of the child, using the Bayley scales of mental and motor development (Bayley 1969). At the age of 4 years the Denver Developmental Screening Test (DDST, Frankenburg and Dodds 1967) was used.

A child was considered to have a motor disability when there were neurological abnormalities leading to motor impairment, with or without developmental delay. Minor neurological dysfunction (MND) was recorded when there was dystonia, asymmetry and/or abnormal reflexes, without any impairment. Developmental delay was diagnosed when the result of the DDST was abnormal; a suspect outcome was not considered as delay.

Statistical methods

Differences between mean gestational age and mean birthweight were assessed by the Kruskal-Wallis test. Differences in the incidences of low Apgar scores (Apgar 5) and of PIVH were assessed with chi square tests. That test was also used to analyse the relationship between serum CK-BB values and outcome at 4 years. Linear regression analysis was used to compare serum CK-BB activity at birth with results on the Bayley scales at 2 years. $P < 0.05$ was considered significant.

Table 1: Perinatal caracteristics of 44 preterm infants and outcome at 4 years of age

	Neonatal death n = 9	Motor disabilities n = 7	mental retardation n = 4	Normal n = 24	p
gestational age					
mean (SD)	27.3 (2.0)	28.3 (1.3)	31.2 (0.2)	30.4 (1.8)	< 0.01
birthweigth					
mean (SD)	1121 (384)	1079 (191)	1345 (564)	1437 (370)	< 0.05
Apgar scores < 5					
1 min	6	5	3	13	ns
5 min	4	2	1	2	ns
PIVH					
none	2	3	3	18	
grade I		1		2	
grade II	3	2	1	2	< 0.05
grade III				2	
grade IV	4	1			
CK-BB (U/L)					
median (range)	11.0(0.4-57.2)	0.0(0.0-5.0)	30(25.2-41.7)	4.8(0.0-125)	

Results

Nine of the initial 45 infants died during the neonatal period, and one child was lost to follow-up. Therefore the final study group available for follow-up at 2 and 4 years corrected age consisted of 35 children. Their mean gestational age was 30.1 (SD 1.8) weeks and mean birthweight was 1370g (SD 414g) grams.

Perinatal data of the studied infants are given in table 1. Gestational age and birthweight were lower for children with motor disabilities, and for infants who died neonatally. Also, low Apgar scores (Apgar 5) and PIVH were more frequent in children with motor disabilities, but the differences did not reach statistical significance.

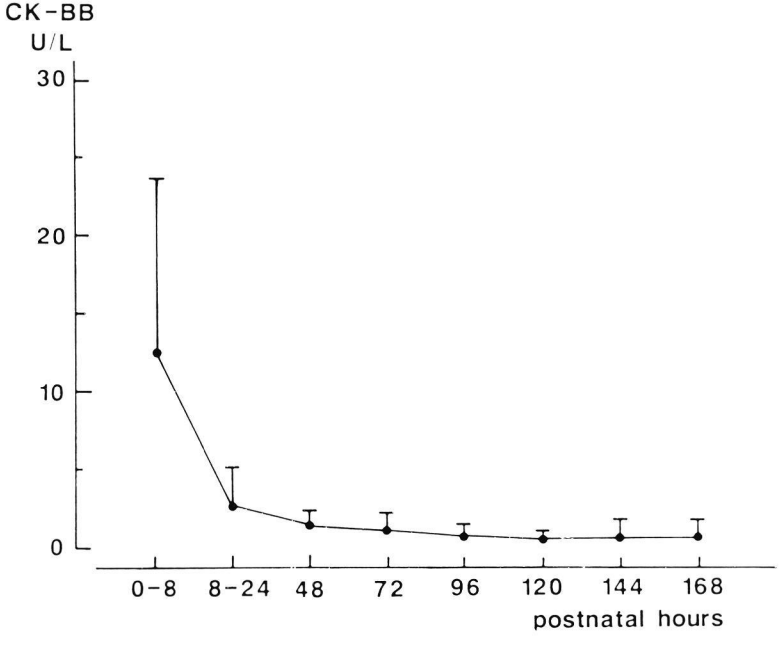

Figure 1: Decline of serum CK-BB in the first days after birth.

Serum CK-BB activity determined immediately after birth ranged from non detectable CK-BB to 125 U/L (mean 13.3, SD 22.2). Mean serum CK-BB activity declined rapidly thereafter, to a level of 0.3 U/L on day 7 (Fig. 1).

Motor disabilities were found in 8 children at the age of 2 years. Seven of these retained this diagnosis at 4 years; the eight was diagnosed as MND at 4 years. MND was found in seven children at 2 years, 4 of whom were considered normal at 4 years.

The Bayley DQs of children without motor disabilities ranged from 54 to 129. Six children had a score of less than 80 at 2 years of age, four of whom also had abnormal results on the DDST at 4 years. All are in need of special schooling.

Visual problems were found in 6 children (4 squint, 2 squint and myopia), 3 of whom also had motor disabilities. One of the retarded children had a moderate perceptual hearing loss. No relation between motor disabilities and initial serum CK-BB activity was found (table 2).

There seemed to be a relationship between low Bayley scores at 2 years and high serum CK-BB activity after birth but, this was not statistically significant (correlation coefficient -0.67, $p < 0.0001$) (Fig. 2). At the age of 4 years 4 children appeared to be retarded; all 4 had high serum CK-BB activity after birth (25.2-41.7 U/L) (table 2). However, 1 child with exceptionally high serum CK-BB activity after birth (125 U/L) was completely normal at follow up.

Table 2: Relationship between outcome at four years and serum CK-BB activities after birth

CK-BB (U/L)	total n=44	neonatal death n=9	CP n=7	mental retardation without motor disabilities n=4	Normal n=24	p
0-25	36	6	7	-	23	
>25	8	3	-	4	1	<0.025

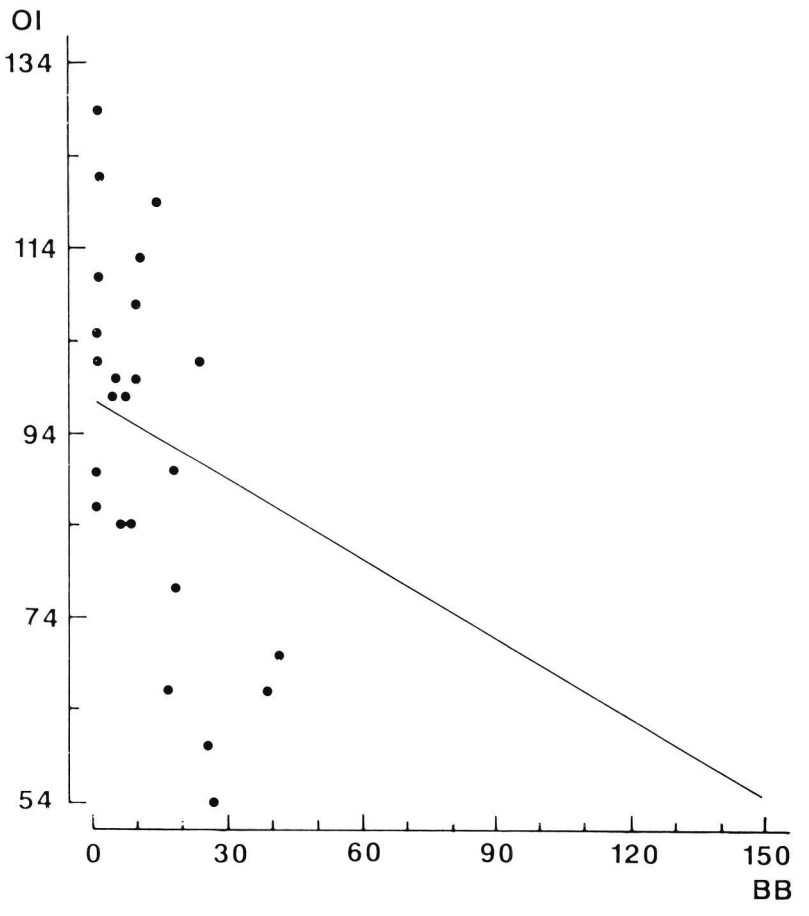

Figure 2: Serum CK-BB activities after birth in relation to Bayley scores at 2 years of age.

Discussion

The relationship between increased serum CK-BB activity on the one hand and brain damage and mortality on the other hand is well established: Cuestas (1980) found a relationship with neonatal neurological abnormalities, and Speer et al (1983) found significantly higher neonatal mortality.Our study showed a relationship between increased serum

CK-BB activity after birth and mental delay in children without motor disabilities at 4 years of age. This gives further support to the hypothesis that increased CK-BB activity reflects severe and diffuse brain-cell damage.

It is surprising that no relationship was found between motor disabilities and high serum CK-BB activity after birth. The results might be biased, since 5 of the 9 infants who died in the neonatal period had high serum CK-BB activity after birth and 4 of them had grade IV PIVH (Van de Bor et al. 1988). It is possible that these infants had also more extensive brain damage. Using positron emission tomography, Volpe (1987) found that brain damage is much more extensive than the bleeding area alone in infants with intraparenchymal haemorrhage.

Another explanation might be that perinatal damage to brain-cells resulting in mental retardation is more extensive, causing increased serum CK-BB activity, while brain-cell damage resulting in motor disabilities may be more localised (Azzopardi et al, 1989). It is probably more likely that serum CK-BB elevation was not found during the first week of life because the cerebral damage occurred not at birth, but either prenatally or later during the neonatal period. In all 4 children with severe diplegia, the damage may have occurred at other times; 1 probably prenatally -twin gestation, the other infant died before birth (Barth and van der Harten 1985)- and 3 postnatally -2 had severe hypocarbia on the second day of life (Greisen and Trojaborg 1987) and 1 had severe intraparenchymal haemorrhage due to severe thrombocytopenia.

Although a relationship seems to exist between serum CK-BB after birth in preterm infants and developmental delay at 2 years, this relation is not statistically significant. A firmer relationship was found at the age of 4 years, although one child with exceptionally high serum CK-BB activity after birth was completely normal at 4 years of age.

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Chapter 2

CEREBRAL BLOOD FLOW VELOCITY PATTERN DURING THE FIRST WEEK OF LIFE IN THE PRETERM NEWBORN AND NEURO-DEVELOPMENTAL OUTCOME AT 2 YEARS OF AGE

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Developmental Medicine and Child Neurology, 1989, 31, 320-328.

Chapter 2

CEREBRAL BLOOD-FLOW VELOCITY DURING THE FIRST WEEK OF LIFE OF PRETERM INFANTS AND NEURODEVELOPMENT AT TWO YEARS

Summary

Disturbances in perinatal cerebral perfusion appear to be related with unfavourable neurodevelopmental outcome. Using transcutaneous Doppler technique, we investigated cerebral blood-flow velocity patterns in the anterior cerebral artery (ACA) of an intensive care-unit population of preterm infants during the first week of life. The results were correlated with neurodevelopmental outcome at 2 years of age. Children with major disability at 2 years of age had significantly higher pulsatility index (PI) values, mainly increased peak systolic flow velocity (PSFV), compared with children with normal or more favourable outcome. End diastolic flow velocity (EDFV) and area under the velocity curve (AUVC) values of the ACA did not differ between the groups, indicating that cerebrovascular resistance and cerebral blood flow were not different. It is thought that the higher PI and PSFV values were caused by increased compliance of the vascular bed supplied by the ACA, possibly induced by congestion and edema of the periventricular white matter due to ischaemic lesions, which also cause periventricular leukomalacia.

Introduction

Several studies have established a relationship between abnormal perinatal and neonatal conditions such as birth asphyxia, periventricular/intraventricular haemorrhage (PIVH), periventricular leukomalacia (PVL) and respiratory distress syndrome on the one hand, and unfavourable neurodevelopmental outcome on the other (Sarnat and Sarnat 1976, Nelson et al. 1981, Finer et al. 1981, Adsett et al. 1985, Szymonowicz et al. 1986, Bozynski et al. 1987). Disturbances in cerebral perfusion occur in most of these conditions (De Reuck 1971, Cooke et al. 1979, Takashima et al. 1986, Van Bel et al. 1987a, Van Bel et al. 1987b). Recent investigations of the newborn cerebral circulation, using Doppler ultrasound, report a relationship between the pattern of cerebral blood flow velocity (CBFV) in early neonatal life and neurodevelopmental outcome for the more mature infants (Archer et al. 1986a, Den Ouden et al. 1987).

The object of this study was to investigate whether the pattern of CBFV of preterm infants in the neonatal period is also related to neurodevelopmental outcome. For this purpose we studied CBFV prospectively during the first week of life in a randomly selected, intensive care-unit population of preterm newborns of less than 34 weeks gestation, and correlated the results with neurodevelopmental outcome at 2 years of age.

Patients and method

During one whole year all infants who met the following criteria were enrolled in the study: 1) gestational age less than 34 weeks, determined by maternal dates or Ballard scores (Ballard et al. 1979); 2) appropriate weight for gestational age; 3) admitted within 8 hours of birth; 4) no major congenital abnormalities; and 5) offering the possibility to perform reliable (Doppler) ultrasound investigation of the brain. 60 infants met these criteria and initially participated in the study. Birth weights ranged from 500-2670 grams (mean 1404, SD 473g) and gestational ages from 25-33 weeks (mean 29.4, SD 2.1 weeks).

The study, including its ethical aspects, was approved by the scientific board of the department of pediatrics. Informed parental consent was obtained in all cases.

Investigation of cerebral blood flow velocity

For investigation of CBFV during the first week of life, the blood-flow velocity wave form in the anterior cerebral artery (ACA) was recorded, as described previously (Van Bel et al. 1987a), using a continuous mode bi-directional Doppler flowmeter (Parks elektronics, 1010) with a 9.6 MHz transducer. From at least 10 sequential cardiac cycles, the peak systolic flow velocity (PSFV) and end-diastolic flow velocity (EDFV) were determined and averaged. A pulsatility index (PI) was then calculated, as described by Bada et al. (1979) (PI = (PSFV-EDFV)/PSFV), and used as a relative measure of cerebrovascular resistance and concomitant changes in CBFV. A high PI correlates with increased cerebrovascular resistance and decreased CBFV; a low PI correlates with decreased cerebrovascular resistance and increased CBFV. The area under the velocity curve (AUVC), which represents the mean flow velocity (Batton et al. 1983), was determined and averaged from the same 10 cardiac cycles, using a signal tracing method (BIT PAD I) coupled to a computer (DEC PDP 11/23). AUVC was then corrected for heart rate. From birth or admission until day 3, the Doppler variables PSFV, EDFV, PI and AUVC of the ACA were determined every 8 hours, then every 12 hours

during the following 4 days. Simultaneously with the Doppler investigations, arterial blood gases and arterial blood pressure (Dinamap) were determined. Daily haematocrit estimations were done.

Clinical data

Obstetric and intrapartum data were collected from hospital recordings and neonatal data were collected prospectively. Management decisions were made clinically by the attending staff.

Hyaline membrane disease was diagnosed on clinical features (respiratory distress not attributable to other causes) and chest radiography, for which we used the radiological classification as described by Giedion et al. (1973). All inborn infants of less than 30 weeks gestational age were intubated and ventilated immediately after birth. For the other patients, assisted ventilation was instituted when PaO_2 remained below 6.7 kPa (50 mmHg) at FiO_2 of 0.6, or $PaCO_2$ was 8.0 kPa (60 mmHg) or more and pH less than 7.20. The diagnosis "significant patent ductus arteriosus" was based on clinical features (characteristic murmur, bounding pulses and hyperactive precordium), radiological features (cardiomegaly and pulmonary plethora) and echocardiographic indices (left atrial to aortic root ratio ≥ 1.15) (Ellison et al. 1983). Haematocrit did not exceed 65% in the infants studied during the neonatal period. If necessary, packed red cell infusions were given to keep haematocrit above 40%.

Diagnosis of PIVH and PVL was performed by real time ultrasound, using a mechanical sector scanner (Advanced Technology Laboratories, Mark 300C) with a 5 MHz transducer. In the first week of life real time ultrasound investigations of the brain were performed simultaneously with the Doppler investigations of the ACA; thereafter the investigations were continued on a weekly basis (or more frequently if necessary) until discharge or death. PIVH was graded as mild, moderate or severe, according to the classification of Shankaran et al. (1982). The diagnosis PVL was made if periventricular cysts developed which did not communicate with the ventricular system during the neonatal period (Levene et al. 1983).

Diagnosis of perinatal asphyxia was made if both the following criteria were met: 1) fetal distress, i.e. abormal heart rate pattern and low cord pH (< 7.20), and 2) a five minute Apgar score less than 5.

Assessment of neurodevelopmental outcome

Follow-up at the corrected age of 2 years included neurological screening according to Touwen, vision, hearing and neurodevelopmental screening

with Bayley scales of mental and motor development. Outcome was classified as: 1) normal-normal neurological findings and development; 2) minor impairment-minor neurological abnormalities without functional restrictions and/or DQ scores from 80 to 90; or 3) major disability - definite neurological abnormality with functional disability and/or DQ scores of less than 80. Ultrasound investigations of the brain were repeated in all surviving infants at approximately 3 months of age, and if abnormalities were detected, investigations were continued until closure of the anterior fontanelle.

Statistical analysis

Differences in mean gestational ages and mean birthweights were assessed by one-way analysis of variance. Differences in mode of delivery, incidence of perinatal asphyxia, need for assisted ventilation, occurrence of hyaline membrane disease and of patent ductus arteriosus with a chi-square test. The differences between the mean values of PI, EDFV, PSFV and AUVC of the ACA were assessed by the Student two sample t-test (two-tailed). Correlations were assessed by Spearman correlation coefficients. P-values of < 0.05 were considered statistically significant.

Results

Over-all outcome

Ten infants died during the neonatal period: 5 after severe hyaline membrane disease; 4 because of major PIVH, and one infant because of necrotising enterocolitis. One infant died 8 weeks after birth because of pulmonary insufficiency due to severe bronchopulmonary dysplasia. Two infants were lost from follow-up. Therefore the final study-group available for follow up at 2 years comprised 47 children.

Twenty-nine children had a normal outcome, 11 had minor neurological and/or mental abnormalities, and 7 had major neurological and/or mental abnormalities. Table 1 shows the perinatal data of the different groups. The normal children were somewhat heavier and more mature at birth than those with impairments, but these differences were not statistically significant. It is remarkable that all children with major disability had ventriculomegaly (often severe) at 3 months of age, although only one child had PIVH.

Table 1: Important perinatal data of the 47 infants with different neurodevelopmental outcome

Perinatal data	Normal (n = 29)	Minor impairment (n = 11)	Major impairment (n = 7)	P
birth weight (g)				
mean (SD)	1529(470)	1208(356)	1459(492)	
gestational age (wk)				
mean (SD)	30.0(1.8)	28.9(2.4)	29.4(1.4)	
mode of delivery (n)				
vaginal	19	7	5	
cesarean section	10	4	2	
perinatal asphyxia (n)	10	5	3	
hyaline membrane disease (n)	10	6	2	
assisted ventilation (n)	20	10	6	
patent ductus arteriosus in the first week of life (n)	2	1	1	
ultrasound studies of the brain				
A) neonatal period:				
normal	21	5	4	
mild PIVH	3	2	0	
moderate PIVH	3	2	0	
severe PIVH	2	2	1	
PVL	0	0	2	
B) at 3 months of age: ventriculomegaly				
mild	2	3	3	
marked	0	0	4	.0001

Cerebral blood-flow velocity in the first week of life and neurodevelopmental outcome

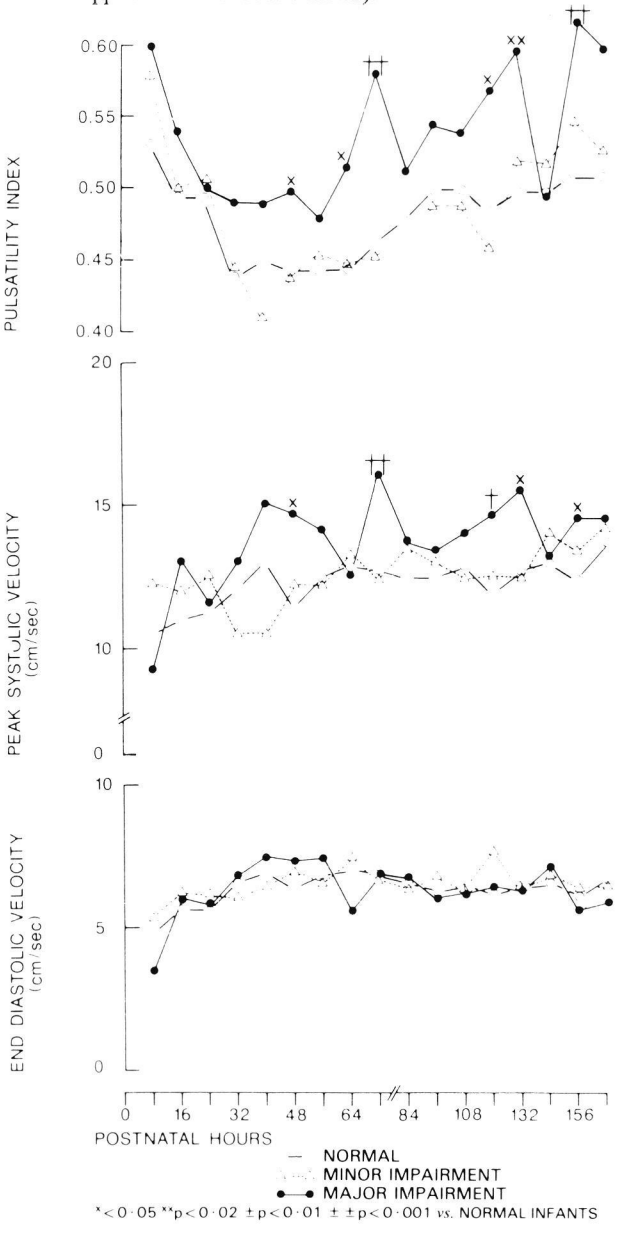
The mean Doppler variables PSFV, EDFV, PI and AUVC of the ACA of children with a normal outcome were compared to those of children with

Table 2: Mean Doppler variables PSFV, EDFV, PI, and AUVC of the ACA for normal and handicapped children.

Postnatal hours	*Peak systolic flow-velocity (cm/sec)*			*End diastolic flow-velocity (cm/sec)*			*Pulsatility index*			*Area under velocity curve (cm/min)*		
	Normal	*Minor impairment*	*Major impairment*	*Normal*	*Minor impairment*	*Major impairment*						
8	10·5 (3·2)	12·4 (4·2)	9·0 (1·0)	4·9 (2·4)	5·2 (3·3)	3·5 (1·5)	0·53 (0·11)	0·58 (0·17)	0·60 (0·15)	486 (182)	579 (250)	529 (208)
16	11·0 (3·8)	12·0 (5·5)	13·0 (3·5)	5·6 (2·0)	6·0 (3·1)	6·0 (1·0)	0·49 (0·10)	0·50 (0·11)	0·54 (0·06)	531 (150)	575 (229)	660 (228)
24	11·4 (2·5)	12·6 (2·1)	11·5 (2·5)	5·8 (1·8)	6·0 (1·5)	5·9 (1·0)	0·49 (0·11)	0·50 (0·09)	0·50 (0·06)	556 (120)	604 (106)	542 (115)
32	12·0 (3·6)	10·8 (2·0)	13·0 (3·0)	6·6 (1·8)	6·0 (1·6)	6·8 (2·0)	0·45 (0·08)	0·45 (0·10)	0·48 (0·07)	621 (200)	530 (116)	607 (135)
40	13·0 (3·2)	10·5 (1·8)	15·0 (3·5)	7·0 (1·5)	6·4 (1·6)	7·8 (2·0)	0·45 (0·09)	0·40 (0·08)	0·48 (0·07)	622 (150)	563 (124)	789 (203)
48	11·5 (3·3)	12·5 (3·6)	14·7 (3·5)[1]	6·4 (2·0)	7·1 (2·2)	7·5 (2·0)	0·44 (0·08)	0·43 (0·06)	0·50 (0·08)[1]	564 (172)	629 (196)	663 (203)
56	12·5 (3·4)	12·0 (2·4)	14·1 (2·0)	6·8 (2·2)	6·8 (1·8)	7·5 (1·0)	0·45 (0·10)	0·45 (0·09)	0·48 (0·07)	630 (175)	617 (126)	664 (138)
64	13·0 (2·9)	13·3 (1·9)	12·5 (3·0)	7·2 (2·5)	7·4 (2·0)	6·0 (1·5)	0·45 (0·08)	0·44 (0·11)	0·52 (0·03)[1]	670 (165)	675 (120)	593 (180)
72	12·8 (4·1)	12·4 (3·3)	16·1 (3·0)[4]	6·8 (2·6)	6·8 (1·6)	6·8 (2·0)	0·47 (0·08)	0·45 (0·08)	0·58 (0·07)[4]	638 (214)	634 (127)	675 (192)
84	12·5 (3·5)	14·0 (2·6)	13·8 (4·5)	6·5 (2·2)	6·7 (2·5)	6·6 (1·4)	0·48 (0·09)	0·50 (0·11)	0·52 (0·08)	628 (195)	707 (136)	694 (268)
96	12·5 (4·1)	13·0 (3·6)	13·3 (4·5)	6·2 (2·0)	6·8 (2·4)	6·0 (2·0)	0·50 (0·10)	0·48 (0·10)	0·55 (0·10)	609 (198)	640 (167)	609 (166)
108	12·9 (3·2)	12·4 (2·1)	14·5 (3·5)	6·4 (2·2)	6·3 (1·4)	6·2 (2·0)	0·50 (0·11)	0·48 (0·07)	0·54 (0·09)	615 (171)	625 (137)	683 (164)
120	11·8 (2·8)	12·9 (3·5)	14·7 (2·5)[3]	6·1 (2·1)	7·0 (3·8)	6·3 (2·5)	0·48 (0·11)	0·46 (0·07)	0·57 (0·10)[1]	588 (162)	663 (211)	666 (149)
132	12·7 (3·1)	12·5 (3·0)	15·6 (4·0)[1]	6·3 (1·7)	6·1 (1·1)	6·2 (2·5)	0·50 (0·06)	0·51 (0·07)	0·60 (0·07)[2]	639 (180)	599 (114)	737 (182)
144	13·1 (2·5)	14·3 (3·1)	13·5 (3·0)	6·5 (1·8)	6·8 (1·4)	7·0 (1·0)	0·50 (0·09)	0·51 (0·08)	0·48 (0·03)	627 (109)	751 (160)	649 (155)
156	12·4 (3·4)	13·4 (3·3)	14·5 (2·0)[1]	6·0 (1·9)	6·1 (1·5)	5·5 (1·5)	0·51 (0·08)	0·55 (0·04)	0·62 (0·05)[4]	598 (182)	627 (149)	679 (141)
168	13·5 (2·8)	14·0 (3·4)	14·5 (2·0)	6·5 (1·6)	6·5 (1·4)	5·8 (2·0)	0·51 (0·09)	0·53 (0·08)	0·60 (0·14)	686 (153)	670 (163)	635 (120)

[1]$p<0·05$, [2]$p<0·02$, [3]$p<0·01$, [4]$p<0·001$, *vs.* normal infants.

Figure 1: Mean PI, AUVC, PSFV and EDFV of the ACA of normal infants and those with minor and major impairments as function of postnatal age. (For reasons of clarity, standard deviations of mean Doppler variables are not shown).



minor and major impairments, respectively, at 2 years of age as a function of postnatal age (Table 2). The results are shown in figure 1. The children with major impairments had consistently higher PI-values until day 7 compared with normal children, and with those with minor impairments. All children showed decreasing PI-values until day 2, but only those in the latter two groups had a gradual and similar increase afterwards. Significant differences in PI between the children with major impairments and the normal children were reached at 48, 64, 72, 120, 132 and 156 hours of age ($p < 0.05$, $p < 0.05$, $p < 0.001$, $p < 0.05$, $p < 0.02$ and $p < 0.001$ respectively). As illustrated in the figure, it appears that the higher PI-values of the children with major impairments were mainly caused by higher PSFV-values of the ACA: significant differences between them and the normal children were reached at 48, 72, 120, 132 and 156 hours of age s($p < 0.05$, $p < 0.001$, $p < 0.01$, $p < 0.05$ and $p < 0.05$ respectively). The EDFV and AUVC values of the normal children did not differ significantly at any time from those of the children with minor or major impairments.

Relationship of the clinical data of the infants with major impairment and the PI of the ACA

Because of the evident differences in the PI of the ACA between the severely disabled group compared with the normal children and children with minor impairments, we correlated the PI and the PSFV of the ACA

Table 3: Correlations between important clinical data (means)and Doppler variables (means) of group with major impairment (n = 7) during the first week of life (17 measuring points)

	PI		PSFV (cm/sec)	
clinical data	r	p	r	p
$PaCO_2$	.30	ns	.16	ns
PaO_2	-.03	ns	.03	ns
systolic blood pressure	-.32	ns	.28	ns
diastolic blood pressure	-.57	ns	.21	ns
haematocrit	.42	ns	.50	ns

of the infants with major impairments with the perinatal factors which are known to influence CBFV and which were collected simultaneously with the Doppler investigations from birth until day 7. These factors were: $PaCO_2$, PaO_2, blood pressure and haematocrit. Table 3 shows the results. No significant correlations were found between any perinatal factor and any of the two Doppler variables.

Discussion

Changes in the PI of the ACA can be induced by factors both proximal and distal to the site of the Doppler recordings. The proximal influences are mainly a haemodynamically important ductus arteriosus (causing an increase in PI mainly because of a decrease in EDFV) (Van Bel et al. 1987), pump function of the heart and changes in blood pressure, insofar as autoregulation of the brain is insufficient. The main factor operating distally to the measuring site is an alteration in cerebrovascular resistance, mainly induced by changes in $PaCO_2$ and/or PaO_2, but also by a change in compliance of the vascular bed. Cerebrovascular resistance is largely controlled by the cerebral arterioles situated distal to the ACA, whereas the ACA itself has little capacity to alter its internal diameter (Huber and Handa 1967, McHedlishvilli 1980, Ahmann et al. 1983), but changes in haematocrit also play a role. In the absence of a haemodynamically significant ductus arteriosus, with intact autoregulation, and no important changes in haematocrit, the PI of the ACA appears to be indicative of changes in cerebrovascular resistance and concomitant changes in cerebral blood-flow. This is the case provided the resistance-related changes in the blood flow velocity curve are reflected mainly by changes in EDFV, as has been shown in recent studies dealing with preterm and term infants (Pourcelot 1974, Bada et al. 1979, Greisen et al. 1984, Archer et al. 1986). Also, the AUVC of the ACA, representing the temporal mean flow velocity, has shown reliable correlations with actual cerebral blood-flow (Hansen et al. 1983, Greisen et al. 1984, Perlman et al. 1985).

In this study we found a strikingly higher PI of the ACA during the first week of life in the children with major disability at two years compared with the other children studied. This finding is in agreement with preliminary results of a study of preterm infants by Bada et al (1985). Because changes in PI were caused mainly by an increase in PSFV, and not by a decrease in EDFV, we presume the higher PI values in our infants with major disability do not indicaten increased cerebrovascular resistance (and concomitant decreased cerebral blood-flow). Moreover,

AUVC-values of the ACA between the 3 groups of infants did not differ significantly, also indicating an absence of changes in cerebral blood-flow. Rather, this finding implies that changes in the shape of the pulsatile velocity signal form the basis of the increase in PSFV and PI (Van Bel et al. 1988). It is not very likely that the changes in PI in the group with major disability were caused by patent ductus arteriosus: only two children with normal outcome, one in the group with minor impairments and one in the group with major impairments, had hemodynamically significant ductus arteriosus in the first week of life. Besides, a patent ductus arteriosus results in a reduced EDFV rather than an increase in PSFV (Van Bel et al. 1987). Also, no correlation was found between PI or PSFV and blood pressure in this study group, indicating intact autoregulation.

How, then, must we interpret our findings? Changes in PSFV may reflect changes in peak flow as a result of changes in compliance of the arterial system, as has been shown, for example, for peak flow in the aorta (Elzinga and Westerhof 1973). Our finding of higher PSFV values of the ACA in the children with major disability suggests that the compliance of the vascular bed, primarily situated in white matter and supplied by this artery, is increased. In infants with posthaemorrhagic hydrocephalus, it has been suggested previously by Alvisi et al. (1985) and by us (Van Bel et al, in press) that periventricular white-matter edema causes an increase in extravascular (tissue) pressure (P_t), which, combined with unchanged blood pressure (P_b), results in a fall in transmural pressure ($P_b - P_t$). This fall causes increased compliance of the vascular bed because of the nonlinear relationship between transmural pressure and vessel diameter (Ross 1980, fig. 2.34). The nonlinear curve itself remains unaltered because the nonlinear elastic properties of the vessel wall are unchanged, but decreased transmural pressure shifts the working point to a steeper part of the curve, causing increased compliance. This explanation is corroborated by the findings for the internal carotid artery by Greenfield and Tindall (1965). We speculate that in our 7 patients, periventricular white matter congestion and edema existed in the first days of life, mainly on the basis of PVL, a common ischaemic lesion in the brains of preterm infants (De Reuck et al. 1972, Pape and Wigglesworth 1979, Levene et al. 1983, Bozynski et al. 1985). Although only 2 of the 7 children showed the typical neonatal ultrasound features of PVL, all seven developed ventricular dilatation within the first 3 months of life; six developed spastic diplegia or quadriplegia, and one child is deaf. These features are strongly indicative for PVL (Weindling et al. 1985, Bozynski

et al. 1987). The 5 MHz transducer used in this study (with resolution not as good as with the 7.5 MHz transducer used more recently) and the first appearance of periventricular cystic formation after discharge may both be held responsible for the fact that the neonatal features of PVL were not discovered in all seven infants.

Although our study population is not large, there is some support to the supposition that PIVH alone is not necessarily associated with an adverse outcome (see table I) (Fawer et al. 1985, De Vries et al. 1985). However, we were not able to compare the neurodevelopmental outcome of infants with severe PIVH and those with PVL because 4 infants with severe PIVH died in the neonatal period.

In conclusion, we found that an elevated PI of the ACA in the first week of life of preterm infants, not due to postnatal influences such as abnormal-blood gases or patent ductus arteriosus, was related to adverse neuro-developmental outcome at 2 years of age. The PI was elevated mainly by an increased PSFV, suggesting increased compliance of the vascular bed supplied by the ACA. This increased compliance possibly is induced by edema in the periventricular white- matter due to ischaemic lesions such as PVL.

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Chapter 3

NEONATAL SEIZURES IN VERY PRETERM AND VERY LOW BIRTHWEIGHT INFANTS: MORTALITY AND HANDICAPS AT TWO YEARS OF AGE IN A NATIONWIDE COHORT.

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Neuropediatrics, 1990, 21, 62-65.

Chapter 3

NEONATAL SEIZURES IN VERY PRETERM AND VERY LOW BIRTHWEIGHT INFANTS:MORTALITY AND HANDICAPS AT TWO YEARS OF AGE IN A NATIONWIDE COHORT

Summary

In a nationwide, prospective survey on very preterm and/or very low birthweight infants (< 32 weeks of gestational age and/or < 1500 g birthweight) we studied the outcome at the corrected age of two years of children with neonatal seizures. Of the 1338 infants, originally enrolled in the study, 72 had neonatal seizures; of these 44 died and 11 developed a major handicap. Using a multivariate statistical method, a significantly increased risk of death as well as handicap was found in infants with seizures compared to infants without seizures. Nevertheless, 16 of the 28 survivors with neonatal seizures were considered normal at the corrected age of two years.

Introduction

In general, seizures in the neonatal period are considered to be powerful predictors of the risk of subsequent death or handicap in term infants (9, 10, 14). The prognosis depends on various factors such as etiology, time of onset and duration, EEG-findings and other neonatal neurological signs. The prognostic value in preterm infants, however, is less clear (13).

As part of a national collaborative survey in the Netherlands on morbidity and mortality in very preterm and/or very low birthweight infants, the relationship between neonatal seizures and mortality and neurodevelopmental outcome at the corrected age of two years was studied.

Materials and method

In 1983, from January 1 to December 31, all infants liveborn with a gestational age of less than 32 completed weeks and/or a birthweight less than 1500 g were enrolled in a prospective national survey. Throughout the Netherlands, paediatricians in 101 paediatric departments participated in the study. Perinatal data on 1338 infants were recorded, representing 94% of all liveborn infants meeting the entry criteria. Results regarding the pre-, peri- and neonatal period and part of the follow-up study have been published previously (1, 4, 5, 6, 7, 17, 18, 19, 24).

On precoded forms concerning the perinatal period, all seizures (clinical definition: including subtle seizures, generalized tonic, multifocal clonic, focal clonic and myoclonic seizures (8,20)) were recorded together as either "absent", or as present "on the first day of life", "on the 2nd till 4th day of life" or "on the 5th day or later". In-hospital mortality was defined as all deaths during the initial hospital stay after birth. After discharge home, all infants were enrolled in a follow-up programme with health examinations at the age of 3, 6, 12 and 24 months corrected for preterm birth. Data were collected on growth, development, illnesses, rehospitalization, and psychosocial problems at the out-patient department by the local paediatrician or at the referral hospital according to the parents preference. Data processing and analyses were performed at the study centre using SPSS-X 2.1 and SAS (15).

At the age of two years, corrected for preterm birth, a neurodevelopmental assessment was made. According to the outcome, each child was categorized into one of three groups: with major handicap, with minor handicap or normal. A major handicap was diagnosed when severe retardation was present (5 or more months retarded or a developmental quotient (DQ) less than 80), and/or a severe neurological disorder existed such as a hemi-or quadriparesis, and/or severe visual or hearing defects, and/or serious psychosocial problems were present. Such disabilities are likely to prevent the child from going to a normal school, or (will) cause serious interference with normal function in society. A child was categorized as having a minor handicap when some retardation was present (3-4 months retarded or DQ between 80 and 90), and/or a mild neurological disorder existed such as a slight hemi-or quadriparesis, and/or a mild visual or hearing defect, and/or moderate psychosocial problems appeared. Such disabilities are unlikely to prevent the child from going to a normal school, or to interfere seriously with normal life (16). All other children were considered to be "normal".

The relationship between neonatal seizures, in-hospital mortality and handicap (major and minor) at the corrected age of two years, was studied using descriptive statistics followed by a multivariate statistical method (logistic regression analysis). In this analysis no distinction was made between the time of onset of the seizures. In the multivariate statistical model various perinatal factors were included as potential confounders to adjust for the possible effects of the uneven distribution of these factors, which as such may be associated with mortality or handicap. Two separate multivariate analyses were performed. In both analyses "seizures" (considered as exposure) and the selected perinatal factors

(considered as potential confounders) were the independent variables. Mortality and handicap, respectively, were dependent variables. The definitions of the selected perinatal factors used as confounders are stated in table 1.

Because the number of cases with the outcome handicap was much lower than the number of cases with the outcome death, the number of confounding factors in the handicap-analysis had to be limited for methodological reasons. Based upon previous reports (18) the following factors were omitted: maternal age, parity, history of preterm birth or abortion, smoking during pregnancy, medication and intoxication, hospital admission during pregnancy, prolonged duration of ruptured membranes, chorioamnionitis, cardiotocography during pregnancy, and elective delivery. In the handicap-analysis bilirubin (expressed as maximal total serum bilirubin level) was included as an extra confounder in view of the association we found previously in this cohort between handicap and the maximal total serum bilirubin level (7).

The results were expressed as an odds ratio (OR): the odds for mortality or handicap in children with neonatal seizures versus the odds for mortality or handicap in children without neonatal seizures. An odds ratio greater than 1 indicates a higher risk; an odds ratio smaller than 1 indicates a lower risk for the children with seizures (exposed), compared to the children without seizures (non-exposed). An odds ratio is significantly different from 1 at the 5% level if, and only if, its 95% confidence interval does not include 1.

Results

Originally, 1338 very preterm and/or VLBW infants were enrolled in the survey. The in-hospital mortality was 25.4% (340/1338). During the two years follow-up period another 29 infants (2.2%) died and 25 were lost to follow-up, mainly because the parents moved abroad or refused further cooperation on financial or religious grounds. Of the remaining 944 children assessed, the data, necessary for the described multivariate analyses, were available in 897 cases. Neonatal seizures were recorded in 5.4% of the infants (n = 72), occurring on the 1st day of life (n = 15), 2nd till 4th day (n = 25), and on the 5th day or later (n = 32).

Mortality

During the initial hospital stay 40 infants with neonatal seizures (56.5%) died, a much higher percentage compared to the infants without seizures (23.7%, 300/1226). Half of them died during the first week of life, another

Table 1: Perinatal factors used in the logistic regression analysis

1. socio-economic class	1 (low) to 6 (high)(22)
2. maternal age	in years
3. pre-existing maternal	including heart disease, epilepsy, diabetes mellitus, renal disease, hypertension (diastolic blood pressure $\geq$ 90 mmHg)
4. parity	>0 versus 0
5. history of preterm birth or abortion	preterm birth and (or) >1 abortion versus none or 1 abortion
6. infants' sex	male versus female
7. smoking during pregnancy	any versus none
8. medication and intoxication	any (medication, alcohol, soft or hard drugs, smoking) versus none
9. maternal hypertensive disorders during pregnancy	diastolic blood pressure $\geq$ 90 mmHg, measured at least twice
10. congenital malformation	any versus none
11. hospital admission during pregnancy	1 or more days versus none or less than 24 hours
12. multiple pregnancy	yes versus no
13. antenatal transport	to a perinatal intensive care centre (level 3)(19)
14. tocolysis	$\geq$ 24 h. suppression of uterine contractions versus none or $<$ 24 h.
15. glucocorticoid administration	$>$ 24 h. administration to the pregnant mother versus none
16. prolonged duration of ruptured membranes	$\geq$ 24 h. versus none or $<$ 24 h.
17. chorioamnionitis	yes versus no
18. cardiotocography during pregnancy	abnormal versus normal tracing
19. fetal presentation	breech and transverse versus vertex presentation
20. gestational age	in days
21. birthweight	in grams
22. small for gestational age	$<10^{th}$ percentile versus $\geq 10^{th}$ percentile (12)
23. hospital of birth	level 1 (low), 2 (intermediate), 3 (high) (19)
24. elective delivery	yes versus no
25. mode of delivery	caesarean section versus vaginal
26. Apgar score 5 min.	<7 versus ≥ 7
27. neonatal transport	to level 2, 3
28. idiopathic respiratory distress syndrome (IRDS)	extra O_2 $>$ 24 h., expiratory grunting, tachypnoea, sternal and intercostal retractions, nasal flaring and typical x-ray
29. intracranial haemorrhage (ICH)	clinical diagnosis (based on rapid or saltatory deterioration fall in haematocrit) and/or confirmation by ultrasound or computerized tomography versus none
30. septicaemia	haemotological findings (typical white blood cell count) and/or positive bloodculture

15 during the first month. After discharge home up to the corrected age of two years another 4 infants died (table 2).

In the logistic regression analysis, after correction for all perinatal factors described in table 1, the odds ratio for in-hospital mortality for infants with seizures versus infants without seizures was 2.7 (table 3).

Table 2: Crude mortality rates of infants with and without neonatal seizures

outcome	neonatal seizures	
	present	absent
	% (n)	% (n)
mortality		
neonatal	49 (35/72)	22 (277/1266)
in-hospital	56 (40/72)	24 (300/1266)
post-discharge	6 (4/72)	2 (25/1266)
total	61 (44/72)	26 (325/1266)

Table 3: Results of the logistic regression analyses comparing infants with neonatal seizures to infants without neonatal seizures

outcome	odds ratio (OR)	95% confidence interval
in-hospital mortality	2.7	(1.4 - 5.3)*
handicaps in survivors		
1st (with factor ICH)	2.9	(1.2 - 6.8)*
2nd (without factor ICH)	3.6	(1.6 - 8.2)*

*p < 0.05

Handicap

Amongst 944 children assessed at the corrected age of two years 774 were considered normal and 170 were handicapped: 59 children had a major and 111 a minor handicap (24). The total numbers and percentages of normal and handicapped children in the groups with or without neonatal seizures, are shown in table 4, further divided by time the seizures occur-

red. From the infants with seizures occurring between their 2nd-4th day of life, 68% died in hospital, none of the survivors, however, was handicapped at the age of two years. Most handicaps emerged in the children with seizures on their 5th day of life or later.

Surprisingly, 16 out of the 28 children surviving with neonatal seizures were considered normal at two years of age. One may wonder why these infants did not develop a handicap. Looking at the clinical neonatal data of these children, it appears that there is a difference in the severity of their neonatal complications. In almost all surviving infants an intracranial haemorrhage (ICH) was diagnosed in the neonatal period as well as an idiopathic respiratory distress syndrome (IRDS). In the infants with a handicap these problems were more severe, necessitating assisted ventilation for longer period. Moreover in 6/11 children with a major handicap a hydrocephalus was diagnosed in the neonatal period.

Table 4: Numbers and percentages of handicapped children in survivors with or without neonatal seizures

neonatal seizures	liveborn	infants assessed at 2 years	normal	handicap		
				total	minor	major
	n	n	n	n (%)	n (%)	n (%)
yes	72	28	16	12(43)	1(4)	11(39)
1st day	15	5	3	2		2
2nd-4th	25	7				
≥ 5th	32	16	6	10	1	9
no	1266	916	758	158(17)	110(12)	48 (5)
total	1338	944	774	170(18)	111(12)	59 (6)

Almost all children with neonatal seizures and handicapped at the age of two years, had developed a major handicap (11/12, 92%); this is contrary to the division of major and minor handicaps in the entire study population (59/170, 35%) or in the group of infants without neonatal seizures (48/158, 30%). In the logistic regression analysis, neonatal seizures appeared to be a strong predictor for later handicap (OR: 2.9) (table 3).

Discussion

The odds for mortality as well as for handicap was significantly increased in infants with seizures during the initial hospital stay, compared to infants without seizures. The relationship between seizures and mortality may be the result of the clinician's tendency to refrain from further treatment of infants who are considered severely neurologically damaged following seizures (23). To investigate this possibility we calculated the percentages of infants with and without seizures, in which further treatment was recorded as withheld or withdrawn. This had happened in 73% (29/40) of the deceased infants with seizures, contrary to the much lower percentage of 50 (149/300) of the deceased infants without seizures (chi-square 5.98; $p < 0.05$) (table 5). This confirms the idea that intensive treatment was often withdrawn in infants with neonatal seizures whose outcome was considered to be probably death or severe handicap (3).
In infants with seizures on their 5th day of life or later about half died

Table 5: In-hospital mortality of infants with and without neonatal seizures divided by way of death

neonatal seizures	liveborn	in-hospital mortality			
		spontaneous	treatment withdrawn/withheld	accidental*	total
	n	n	n (% of total mortality)	n	n
yes	72	11	29 (73)		40
1st day	15	2	6 (75)		8
2nd-4th	25	7	10 (59)		17
≥ 5th	32	2	13 (87)		15
no	1266	146	149 (50)	5	300
total	1338	157	178 (52)	5	340

*death due to medical fault or inaccuracy

either spontaneously or after withdrawal of treatment and the majority of the survivors appeared severely handicapped (table 4). Although we did not study the aetiology of these seizures, our results confirm the idea that late onset seizures have an unfavourable outcome (2,8,21).

When seizures concurred with obvious neurological dysfunction in the neonatal period an extremely high number (7/9) of handicaps were

found. However, even when no neurological dysfunction apart from seizures was signalized during the neonatal period, still 5 out of 19 infants were handicapped (Ouden den, personal communication). Generally, the origin of the seizures predetermines the prognosis of the infant and may vary from good in case of late-onset hypocalcemia or drug-withdrawal to (very) bad in case of intracranial infection or intracranial hemorrhage (ICH). In the present study, ICH was included as a confounding factor in the logistic regression analysis. The clinical diagnosis of ICH was used, to minimize a possible bias caused by underestimation of probable, but unconfirmed ICH. Cases of ICH that may have gone clinically unnoticed were assumed to have been of such a mild nature that neonatal seizures were unlikely to occur; by missing these, the confounder (ICH) might have been present more frequently in the group of infants without seizures. Therefore, the results of the analyses may only underestimate the effect of neonatal seizures alone. After omitting ICH from the logistic regression analysis the odds ratio for handicap was higher (table 3), suggesting that part of the association between seizures and handicaps is indeed due to ICH.

We conclude that neonatal seizures in very preterm and very low birthweight infants are clearly associated with mortality during the initial hospital stay as well as with later handicap; this also holds true after adjustment for intracranial haemorrhage. Still, 16 out of 28 survivors were described as normal at the corrected age of two years. Although the risk of handicap is obviously increased in these children, neonatal seizures do not seem to exclude a normal development.

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Chapter 4

NEONATAL NEUROLOGICAL DYSFUNCTION IN A COHORT OF VERY PRETERM AND/OR VERY LOW BIRTHWEIGHT INFANTS

relation to other perinatal factors and outcome at 2 years.

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Neuropediatrics, 1990, 21, 66-71.

Chapter 4

NEONATAL NEUROLOGICAL DYSFUNCTION IN A COHORT OF VERY PRETERM AND/OR VERY LOW BIRTHWEIGHT INFANTS

relation to other perinatal factors and outcome at 2 years.

Summary

Neonatal neurological dysfunction was found in only a small part of 1192 infants enrolled in an epidemiologic survey on very preterm (less than 32 weeks) and very low birthweight (less than 1500 gram) infants. A routine neurological examination was performed in the neonatal period by the attending paediatrician throughout all levels of care. The incidence of obvious neurological dysfunction was 8.1% and incidence of suspect neurological dysfunction was 6.1%. Multivariate analysis showed that gestational age, birthweight, low Apgar score, IRDS and, most of all, ICH were significantly associated with neonatal neurological dysfunction (N.D.). The mortality rate was very high in obvious and suspect ND infants (81.1% and 35.6% respectively) compared to neurologically normal infants (17.8%). This phenomenon was also found regarding the handicap rate at 2 years of age. Only 6% (n = 6) of the 96 infants with obvious ND survived without handicap. Using routine physical examination, a quarter of the very preterm or VLBW infants with later neurological disturbances were identified. A more standardized neurological examination, incorporated in the routine examination of newborns in all levels of care, might improve early identification of infants at risk for handicaps.

Introduction

The prognostic value of neonatal neurological dysfunction in term asphyxiated infants is well documented (9, 16, 21). In preterm babies neonatal neurological examination is mostly used to establish maturation (1, 3, 11, 13, 19, 20). A relationship between more severe neurological dysfunction in the neonatal period and later neurological abnormalities, however, has been reported in preterm infants, who were repeatedly examined in a standardised way by an experienced childneurologist (12).

To our knowledge, no follow-up studies have been published of neonatal neurological dysfunction in an unselected population of preterm infants. Therefore, we investigated incidence and outcome of neonatal

neurological abnormalities diagnosed by routine paediatric examination in all levels of care in a large collaborative survey on very preterm and/or very low birthweight infants born in the Netherlands in 1983 (27).

Patients and method

In a prospective survey on very preterm and/or small for gestational age infants information was collected on 94% (n = 1338) of all babies, liveborn in 1983 in the Netherlands, with a gestational age of less than 32 completed weeks and/or a birthweight less than 1500 grams (27). In addition to many other perinatal data the incidence of neurological dysfunction in the neonatal period was recorded. Each infant was classified into one of three categories: neurologically normal, with suspect neurological dysfunction (ND) or with obvious neurological dysfunction. Obvious neurological dysfunction was defined as a definite neurological dysfunction shortly after birth, at any time during the neonatal period or at discharge home, including increased or decreased exitability, increased or decreased motility, hypertonia, hypotonia and/or asymmetry (15). Seizures without other neurological abnormalities were excluded from the present analysis, since they are qualitatively different from non paroxysmal neurological disturbances. Separate analysis of seizures as predictor of later disability is in progress. Infants were classified as suspect in all cases where the attending paediatrician recorded symptoms of neurological dysfunction without a specific neurological syndrome at any time during the neonatal period.

Follow-up examinations were performed at 3, 6, 12, and 24 months of age, corrected for preterm birth. A continuation of the follow-up till the age of 5 years is in progress. In this paper the outcome at 2 years is reported. Neurodevelopmental outcome was assessed by the attending paediatrician and when necessary by a multidisciplinary team. An overall developmental level was assessed using the Gesell test adapted for Dutch children (23) and by routine neurological, visual and hearing examinations. A detailed neurological examination, which could reveal mild neurological abnormalities also (6), was not possible at this stage for methodological reasons but will be carried out at the age of 5 years.

According to the outcome of the assessment, each child was categorized into one of three groups: with major handicap, with minor handicap or normal. A major handicap was diagnosed when severe retardation was present (5 or more months retarded or DQ less than 80) and/or at least one of the following; a severe neurological disorder, severe visual or hearing defects, or serious psychosocial problems. Such disabilities would

probably stop the child going to a normal school or cause serious interference with normal function in society. A minor handicap was diagnosed when some retardation was present (3-4 months retarded or DQ between 80 and 90) and/or at least one of the following; a mild neurological disorder such as a slight hemiparesis or quadriparesis, mild visual or hearing defects, or moderate psychosocial problems. Such disabilities were unlikely to prevent the child from going to a normal school, or to interfere seriously with normal life (24). All other children were considered "normal". Since congenital malformations were considered to influence not only neonatal neurological function but also mortality and later handicap, all 146 babies with congenital malformations were excluded, leaving 1192 infants for the present study.

Univariate statistical analyses were then performed such as chi square tests with an alpha of 5% whenever appropriate. For the analysis of differences in gestational age and birthweight a non-parametric analysis of variance (Kruskal-Wallis) was used. Because of the many interdependencies between the various perinatal factors studied, the exclusive use of univariate analysis is not adequate and might give biased results. A multivariate analysis consisting of a stepwise backward logistic regression analysis (22) with neurological dysfunction as a dependent variable and the same perinatal risk factors as independent variables was performed.
Perinatal data studied included sex, multiple pregnancy, fetal presentation, mode of delivery, gestational age, birthweight, level of care in the hospital of birth, low Apgar score, idiopathic respiratory distress syndrome (IRDS), intracranial haemorrhage (ICH), seizures and meningitis. Fetal presentation was divided into vertex or non-vertex (breech or transverse) presentation. Mode of delivery was recorded as either vaginal delivery or caesarean section. For gestational age we used the "best obstetrical estimate of length of gestation"(26, 27). The classification of the hospital of birth into three levels of care was based on a scoring system similar to that used by Paneth et al (18, 28). Low Apgar score was defined as an Apgar score of 6 or less at 5 minutes. Diagnostic criteria for IRDS included the need of extra oxygen for more than 24 hours, exspiratory grunting, tachypnea, sternal and intercostal retractions. Since ultrasound monitoring of the brain was not feasable in all hospitals involved in the study, in part of the infants under study the diagnosis of ICH was based on generally accepted clinical symptoms, such as rapid or saltatory deterioration associated with an unexplained fall in haematocrit (29). Meningitis was diagnosed in the presence of positive cultures of cerebro-spinal fluid. Since Apgar scores were missing for 102 infants in

the study population two models were compared, one including the Apgar score coded by two dummy variables (unknown versus known, and low versus high), the other without the two variables. Comparing the log likelihoods of the two models and their difference in degrees of freedom, is a formal test for the significance of the association between Apgar scores and neurological dysfunction. This test yields a p value of <0.02, indicating the need to include the two dummy variables in the model. All independent variables were arranged chronologically in four "time categories". The results were expressed as odds ratios, adjustment was made only for variables occurring in the same and previous time categories. An odds ratio > 1 indicates a higher risk, an odds ratio < 1 indicates a lower risk. Obvious and suspect ND were analysed as a single group; separate analysis was not feasible because of small numbers.

Results

Incidence

Out of 1192 study infants 36 (3.0%) died before neonatal neurological examination could be performed. These 'unknown' infants were classified as neurological normal, and hence we are sure not to overestimate the effect of neurological dysfunction on mortality. In 96 (8.1%) of the babies there was obvious neurological dysfunction and in 73 (6.1%) suspect dysfunction.

Relation to perinatal factors: univariate analysis

All perinatal factors divided in to the four time categories are shown in table 1. Of the prenatal factors, only non-vertex presentation was significantly more frequent in obvious and suspect ND infants. The difference in sex was not significant and the relation to multiple pregnancy could not be interpreted. Both low gestational age and low birthweight were significantly associated with neurological dysfunction. The difference in caesarean section rate was not significant, no significant relation between obvious and suspect ND and the level of care was found. Low Apgar score occurred more frequently in both obvious and suspect ND groups, even though we classified the 'unknown' infants as normal. Evidence of IRDS was found in 561 infants (47.1%) in the study population; 85% of them needed ventilatory support. ND infants appeared to have suffered significantly more frequent from IRDS (67.1% and 75% in suspect and obvious ND respectively) than neurologically normal infants (43%). As expected,

Table 1: Relation of neonatal neurological dysfunction to perinatal factors. Univariate analyses.

	neurol normal n = 1023		suspect ND n = 73		obvious ND n = 96		p
	n	%	n	%	n	%	
time category I							
sex (male)	530	51.9	39	53.4	54	56.3	ns
multiple pregnancy	243	23.8	12	16.4	35	36.5	< 0.01
non-vertex presentation	256	25.0	22	30.1	35	36.5	< 0.03
gestational age (mean ± sd)	30.4 (2.8)		29.6 (2.6)		28.9 (2.7)		< 0.01*
birthweight (mean ± sd)	1270(318)		1202(312)		1113(276)		< 0.01*
time category II							
caesarean section	435	42.5	35	47.9	33	34.4	ns
level I	376	36.8	19	26.8	37	36.5	ns
level II	274	26.0	28	38.4	22	35.6	ns
level III	373	38.5	26	22.9	37	38.5	ns
time category III							
low Apgar score	160	15.6	21	28.8	34	35.4	< 0.01
time category IV							
IRDS	440	43.0	49	67.1	72	75.0	< 0.01
ICH	184	17.9	39	53.4	71	74.0	< 0.01
seizures	25	2.4	10	13.7	30	31.3	< 0.01
meningitis	5	0.5	5	6.8	4	4.3	< 0.01

*non-parametric analysis of variance (Kruskal-Wallis);
otherwise chi-square analysis.

other disorders of the central nervous system in the neonatal period (ICH, seizures and meningitis) were much more frequent in the infants with neurological dysfunction.

Relation to perinatal factors: multivariate analysis

All perinatal factors listed in table 1 were included in the logistic regression model, except seizures and meningitis, because of the low frequency in which they occurred. Stepwise logistic regression analysis showed that gestational age, birthweight, low Apgar score, IRDS and ICH were significantly associated with the odds for neurological dysfunction. ICH was by far the most predictive (table 2). Of all other perinatal factors considered only non-vertex presentation was associated with neurological dysfunction, but not significantly at the 5% level.

Table 2: Adjusted odds ratios (OR), 95% confidence intervals (CI) and p values for neurological dysfunction

time category	risk factor	OR	CI	p
I	male vs female	1.16	0.8 -1.6	ns
	multiple vs singleton	1.1	0.8 -1.6	ns
	non vertex vs vertex	1.4	0.98-2.0	ns
	gestational age per wk	0.89	0.83-0.96	< 0.01
	birthweight per 100 gr	0.93	0.88-0.99	< 0.03
II	caesarean section	1.3	0.9 -1.9	ns
	level 1 vs 3	1.06	0.7 -1.6	ns
	level 2 vs 3	1.3	0.9 -2.0	
III	Apgar score			
	(low vs high)	2.0	1.3 -3.0	< 0.01
	(unknown vs known)	1.2	0.6 -2.2	ns
IV	IRDS	1.9	1.5 -3.4	< 0.01
	ICH	6.9	4.7 -10.3	< 0.01

Mortality

Of the total population under study (n = 1192), 287 infants (24.1%) died during their initial hospital stay ("in-hospital" mortality). The in-hospital mortality in neurologically normal infants was 17,8% (n = 183). In infants with neurological dysfunction this mortality was considerably higher: 35.6% (n = 26) in the suspect ND infants, and 81.1% (n = 78) in the obvious ND infants.

Follow-up at 2 years

The outcome at the age of 2 years, corrected for preterm birth, is shown in table 3. Of the 905 infants surviving the initial hospital stay follow-up data at 2 years of age were available for 879 (96.1%). Outcome data were available of 815 infants without neurological problems in the neonatal period: 16 (2.0%) died in the first 2 years, 31 (3.1%) had a major handicap and 79 (9.7%) a minor handicap. The remaining 689 children (84.5%)

Table 3: Neonatal neurological dysfunction and outcome at 2 years in infants discharged alive

	neur norm n = 840		suspect ND n = 47		obvious ND n = 18		total n = 905	
	n	%	n	%	n	%	n	%
later death	16	2.0	4	8.7			20	2.3
major handicap	31	3.8	7	15.2	9	50.0	47	5.3
minor handicap	79	9.7	11	23.9	3	16.7	93	10.6
no handicap	689	84.5	24	52.2	6	33.3	719	81.8
unknown	25		1				26	

Table 4: Handicaps in infants with suspect and obvious neurological dysfunction.

	suspect ND	obvious ND
major handicaps	n = 7	n = 9
mental retardation	3	6
cerebral palsy	6	8
epilepsy	1	2
visual impairment	2	3
squint	3	4
hearing impairment	3	
ventriculo-peritoneal drain	2	3
minor handicaps	n = 11	n = 3
mental retardation	7	2
cerebral palsy	6	2
squint		2
hearing impairment	1	1
behavioural disturbances	2	1
other	3	1

were without handicap, although 5 of them were reported to have mild neurological abnormalities at that time.

The outcome data of the infants with suspect ND was less satisfactory; of the 46 survivors, available for follow up, 4 (8.7%) died during the first 2 years, 7 (15.2%) had a major handicap and 11 (23.9%) a minor handicap. Only 24 were without handicap or neurological abnormality. In the infants with obvious ND the outcome was even worse. Of the 18 survivors 9 (50%) had a major handicap and 3 (16.6%) a minor handicap. The remaining 6 children were reported to be without handicap at the age of 2 years, although all of them had neurological abnormalities during the first year, that were still present in 2 of the "normal children at the age of 2 years. The handicaps in the suspect and obvious ND infants are described in table 4. Many children had more than one disability. A more detailed description of all children with handicaps at 2 years of age, including the children with congenital malformations, is recently published (32).

To enable comparison with other studies the incidence, mortality rate and handicap rate of neurological dysfunction is listed separately for very preterm (less than 32 weeks) and VLBW infants (less than 1500 gram) (table 5).

Table 5: Incidence, mortality and major handicaps in preterm (<32 weeks) and VLBW infants (<1500 grams)

	<32 weeks n=914				<1500 grams n=971			
	suspect ND		obvious ND		suspect ND		obvious ND	
	n	%	n	%	n	%	n	%
incidence	60	6.5	86	9.4	61	6.2	89	9.1
in-hospital mortality	28		72		26		72	
major handicap	7		7		4		8	
no major handicap	25		7		31		9	

Discussion

The incidence of neurological abnormalities in the neonatal period found in the present study population (14.1%) is much lower than the 46.5%

found by Dubowitz et al (12). This is mainly the result of a difference in definition of neurological abnormality. Whereas Dubowitz used a standardized and repeated neurological examination - which needs an experienced observer - in our study only infants were included who had neurological disturbances severe enough to be diagnosed by routine paediatric examination in all levels of care, mostly without a standardized, detailed neurological examination. The lower incidence is further explained by a difference in study populations: infants in a neonatal intensive care centre, versus a national birth-cohort of which 55% was treated in a general hospital.

Of all perinatal factors examined gestational age, birthweight, low Apgar score, IRDS and ICH were significantly associated with neonatal neurological dysfunction both in univariate and multivariate analysis.
Apgar scores are known to be related to the maturity of the newborn; low Apgar scores can be expected in the more immature infants (10). But also when the lower gestational age of the neurological dysfunctioning infants is taken into account (multivariate analysis) low Apgar score in this group is significantly more frequent. The relation between gestational age, birthweight and low Apgarscores on the one hand and neonatal neurological abnormality on the other is in agreement with the results of the Groningen Perinatal Project (14, 15, 25).

The occurrence of IRDS was taken as a measure of illness in the neonatal period. Therefore the association with neonatal neurological dysfunction is not surprising. The association between ICH and neonatal neurological dysfunction is obvious.

The in-hospital mortality rate was strikingly high in the neurologically affected infants even while early deaths without neurological examination were classified as 'normal'. This high mortality rate in the neurologically dysfunctioning infants may be partly explained by their being younger, smaller and more acutely ill than the neurologically normal infants, and by increased withdrawal of treatment, because further treatment was thought either impossible or unethical.

At most 18% of the infants with neurological abnormalities (obvious and suspect) survived without handicap. Only 6% of the children with obvious neurological abnormalities during the neonatal period appeared to be without handicap at 2 years, although neurological abnormalities persisted during the first year. Close follow-up in later years will be necessary, because the risk of later developmental problems (e.g. learning disturbances) is still considerable in children with transient neurological problems in the first year of life (17).

The specificity of normal neonatal neurological function as a predictor of absence of later death and handicaps is excellent (686/719: 95.8%). The sensitivity however is low (34/160: 21.2%). Only 16 of the 47 children with a major handicap could be pointed out by neonatal neurological examination.

Other methods of investigation of neurological functioning (e.g. ultrasound examination of the brain, cerebral bloodflow measurements, magnetic resonance imaging) may prove better predictors of later neurological disturbances in the very preterm and/or VLBW population (4, 5, 7, 8, 30, 31) than routine paediatric examination. These methods, however, are not routinely available for all infants at risk for developmental problems and probably never will be. Moreover, it is likely that a standardized and repeated neurological examination is an even better predictor of later neurological disturbances (2, 12).

The present study suggests that, using routine physical examination, a quarter of the very preterm or VLBW infants with later neurological disturbances may be identified. The regular use of a more standardized neurological examination could be incorporated in the routine examination of newborns in all levels of care. This may improve the sensitivity of the neonatal neurological examination and thereby improve early identification of infants at risk for handicaps.

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Chapter 5

PREDICTION OF NEURODEVELOPMENTAL OUTCOME IN THE PRETERM INFANT: MR-STAGED MYELINATION COMPARED WITH CRANIAL US

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Pediatric Radiology, 1990, 175, 107-109.

Chapter 5

PREDICTION OF NEURODEVELOPMENTAL OUTCOME IN THE PRETERM INFANT: MR-STAGED MYELINATION COMPARED WITH CRANIAL US

Summary

In this prospective study, 26 very preterm infants underwent magnetic resonance (MR) imaging of the brain at 44 weeks postmenstrual age (PMA) for staging of myelination. Neurodevelopmental outcome was assessed at 1 year of age. A significant correlation was demonstrated between delayed myelination and neurodevelopmental outcome (χ^2 = 16.6, p = .01). A significant correlation was also found between ultrasound (US) findings in the neonatal period and outcome at 1 year (χ^2 = 22.9, P = .03). To establish the criterion with the best predictive value, a

multiple regression analysis was performed with periventricular-intraventricular hemorrhage, periventricular leukomalacia (PVL), and the stage of myelination at 44 weeks PMA as independent variables and neurodevelopmental outcome at 1 year of age as a dependent variable. Staging of myelination with MR imaging in the early postnatal period of very preterm infants had predictive value with regard to neurodevelopmental outcome. Detection of PVL with US, however, showed a better correlation with outcome, a result that seems to limit the potential role of MR imaging in this population for this purpose only.

Introduction

A unique property of magnetic resonance (MR) imaging in the neonatal period is its ability to depict myelin.[1,2,3] Normal myelination patterns in healthy full-term and preterm infants have been extensively described.[3,4,5] Delayed myelination has been experimentally associated with brain abnormalities.[6] MR studies have shown delayed myelination in patients with hydrocephalus,[2] congenital infections,[7] and hypoxic-ischemic brain injury[7,8,9] and in developmentally handicapped children at different ages.[5,7] Several authors have indicated that the greatest impact of MR imaging in neonates may be its demonstration of myelin and its potential in predicting poor neurologic outcome in infants with delayed myelination.[5,7,8,9] In the literature it has also been stressed that long-term MR and

neurodevelopmental follow-up studies are indicated to answer the question: To what extent will MR imaging contribute in predicting neurological defects?[7,8,9]

We prospectively studied a population of very preterm infants[10,11] evaluated them for periventricular-intraventricular hemorrhage (PIVH), periventricular leukomalacia (PVL), delay in myelination, and abnormal neurodevelopmental outcome to establish whether there was a significant relationship between the stage of myelination in the early postnatal life and neurodevelopmental outcome at 1 year of age and whether MR findings in the neonatal period correlated significantly better with neurodevelopmental outcome than cranial ultrasound (US) parameters.

Patients and method

This study was approved by the Research Ethics Committee of our institution, and informed consent was obtained from a parent or guardian before the patient was enrolled in the study.

Patients who met the following criteria participated in the study: (a) admission to the neonatal intensive care unit of our hospital in 1987, (b) birth at a gestational age of less than 30 weeks postmenstrual age (PMA), (c) daily US examination of the brain in the 1st week of life and twice weekly until discharge, (d) MR examination of the brain at 44 weeks PMA, and (e) neurodevelopmental assessment at 1 year of age. Twenty-six infants fulfilled these criteria.

US examinations were performed with a mechaninal sector scanner equipped with a 7.5-MHz transduce (Advanced Technology Laboratories, Bothell, Wash). PIVH was graded according to the grading system by Volpe[12]: grade 1 = germinal matrix hemorrhage with no or minimal intraventricular hemorrhage; grade 2 = intraventricular hemorrhage, 10%-50% of ventricular area; grade 3 = intraventricular hemorrhage, more than 50% of ventricular area. PVL was defined as one or more areas of increased echogenicity in the periventricular hemorrhage, more than 50% of ventricular area. PVL was defined as one or more areas of increased echogenicity in the periventricular regions, seen in both coronal and sagittal planes, followed by cystic degeneration and ventricular dilatation 3-6 weeks later.[13]

MR imaging examinations were performed with a 0.-T Gyroscan unit (Philips Medical Systems, Shelton, Conn). Infants were examined during sleep after feeding and oral sedation with 80-100 mg/kg of choral hydrate. Respiratory and heart rate control were monitored throughout the procedure. A head coil was used, and a blanket kept the infant warm. T1-

weighted (spin-echo, 300/30 [repetion time msec/echo time msec]) axial images were obtained with six measurements. The acquisition matrix was 128 x 256, the displayed matrix was 256 x 256, and section thickness was 7 mm. Myelin was recognized by its high signal intensity. Myelination was graded for the right and left hemispheres according to its most cephalic location in the grading system by McArdle et al[3]: M1 = pons around the fourth ventricle, vermis, and cerebellar hemispheres; M2 = posterior limb of the internal capsule and adjacent structures of the thalamus and lenticular nucleus; M3 = corona radiata; M4 = centrum semiovale; M5 = cerebral gyri. The stage of myelination was determined immediately after the examination. Prior to staging, the observers were not informed about the US and clinical findings in early postnatal life.

An overall developmental level was assessed with the Gesell test adapted for Dutch children[14] and supplemented by neurologic, visual, and hearing examinations. Neurodevelop-mental deficit was graded as follows: No handicap was graded H0; a child was considered to have no handicap when the developmental quotient was more than 90 and no neurologic, visual, or hearing abnormalities were present. A minor handicap was graded H1; a moderate handicap was defined as some retardation and/or moderate cerebral palsy and/or hearing and visual defects. A major handicap was graded H3; an infant was considered to have a major handicap when severe retardation was present (the infant had a developmental quotient less than 80 or was more than 5 months retarded) and/or the infant had severe cerebral palsy, hearing, and visual defects.

Prior to the determination of the handicap score, the observers were not informed about the US and MR findings. The correlations between (a) neurodevelopmental outcome and the occurrence and grade of PIVH and PVL and (b) neurodevelopmental outcome and the MR stage of myelination at 44 weeks PMA were assessed with chi-square tests. A P value <0.05 was considered significant. A multiple regression analysis was performed to find the most appropriate redicting factor for neurodevelopmental outcome.

Results

Table 1 demonstrates the occurrence and grade of PIVH and PVL in the 26 patients in our study and the correlation with neurodevelopmental outcome at 1 year of age. The χ^2 test showed a significant relation ($P = 0.03$). Cystic degeneration had occurred in both hemispheres in all infants with PVL.

Table 1: Neurodevelopmentel Outcome at Year of Age and Occurrence and Grade of PIVH and PVL

Outcome		H0	H1	H2	H3	Total
No PIVH/PVL		10	2		1	13
PIVH grade 1		1				1
PIVH grade 2		1	1			2
PIVH grade 3		2	2	1		5
PVL		1			4	5
	Total	15	5	1	5	26

Note. - χ^2 = 22.3, df = 12, P = .03. H0 = no handicap, H1 = minor handicap, H2 = moderate handicap, H3 = major handicap.

Table 2 demonstates the distribution of myelination stages in all infants at 44 weeks PMA and its correlation with neurodevelopmental outcome at 1 year of age. The test showed a significant correlation (P = .01).

Table 2: Neurodevelopmental Outcome at 1 Year of Age and Stage of Myelination at 44 Weeks PMA

Outcome		H0	H1	H2	H3	Total
M2		1			4	5
M3		7	3			10
M4		7	2	1	1	11
	Total	15	5	1	5	26

Note. - χ^2 = 16.6, df = 6, P = .01. H0 = no handicap, H1 = minor handicap, H2 = moderate handicap, H3 = major handicap.

In all except one infant, the myelination stage in both cerebral hemispheres was the same. This infant had stage M3 in the left hemisphere and stage M4 in the right hemisphere. For practical reasons this infant was considered to have stage M4. Finally, a myltiple regression analysis was performed with PIVH, PVL. and the stage of myelination at 44 weeks

PMA as independent variables and neurodevelopmental outcome at 1 year of age as a dependent variable (Table 3). The absence or presence of PVL had the best correlation with outcome (F-ratio = 18.29, P = .003).

Table 3: Results of Multiple Regression Analysis

Indepent variable	F-Ratio	P
PIVH	0.34	.57
PVL	18.29	.003
Myelination	0.89	.37

Note. -Neurodevelopmental outcome at 1 year of age was a dependent variable.

Discussion

We prospectively studied very preterm infants. In such a population, PIVH, PVL, and abnormal neurodevelopmental outcome are expected to be relatively frequent.[10,11] Other pathological conditions of the central nervous system that have been shown to affect myelination of the brain were excluded.

We standardized the time of the MR imaging examination at 44 weeks PMA for three reasons: First, in previous studies, patients were studied at different ages, so that a prospective comparison of results was very difficult. Second, at 44 weeks PMA, patients usually do not need assisted ventilation anymore. Third, it was our purpose to compare the myelination patterns in these preterm infants with healthy term and preterm subjects. We have demonstrated and reported that healthy term and preterm infants had reached myelination stages M3 and M4 at 44 weeks PMA,[15] data similar to those reported by others.[3,4] We have also reported that all very preterm infants who had PVL showed delayed myelination (stage M2) at 44 weeks PMA.[16] All infants without PVL, including those with PIVH, had a normal pattern (stage M3 or M4) at 44 weeks PMA.

The present study shows that very preterm infants with stage M2 myelination at 44 weeks PMA have a significantly poorer neurodevelopmental outcome at 1 year of age than preterm infants who have reached stage M3 or M4. This prospective study therefore seems to answer the expectations of many investigators[7,8,9] that myelination staged with MR imaging in

early postnatal life has predictive value with regard to neurodevelopmental outcome in later life.

However, of the 21 patients who had stage M3 or M4 myelination, one patient (4.8%) had a moderate handicap. Moreover, one patient had a major handicap (4.8%) at 1 yar of age. This infant developed severe bronchopulmonary dysplasia and had several periods of severe respiratory insufficiency in the first 6 months of life. Hypoxic events in this patient may have led to brain damage after myelination of the corona radiata.[17] This may explain the normal stage of myelination at 44 weeks PMA in combination with a poor outcome. Of the five patients with stage M2 myelination, one patient had a normal neurodevelopmental outcome at 1 year of age. The demonstration of delayed myelination in this individual case was not associated with a poor outcome. This apparently controversial result may be explained in two ways.

Hypoxic-ischemic events in this patient were less severe, and the process were less severe, and the process of myelin formation may have been reactivated in the 1st year of life, resulting in a normal outcome. In the other four patiens, irreversible impairment of myelination may have occurred, leading to a poor outcome. Assumptions regarding reversible delay and irreversible impairment of the myelination process cannot be verified at this moment. Therefore we intend to evaluate the entire patient population with follow-up neurodevelopmental tests and MR studies at age 3 years. In this manner we may learn whether there is a reversible delay of myelination that is associated with a good outcome.

Antoher explanation may be that neurodevelopmental deficits may not yet be clinically evident at age 1 year.[18] In this case, too, follow-up studies will clarify apparently controversial results between the stage of myelination and neurodevelopmental outcome in this patient.

We have demonstrated that the occurrence of PIVH is not associated with a delay of myelination at 44 weeks PMA[16] and that its occurrence has no predictive values with regard to outcome (Table 1). It seems that PIVH does not damage the glia precursors in the germinal matrix to such an extent that the capability of myelin production is affected. The proliferation and differentiation of glia cells, which are responsible for the formation of myelin,[12] seem to be more affected by hypoxic-ischemic injury in PVL. We were not able to study the effects of intraparenchymal hemorrhages on myelination and outcome, because all patients with this complication did not survive longer than 44 weeks PMA.

The multiple regression analysis showed that the presence of PVL detected with US had the best predictive value with regard to neuro-

developmental outcome in these very preterm infants. Consequently it seems premature at this moment to advocate MR studies in these infants only because of the potential of MR imaging to predict neurodevelopmental outcome. MR imaging-staged myelination of the central nervous system may prove to be a valuable method for the prediction of neurodevelopmental outcome in patients with conditions that cannot be adequately monitored with US.

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PART II

PREDICTIVE VALUE OF INVESTIGATIONS IN INFANCY

Chapter 6

NEUROLOGICAL ABNORMALITIES IN THE FIRST YEARS OF LIfE IN VERY PRETERM INFANTS

relation to outcome at 5 years of age

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Chapter 6

NEUROLOGICAL ABNORMALITIES IN THE FIRST YEARS OF LIFE IN VERY PRETERM INFANTS

relation to outcome at 5 years of age

Summary

In a national prospective survey of very preterm and/or VLBW infants the rate of neurological abnormalities in early childhood and the relation to neurological outcome and other CNS probems at 5 years of age was studied. Neurological abnormalities before 2 years of age were found in 295 (33%) of these children; at 5 years of age they were resolved in half of them. The rate of associated CNS problems was higher in children with neurological abnormalities that resolved than in children who were never neurologically abnormal. The differences between normal children and children with transient abnormalities were too small to predict normal outcome at any age. A specialized follow-up programme at least until school age will be needed for all these high risk infants.

Introduction

Neurological abnormalities in early childhood may resolve with maturation. This phenomenon has already been observed in the 19th century (Little 1862, Freud 1897) and was recently confirmed by the large epidemiological survey of Nelson and Ellenberg (1982). Drillien (1972) described particular neurological abnormalities in low birthweight children as 'transient dystonia associated with low birthweight'. The signs were the same as those found in the dystonic stage of diplegia but in most cases did not lead to overt cerebral palsy. Piper et al (1988) found that approximately one quarter of their high risk infants were still neurologically suspect at 1 year, while slightly more than half of these suspect infants were normal by 2 years of age.

Partly these neurological abnormalities may be really transient and resolve as a result of the plasticity of the brain. Partly they may only seem transient, because of the wide range of normality and the inability to track mild motor abnormalities after 18 months until at a later age more sophisticated tests can be performed (Amiel-Tison, 1978). Many investigators (Drillien et al 1980, Nelson and Ellenberg 1982, Amiel-Tison 1978, Rubin and Balow 1980) found a higher risk for later manifestations of intellec-

tual and behavioural problems in children in whom neurological signs had resolved. This suggests that although neurological signs are not stable over time, they are the manifestation of brain damage that may produce permanent effects.

The purpose of the present study was to establish the rate of neurological abnormalities as diagnosed by routine paediatric examination in the first two years of life in very preterm infants. Furthermore we investigated whether these early neurological abnormalities may resolve and if transient neurological abnormalities are related to other manifestations of cerebral dysfunction at 5 years of age.

Patients and method

In a prospective survey on very preterm and/or very low birthweight infants information was collected on 94% (n = 1338) of all very preterm (less than 32 weeks gestation) and/or very low birthweight (VLBW, less than 1500 grams) infants born alive in 1983 in the Netherlands.

After discharge home all infants were enrolled in a follow-up programme with examinations at the age of 3, 6, 12, and 24 months corrected for preterm birth. These follow-up examinations were performed by the local paediatrician or at the referral centre according to the parents wishes. Data on health, growth, development and psychosocial problems were recorded on precoded forms and analysis was performed at the study centre, using SPSS-X2.1. At each follow-up examination the results of the neurological examination were recorded as either normal, suspect or abnormal. Because the neurological examination was included in the normal pediatric examination and it was not standardized the results from various centres can differ considerably. We assumed that the groups with suspect or abnormal results would contain all children with severe neurological abnormalities, as well as part of the children with mild neurological abnormalities, which can only be detected by specific neurological examination. The group with normal results will contain all neurologically normal children as well as an unknown number of children with undetected mild abnormalities.

In contrast to the study design until the age of 2 years, at 5 years of age a centralized follow-up programme was used. This way it was possible to minimize inter-observer variability (Schreuder et al). Each child was examined during a home-visit within 6 weeks after his or her 5th birthday. The assessment covered congenital malformations, neuromotor development, mental development, hearing and visual functions, language and speech development, behaviour, respiratory tract, and biometrics. Ad-

ditional information on these areas as well as on psychological tests, school achievement or the need for special education, behaviour, socio-economic status and family factors was acquired by a parents questionnaire.

The neurological examination aimed at the detection of central motor deficit and minor neurological dysfunction (Touwen, 1979). The children were assigned to 1 of 3 categories ;

Normal; no neurological abnormalities.

Minor neurological dysfunction (MND); neurological abnormalities without influence on normal posture or movement.

Cerebral palsy (CP); neurological abnormalities with abnormal posture or movements.

Mental development was assessed by the cognitive functioning during the overall assessment and by the Denver developmental screening test sections on social and adaptive abilities (Cools and Hermanns 1977).

Language and speech development were assessed with a formal test for Dutch children from 3 to 6 years of age (Gerritsen), which included language comprehension, active language use and articulation.

Vision was tested by the Landolt-C test for near vision, Stycar test of visual range, fly test for depth perception and covertests for squint (Van Hof-Van Duin and Pott 1990).

Hearing was tested by pure tone audiometry.

Behaviour was assessed by the examiners judgement of the child's behaviour during the assessment.

Associated CNS problems were defined as an impairment in mental functioning, speech, vision, hearing and/or behaviour. Impairments were categorized as impairment, disability or handicap according to the international classification of the World Health Organization (WHO 1980, Veen et al, submitted for publication).

For the statistical evaluation of the relation between outcome at 5 years of age and the neurological status in the first 2 years chi square tests were used.

Results

Of the 966 survivors 927 (96%) were available for follow-up until 5 years of age. Data on the neurological status in the first years were incomplete in 46 children. Of the remaining 881 children 67% (n = 586) were considered normal on all examinations during the first 2 years, 33% (n = 295)

were considered neurologically abnormal or suspect at one or more examinations during the first 2 years. The relation between neurological status in early childhood and the neurological outcome at 5 years of age is given in table 1. Of the children with neurological abnormalities in the first years 26% had cerebral palsy at 5 years of age; this was only 4 % in the children who were considered normal. The percentage of children with MND did not differ between the two groups. About half of the children who were abnormal in early childhood were neurologically normal at 5 years of age. The majority of children with incomplete data in the first 2 years appeared neurologically normal at 5 years of age.

table 1: Relation between neurological status in the first 2 years of life and the neurological outcome at 5 years of age (n = 927).

neurological outcome at 5 years	neurological status in the first 2 years normal	abnormal at ≥ 1 exam	incomplete data
	n %	n %	n %
normal	449 (76)	155 (52)	38 (83)
MND	114 (19)	64 (22)	7 (15)
CP	23 (4)	76 (26)	1 (2)
total	586 (63)	295 (32)	46 (5)

Next we examined whether the age at which neurological abnormalities resolved had prognostic relevance for the neurodevelopmental status at 5 years of age. We examined whether children with transient neurological abnormalities (TNA, children who had neurological abnormalities in the first years of life but were neurologically normal at 5 years of age) had a higher incidence of other neurodevelopmental impairments than children who were never neurologically abnormal. To establish whether the time period of recovery from neurological abnormality might have prognostic relevance children were grouped according to the last examination at which they were considered abnormal (table 2).
Most of the children who recovered from their neurological abnormality at an early age appeared neurologically normal at 5 years, but even of the

children who were still abnormal at 2 years of age one quarter was neurologically normal at 5 years.
Other neurodevelopmental impairments like mental retardation, language delay, visual and hearing impairments,behavioural problems and the use of special education might be related to CNS damage. The relation between the neurological status in the first 2 years and these neurodevelopmental impairments at 5 years of age is also given in table 2.

table 2: Relation between the age at which neurological problems resolved in the first 2 years of life and the outcome at 5 years of age.

outcome at 5 years	neurological status in the first 2 years normal	abnormal till 3 mo	6 mo	12 mo	24 mo
	n = 586	n = 64	n = 64	n = 55	n = 112
	n %	n %	n %	n %	n %
CP	23 (4)	1 (2)	3 (5)	8(15)	64 (58)
MND	114(19)	10(16)	19(30)	17(31)	18 (16)
mental retardation	65(11)	4 (6)	14(22)	9(14)	55 (49)
language delay	202(34)	18(28)	28(44)	27(49)	64 (57)
visual impairment	133(23)	15(23)	20(31)	17(31)	53 (47)
hearing impairment	30 (5)	6 (9)	5 (8)	3 (5)	7 (7)
behavioural disturbance	85(15)	8(13)	12(19)	13(24)	31 (28)
normal	136(23)	12(19)	11(17)	6(11)	9 (8)

The incidence of these impairments is much higher in children with neurological abnormalities which persisted until 2 years of age than in children who were neurologically normal. Only hearing impairments, mostly conductive hearing loss, were not related to the neurological status; perceptive hearing loss was too infrequent to establish a relation. The risk of other neurodevelopmental impairments and the use of special education increased with increasing age of recovery. The differences however, were too small to be of any prognostic use.

In order to evaluate the second question, whether children with TNA had a higher incidence of other neurodevelopmental impairments

than children who had no neurological abnormalities in early childhood we studied the incidence of these impairments retrospectively (table 3).

table 3: Neurodevelopmental impairments in children who were neurologically normal at 5 years of age related to the neurological status in the first years of life. (n = 604)

impairments at 5 years	neurological status in the first 2 years normal n = 449	abnorm n = 155	chi square
mental retardation	31 (7)	17 (11)	$p < 0.1$
language delay	129 (29)	52 (34)	$p < 0.1$
visual impairment	87 (19)	40 (26)	$p < 0.01$
hearing impairment	19 (10)	13 (8)	
behavioural disturbance	49 (11)	25 (16)	$p < 0.1$
special education	15 (3)	15 (10)	$p < 0.005$

In 604 children who were neurologically normal at 5 years of age the incidence of these other neurodevelopmental impairments was higher in children who had been neurologically abnormal in the past than in children who never were neurologically abnormal. This difference however, was not statistically significant. Only visual impairments, which were in majority mild, were found significantly more frequent in children with TNA ($p < 0.01$).

The relationship between transient neurological abnormalities and the overall classification of impairments, disabilities and handicaps at 5 years of age in is given in table 4. The percentage of children with a handicap was significantly greater in children with TNA ($p < 0.02$).

Discussion

The rate of early neurological abnormalities we found in this study (33%) is comparable with the findings in high risk populations of heterogeneous origin (Calame et al 1976, Piper et al 1988). It is however, lower than the rate among children with a birthweight less than 1500 grams as found by

Drillien (1972), Drillien et al (1980), and Vohr et al (1985). This is in accordance with a suspected underrecognition of neurological abnormalities in this study, due to the study design.

table 4: Overall classification of handicaps at 5 years of age in children who were neurologically normal at 5 years of age (n = 604) Comparison between children who were neurologically normal and abnormal in the first 2 years.

overall classification at 5 years	neurological status in the first 2 years	
	normal n = 449	abnormal n = 155
normal	136 (30)	38 (25)
impairment	243 (54)	81 (52)
disability	50 (11)	18 (12)
handicap	20 (5)	18 (12)

More than half of the children with neurological abnormalities in the first years appeared to be neurologically normal at 5 years of age. Even after 2 years of age recovery was not unlikely; one fourth of the children who were abnormal at 2 years were normal at 5 years of age. The 50 % recovery rate we found in this study is similar to the rate found by Nelson and Ellenberg (1982) in a general population and with the rates found in the above mentioned studies of VLBW infants.

The high rate of neurodevelopmental impairments we found in children with transient neurological abnormalities seems to confirm the hypothesis that neurological abnormality is a manifestation of CNS damage with permanent effects. however, the rate of neurodevelopmental impairments in children who were never neurologically abnormal was also very high and the difference between these children and children with transient abnormalities was relatively small. It is hardly likely that the high rate in 'normal' children is exclusively the result of underrecognition of neurological abnormalities in the first years in this study.

Prospectively the incidence of various neurodevelopmental impairments at 5 years of age increased with increasing age of recovery from neurological abnormalities. The differences, however, were too small to be of use in the prediction of later neurodevelopmental outcome. When

neurological abnormalities persisted until 2 years of age it was unlikely that the child was completely normal at 5 years of age.

We conclude that CNS damage as expressed in neurological abnormalities in early childhood is frequent in very preterm and/or VLBW infants; the percentage (33%) we found is probably still a serious underestimation of the real problem. The rate of neurodevelopmental abnormalities at 5 year of age is very high in these very preterm children. Although children with transient neurological abnormalities had a higher risk for developmental problems, even in children who seemed neurologically normal in the first years of life the chance of later developmental problems was high. The absence of or the recovery from neurological abnormalities as diagnosed by routine paediatric examination did not appear very helpful to identify children with a normal outcome, it did indicate children at risk for developmental problems. The persistence of neurological abnormalities until 2 years of age made it unlikely that the child would be completely normal. Although the examination at 5 years of age identifies children who will probably meet problems in normal school further examination at a later age is necessary to reveale whether these predictions are true. More comprehensive neurological examinations in the early years can differentiate between children with low and high risks for problems at school-age. Specific follow-up programmes extended until school age in clinics with adequate staff and education services will be needed to give these children the opportunity to cope with the demands of normal life.

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Chapter 7

COMPARISON OF A CHILD HEALTH CARE DEVELOPMENTAL ASSESSMENT AND THE BAYLEY SCALES IN PRETERM AND VERY LOW BIRTHWEIGHT INFANTS.

relation to outcome at 5 years of age.

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Chapter 7

COMPARISON OF A CHILD HEALTH CARE DEVELOPMENTAL ASSESSMENT AND THE BAYLEY SCALES IN PRETERM AND VERY LOW BIRTHWEIGHT INFANTS.

relation to outcome at 5 years of age.

Summary

We compared the developmental assessment, used in dutch child health care (the Van Wiechen asessment) with the Bayley scales of mental and motor development in 117 preterm children at the age of 2 years. Correlation between the two assessments was not strong, but relationship of both assessments with the outcome at 5 years of age did not differ much. Both assessments had good specificity causing few overreferrals, but sensitivity of both assessments was disappointingly low. Handicaps or disabilities due to mild mental retardation or language disorders were often not diagnosed, while impairments like minor neurological dysfunction, mild language delay or visual disturbances were almost never found at 2 years of age irrespective of which assessment was used. Specific follow-up until preschool age is needed to identify these disorders, which are frequently found in this preterm population.

Introduction

Children who are born very preterm or with a very low birthweight (VLBW) run a higher risk of handicaps (Stewart et al.1981). Long term follow-up studies reveal that also for children without handicaps there is a high incidence of developmental problems and many children require special education services (Vohr et al. 1985). Therefore many neonatal intensive care centres offer a more or less structured follow-up program until preschool or school age. Approximately 40% of infants in the very preterm or VLBW group in the Netherlands are born in level 1 or 2 hospitals and not referred to a tertiairy care centre (Verloove-Vanhorick et al. 1988). Follow-up at the local hospital is feasible for these children, but this is mostly not extended over the age of 15 to 18 months, unless specific problems arise. Most of the children however, continue to visit child health care clinics where growth and development are surveyed until school age.

The aim of the present study was to investigate whether the developmental assessment used in our child health care system (the Van Wiechen assessment) can accurately identify children with developmental disturbances in a high risk population. Therefore we compared in 117 preterm babies the results of the Van Wiechen assessment at 2 years of age, corrected for preterm birth, with the results of the Bayley scales of motor and mental development at the same age , and related these results to the outcome at 5 years of age.

Patients and methods

The study population consisted of 2 groups of preterm infants, 117 in total.

A) 75 preterm infants selected from the Project On Preterm and Small for gestational age survey (POPS) which included 94% of all babies born in 1983 in the Netherlands with a gestational age less than 32 weeks and/or a birthweight less than 1500 grams (Verloove-Vanhorick and Verwey 1987). The children were selected on birthdate (the last 3 months of 1983) and address (living near one of the 4 centres cooperating in the present study). Handicap rate at 2 years of age did not differ significantly from the total POPS population (6.7% major and 14.7% minor handicap in the study group versus 6.3% major and 11.8% minor handicaps in the POPS population) (Van Zeben-van der Aa et al. 1989).

B) 42 preterm infants less than 34 weeks gestation born in 1984 and cared for in our own hospital. Although handicap rate at 2 years in these children (11.9% major and 14.2% minor handicap) was higher than in the POPS population, this difference did not reach statistical significance.

At 3, 6, 12 and 24 months of age corrected for preterm birth, development was assessed by the attending paediatrician using the Van Wiechen assessment. The Bayley Scales (Bayley 1969) were applied at 2 years of age by psychologists who did not know the neonatal history or present functioning of the children. At 5 years of age the children were assessed during a home visit by a specially trained paediatrician.

The Van Wiechen developmental assessment is used in Dutch child health care as a continuing surveillance of development for children from 4 weeks until 5 years of age. It is based on developmental milestones, alarmsymptoms as defined by Touwen (1982), such as asymmetry, dystonia and the persistence of infantile reflexes, and hearing or visual disturbances. In each age category 5-8 items are assessed, divided into the

5 fields of development as described by Gesell and Amatruda (1974). The items are chosen in such a way that at least 90% of a normal population will achieve them at the scheduled age (Schlesinger-Was 1982). Because the 7 items appropriate for 2 years of age appeared to be representative for the complete developmental assessment until 2 years of age, only these items were used in this study (table 1). A failure on 2 or more items was considered as developmental disturbance.

table 1: Developmental items used in the Van Wiechen assessment at 2 years of age*.

developmental item	number with pos score
tower of 3 cubes	96
imitates others	112
drinks from a cup	107
2 word sentences	91
puts ball in box when asked	105
squats	107
walks free and easily	103

* The full assessment consists of 76 items examined at different ages.

The Bayley Scales of infant development (Bayley 1969) are widely used in the examination of high risk children until the age of 30 months. This test has been validated for Dutch children (Van der Meulen and Smrkovsky 1984). The results are given as Kouwer (K) scores ranging from 2 to 9. A K score of 4 corresponds with a developmental quotient of 70 to 79. To enable comparison with the van Wiechen assessment a K score of less than 4 on either motor or mental scale was considered as a significant delay.

At 5 years of age each child was assessed during a home visit within 6 weeks after his 5th birthday. The assessment concerned congenital malformations, neuromotor development, mental development, hearing and visual functions, language and speech development, behaviour, respiratory tract, and biometrics. Additional information on these areas as well as on seizures, psychological tests, school achievement or the need for special education, socio economic status and family factors was obtained by a parents questionnaire (Schreuder et al. submitted for publication).

Each child was classified as either normal, impaired, disabled or

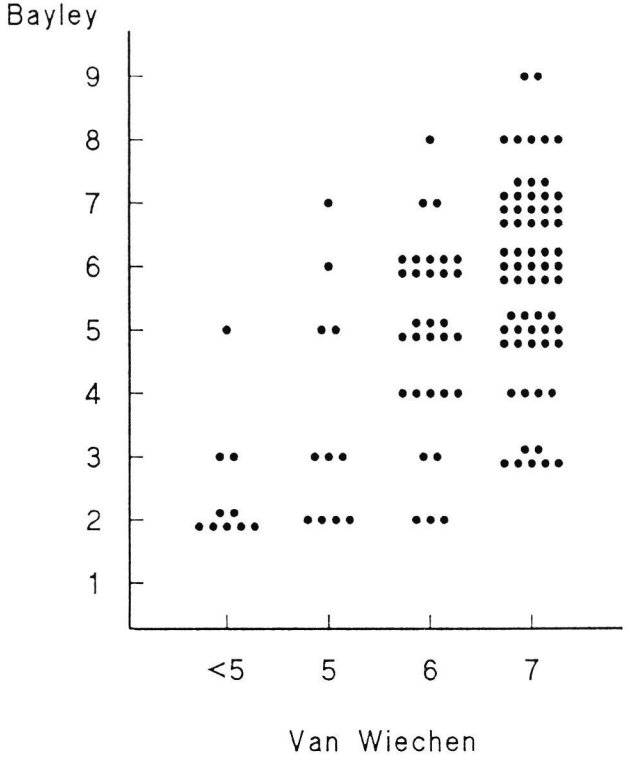
handicapped, according to the international classification of the World Health Organisation (WHO 1980, Veen et al submitted for publication).

Spearman correlation coefficients were used to compare the results of the Van Wiechen assessment and the Bayley scales with each other and with the outcome at 5 years.

Results

On the Van Wiechen assessment 65 children had a positive score for all 7 items, 31 had one failure, 11 had 2 failures and 10 children had 3 or more failures. On the Bayley scales 28 children had a K score of less than 4 (17 on the mental scale, 6 on the motor scale and 5 on both scales).

figure 1: Correlation between Van Wiechen assessment and Bayley scales at 2 years of age.



Spearman correlation coefficient 0.52, chi square 36, $p < 0.001$.

The relation between the results of the Van Wiechen assessment and the lowest K score on either mental or motor Bayley scale is given in figure 1. Spearman correlation coefficient was 0.52, chi square 36, $p < 0.001$.
At 5 years of age 16 children were handicapped (7 had a major handicap, 9 had a minor handicap) and 17 had a disability, not causing a handicap (all minor). Of the remaining 84 children 35 had an impairment, not causing any disability or handicap (15 minor neurological dysfunction or mild cerebral palsy, 12 decreased visual acuity and/or squint, 8 mild language delay). The main diagnosis in children with a handicap or disability is given in table 2.

table 2: Main diagnosis at 5 years of age.

	disability n = 17	handicap n = 16
mental retardation	7	8
cerebral palsy	4	5
language delay	5	3
visual impairment	1	

The relation between the Van Wiechen assessment at 2 years of age and the outcome at 5 years (handicaps and disabilities) is shown in table 3

table 3: Relation between Van Wiechen assessment at 2 years of age and outcome at 5 years of age.

positive items Van Wiechen at 2 years	outcome at 5 years normal n = 84	disability n = 17	handicap n = 16
7 n = 65	59	4	2
6 n = 31	23	5	3
5 n = 11	2	6	3
< 5 n = 10		2	8

Spearman correlation coefficient 0.56

(Spearman correlation coefficient 0.56). Sensitivity was 0.58; 14 of the 33 children with a handicap or disability (42%) were not identified by the Van Wiechen assessment. Specificity however, was very good (0.98); only 2 children were incorrectly identified as abnormal.
The relation between the results on the Bayley scales of infant development and outcome at 5 years is shown in table 4. (Spearman correlation coefficient 0.56). Sensitivity of this assessment was 0.67; 11 of the 33 children with a handicap or disability were not identified as abnormal. Specificity was 0.93; 6 children were incorrectly identified as abnormal.

table 4: Relation between Bayley scales of mental and motor development at 2 years of age and outcome at 5 years of age.

lowest K score at mental or motor Bayley scale		outcome at 5 years normal n=84	disability n=17	handicap n=16
>6	n=29	27	2	
6	n=26	24	2	
5	n=25	20	4	1
4	n=9	7	2	
<4	n=28	6	7	15

Spearman correlation coefficient 0.56

Of the 35 children with an impairment only 6 were identified at 2 years of age.

Seven children without any failure on the Van Wiechen assessment had unexpected low Bayley scores (fig 1). At 5 years of age 5 of them were without handicap or disability, 1 had a disability (mild retardation) and 1 was handicapped (language delay). Of the 5 children with one failure on the Van Wiechen assessment and low Bayley scores 3 were handicapped (1 mild retardation, 2 language delay) and 1 had a disability (decreased visual acuity). Of the children with more than 1 failure on the Van Wiechen assessment 5 had unexpected high Bayley scores. Three of them had a disability at 5 years of age (2 mild mental retardation, 1 language delay) and 2 children had a normal outcome.

The relation between similar or discrepant results of the 2 year assessments and the outcome at 5 years of age is given in table 5.

table 5: Relation between the results of both 2 year assessments with the outcome at 5 years of age.

results at 2 years of age	outcome at 5 years of age		
	normal n=84	disability n=17	handicap n=16
both normal	76	7	1
Van Wiechen normal Bayley abnormal	6	2	4
Van Wiechen abnormal Bayley normal	2	3	
both abnormal	5	11	

Discussion

The high risk for developmental problems in a population of preterm or very low birthweight infants is illustrated in the high percentage of children with a handicap or disability in this study (13.7 and 14.5 respectively). The follow-up of preterm infants by a paediatrician is often discontinued by the age of 18 months, but these children continue to visit the child health clinics. Therefore we wanted to investigate whether the developmental assessment used in the dutch child health care is suitable to identify developmental disturbances in children, who belong to this high risk population.

In this study the 2 year part of the Van Wiechen assessment gave a fair estimate of the results a child will get on a full scale developmental assessment. Of the children who failed 2 or more items on the Van Wiechen 76 % had also a DQ <70 on the Bayley scales; when there were 3 or more failures this was 90 %. Of the children with 1 failure on the Van Wiechen 16 % had low Bayley scores, but in the children without any failure on the Van Wiechen assessment still 7 out of 65 had a low result on the Bayley scales.

A possible explanation for the unexpected low Bayley scores in the 7 children without any failure on the Van Wiechen assessment could be that 3 of them were from non-dutch speaking parents. In these cases the paediatrician performing the Van Wiechen assessment may have relied on

the information of the parent that the child used words and sentences in their own language while on the other hand the child failed during the Bayley test because he could not understand the Dutch instructions of the psychologist. The other 4 children with unexpected low Bayley scores were reported to have behavioural disturbances at the age of 2 years. Therefore they may have lacked the attention span to concentrate on their tasks during the Bayley assessment, while the few items assessed by the Van Wiechen caused no problem. At 5 years of age one of these children from non-dutch speaking parents had mild mental retardation leading to a disability, and one child with behavioural disturbances had a severe language disorder, all others appeared to be normal.

Since the developmental items of the Van Wiechen assessment were chosen in such a way that up to 10 % of normal children will fail them at the appropriate age we considered children with 1 failure normal. If these children would be considered abnormal, the sensitivity of the Van Wiechen assessment would increase to 0.84. Specificity however would decrease to the level of 0.71 and almost 30 % of the normal children would be uncorrectly identified as abnormal.

On the Bayley scales a DQ between 70 and 79 is certainly below age level. If this score would be considered abnormal in this study, sensitivity would increase to 0.72. Specificity would then decrease to 0.84.

The relation between the Van Wiechen assessment and outcome at 5 years did not differ from the relation between the Bayley results and outcome at 5 years; both had a correlation coefficient of 0.56. Although the sensitivity of the Bayley (0.67) was better than the sensitivity of the Van Wiechen (0.58), they were both not able to predict developmental problems at 5 years of age in many 2 year old children. In this respect both assessments are comparable to the often used Denver Developmental Screening Test which is reported to have a low sensitivity (Meisels 1989).

Handicaps and disabilities that were not predicted by either of the assessments at 2 years of age were mostly mild mental retardation or language disorders. Developmental impairments not leading to disability or handicap were not predicted by either assessment in almost all children. It is obviously impossible to identify these disorders at the age of 2 years with either of the used assessments. This is in acccordance with the litterature (Anderson 1939, Bayley 1955, Thomas 1970, McCall et al. 1973, Hunt 1981).

We conclude that the 2 years part of the assessment used in Dutch child health care is adequate to identify children with major handicap, but

it is inadequate to identify most children with minor handicap or disability in a high risk population. In this respect it is almost comparable to the Bayley scales of mental and motor development and can be used in medical practice. The Bayley scales give of course more specific and detailed information. If the Van Wiechen assessment identifies a child as abnormal this child should be referred for specific neurological examination and psychological assessment of development -for instance with the Bayley scales of infant development- to establish which help can be offered. If a child fails on one developmental item on the Van Wiechen assessment close surveillance is needed because 25 % of these children appeared to have a more or less serious developmental problem at a later age. If a child has a completely normal score this is no garantee for normal development. Mild mental retardation, minor neurological dysfunction and language disorders are frequently encountered diagnoses in this high risk population which can often not be diagnosed at 2 years of age with either assessment. A longer follow-up program at least until pre-school age with special attention for these disorders should be caried out in order to give timely help to children who will probably meet difficulties in an ordinary school.

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Chapter 8

IS IT CORRECT TO CORRECT? DEVELOPMENTAL MILESTONES IN 555 "NORMAL" PRETERM INFANTS COMPARED WITH TERM INFANTS.

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Journal of Pediatrics,1991, 118, 399-404.

Chapter 8

IS IT CORRECT TO CORRECT? DEVELOPMENTAL MILESTONES IN 555 "NORMAL" PRETERM INFANTS COMPARED WITH TERM INFANTS.

Summary

To determine whether correction for preterm birth should be applied during developmental assessment, we conducted a prospective national survey of very preterm infants (born at <32 weeks of gestation); neurodevelopment in the first 2 years was studied with the Dutch child health care developmental assessment. In 555 preterm children who had no evidence of handicap at 2 years of age, the age at which developmental milestones were reached was established. The results were compared with the results of the same assessment in Dutch children born at term. During the first year, the development of the very preterm children equalled the development of normal children when full correction was applied. At 2 years of age, development was equal or even better than normal children's development without correction. We conclude that full correction for prematurity should be applied in the first year to avoid overreferral for developmental stimulation, whereas at 2 years of age correction is not necessary.

Introduction

A still unresolved issue in the developmental assessment of preterm infants is whether correction for preterm birth should be applied. The aim of assessment is to identify children with developmental delay or neurologic, visual or hearing impairments who would benefit from stimulation programmes. For early identification, the use of chronologic age might be advocated. On the other hand, undue parental anxiety and overreferral for stimulation programs should be avoided, and therefore the use of corrected age may be preferred.

Different authors prefer full correction, half correction or no correction at all for various reasons. Even for a single milestone such as the first smile, Foley [1] concluded that half correction should be applied; Crow and Gowers,[2] in a similar study, argued for full correction. Full correction before 12 months is favoured because uncorrected developmental quotients tend to increase during the first two years of life.[3]

Corrected DQ's also have corresponded better with DQ's in term infants,[4] and corrected scores in the first year have correlated better with scores at 3 and 5 years of age.[5] However, some overcorrection is probable.[3] Miller et al.[6] and Barrera et al.[7] reported that differences between motor and mental development resulted in overestimation of motor scores when full correction was applied. A 50% correction was advocated by Mauk and Ting,[8] and Caputo et al.[9] stated that uncorrected scores at 12 months of age correlated better with follow-up findings at 7-9 years of age.

The aim of our study was to shed some light on this issue. Therefore both the corrected and chronologic ages at which frequently used developmental milestones are reached were determined in a large cohort of preterm infants. These data were compared with the age at which term infants reached the same milestones. Because a different handicap rate in preterm and term children might influence the results of the comparison, children with handicaps were excluded in both groups.

methods

patients

The preterm population consisted of 1010 very premature infants with a gestational age of <32 weeks, representing 95% of all such infants born alive in 1983 in the Netherlands. Gestational age was based on the best obstetrical estimate, including last menstrual period, results of pregnancy testing, and ultrasonography findings if necessary. Distribution of socioeconomic class, obtained in 60% of the children, did not differ from that of the total Dutch population. A full description of the perinatal data was given by Verloove- Vanhorick and Verwey.[10] At the corrected age of 2 years, 97% of the survivors were available for follow-up; the developmental outcome in these children has been published.[11] All children with major and minor handicaps at the time of the last assessment were excluded, leaving 555 children for our study (table 1).

A minor handicap was diagnosed when some retardation was present (3-4 months retarded or DQ between 80 and 90) or when at least one of the following was present: a mild neurologic disorder, mild visual or hearing defects, or mild psychosocial problems. Such disabilities were unlikely to prevent the child from going to a normal school or to interfere seriously with normal life. A major handicap was diagnosed when severe retardation was present (≥ 5 months retarded or DQ <80) or when one of the following was present: a severe neurologic disorder, severe visual or hearing defects, or serious psychosocial problems. Such disabilities

table 1: Descriptive data of study population

gestational age (wk)	total number liveborn	mortality rate	handicap at 2-year assessment	available for present study
< 24	8	8		
24-25	67	62	3	2
26-27	180	96	14	70
28-29	307	89	50	168
30-31	448	77	56	315
total <32	1010	332	123	555

would probably prevent the child's going to a normal school or cause serious interference with normal function in society.

Follow-up visits of the preterm children were scheduled at 3, 6, 12 and 24 months of corrected age. At each visit, developmental items for the scheduled age and items for the age category before and after the scheduled age were recorded. For our study, only items appropriate for the scheduled age and items that were examined on more than one occasion were used (table 4). Assessments were performed by the local pediatrician participating in the study, after oral and written instructions.

The control group consisted of 550 term infants born between 1970 and 1972. These children were followed for 5 years or more; the same developmental items and the same criteria for "passing" or "failing" an item were used. Because the object of the study in this group was to establish percentiles for normal development in Dutch children, the assessments were performed by 2 child health care doctors and all children with handicaps were excluded.[12,13] Socioeconomic class in the control group was representative of the total Dutch population.

developmental assessment

Development was evaluated with the Van Wiechen neurodevelopmental assessment, which is used in Dutch child health care for children from 4 weeks to 5 years of age. It is based on milestones and warning symptoms defined by Touwen,[14] such as asymmetry, dystonia, persistence of primitive reflexes,and hearing or visual disturbances. In each age category, five to eight items, covering the five fields of development as described by Gesell and Amatruda, are examined.[15] The items were chosen in such a

way that at least 90% of a normal population will achieve them by the age at examination.[12]

Statistics

Although the majority of children were examined within 2 weeks of the scheduled date in the first year of life and within 4 weeks at 2 years of age, the age at which examinations took place ranged widely (table 2).

table 2: Variation in age (in weeks) at which developmental items were assessed.

	scheduled corrected age			
developm. items	3 months corr chron	6 months corr chron	12 months corr chron	24 months corr chron
1- 3	4-25 12-31	16-42 24-48		
4- 8	4-25 12-31	16-42 24-48		
9-14		16-42 24-48	36-73 49-76	
15-20			36-73 49 76	
21-26				77-156 86-167

corr = corrected age
chron = chronologic age

This variability in age at examination allowed us to calculate the age at which 50% and 90% of the children had a positive score (50th and 90th percentiles) for each developmental item. Theoretically, development is a nondecreasing function of time. We used stepwise isotonic regression to avoid chance fluctuations that occur in a transversal study. This non-parametric regression technique fits a nondecreasing step function to the data.[16] An example of this stepwise isotonic regression is given in the figure. No model assumptions were made except for this monotony.

A possible source of bias might be an association between the actual age at examination and the developmental status of the infant. For instance, it is conceivable that retarded children were examined, on the average, at an earlier time than children who were completely normal. If this bias existed in the group of nonhandicapped children, it would be visible in the children who are handicapped. Therefore the mean age at examination in the children excluded because of handicap was compared with the age at examination of the studied children. No systematic difference was found between handicapped and nonhandicapped children (table 3), so the existence of such an effect within the nonhandicapped group is unlikely.

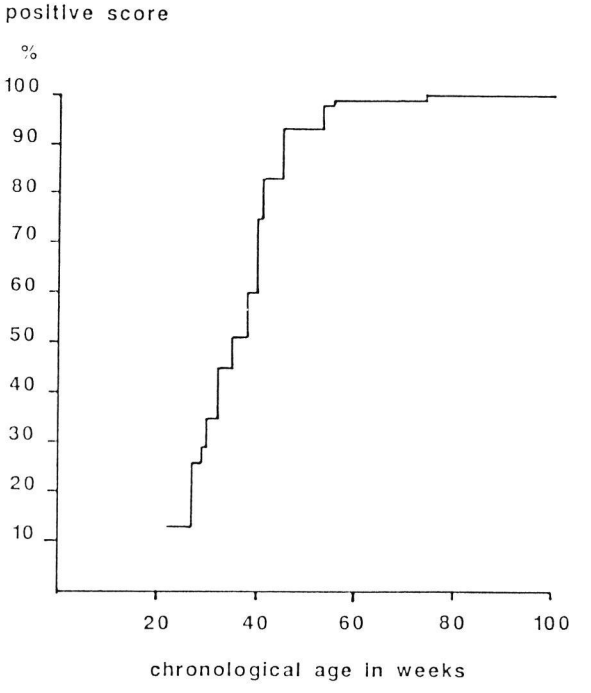

figure: Example of stepwise isotonic regression for rolls from prone to supine and back.

table 3: Comparison of mean corrected age at examination (weeks) in children with and without a handicap at 2 years of age.

	scheduled age			
	3 months	6 months	12 months	24 months
no handicap	12.6±2.8	25.9±3.4	52.5±4.7	106.0±11.5
minor handicap	13.1±2.5	26.9±3.4	53.7±6.2	105.7±11.0
major handicap	13.3±2.4	26.8±3.1	51.7±6.5	106.0±11.0

values expressed as mean ± SD.

Results

The examined developmental items are given in table 4 with the calculated percentage of children with a positive score at the appropriate chronologic and corrected age.

table 4: Assessed developmental items and percentage of children with a positive score at the appropriate age.

developmental item	children with pos score (%) chron	corr
3 months		
1 holds head up 45' in prone position	60	80
2 responsive vocalizing	67	93
3 looks at own hands	47	82
6 months		
4 turns head to sound	35	95
5 holds head up 90' in prone position	61	99
6 hands playing in midline	50	98
7 no headlag when pulled to sit	56	98
8 grasps toy within reach	29	97
9 months		
9 plays with both feet	58	91
10 transfers toy easily, hand to hand	61	86
11 rolls from prone to supine and back	65	88
12 head held up in sitting position	82	92
13 picks up one small toy and than second	82	89
14 says dada, baba or gaga	50	87
12 months		
15 jabbering	50	98
16 crawls	50	94
17 sits without support	60	98
18 picks up crumb thumb and indexfinger	88	95
19 waves 'bye-bye'	67	93
20 pulls himself to standing position	69	92
24 months		
21 puts ball in box when asked	93	97
22 drinks from a cup	94	98
23 imitates every day activities	99	99
24 squats	93	98
25 makes tower of 3 cubes	96	97
26 2 word sentences	80	82

table 5: Age in weeks at which 50% and 90% of the study population had a positive score compared with the 50th and 90th percentile in a similar study in normal dutch children.

developmental item	chron		corr		controls	
	50%	90%	50%	90%	50%	90%
1 holds head up 45'in prone position	10	26	1	14	6	12
2 responsive vocalizing	10	18	1	11	7	10
3 looks at own hands	18	25	3	15	9	13
4 turns head to sound	28	30	16	21	10	14
5 holds head up 90'in prone position	20	30	11	21	11	17
6 hands playing in midline	26	30	14	21	15	19
7 no headlag when pulled to sit	20	30	11	21	19	25
8 grasps toy within reach	28	32	18	21	20	22
9 plays with both feet	38	53	26	38	21	29
10 transfers toy easily, hand to hand	36	55	25	44	23	31
11 rolls from prone to supine, back	37	52	26	42	24	32
12 head held up in sitting position	31	52	19	30	25	32
13 picks up 1 small toy, than second	29	46	19	41	20	35
14 says dada, baba or gaga	39	52	28	42	30	38
15 jabbering	38	55	36	45	35	41
16 crawls	51	55	40	45	36	46
17 sits without support	49	53	26	43	37	44
18 picks up crumb thumb and finger	<49	58	<36	48	37	44
19 waves 'bye-bye'	36	60	26	51	44	48
20 pulls himself to standing position	51	60	40	52	42	53
21 puts ball in box when asked	<77	82	<86	73	*	87
22 drinks from a cup	<77	104	<86	95	*	89
23 imitates every day activities	<77	82	<86	73	*	90
24 squats	<77	94	<86	82	*	97
25 makes tower of 3 cubes	<77	82	<86	73	79	102
26 2 word sentences	<77	119	<86	108	95	129

* not available

During the first year, the percentage of children with a positive score varied from 80% to 99% when corrected age was used, but only 30% to 80% had a positive score when chronologic age was used. At 2 years of age, more than 90% had a positive score irrespective of the use of corrected or chronologic age, except for 2 word sentences; the 90th percentile in term children was also later than 24 months for this item.

Table 5 shows the age at which 50% and 90% of the children had a positive score for each assessed item compared with the results for the

control group. The 50th percentile could not be calculated for all items because >50% of the children had a positive score for these items, even at the youngest age examined. For instance, 67% of the children could pick up a crumb between thumb and index finger at the corrected age of 36 weeks. The chronologic age at which 50% of the preterm children had a positive score was much later than that of term children throughout the first year. With full correction, developmental items were passed either a few weeks earlier or a few weeks later. When the 90th percentiles were compared, even after full correction, most items were passed slightly later in preterm infants during the first year. At the 2-year assessment, however, 90% of the preterm children had positive scores earlier than term children, even when chronologic age was used. The 50th percentile at this age could not be calculated because >50% of the preterm children had a positive score at each examined age for all items.

The difference between the 50th and 90th percentiles was much larger in preterm infants than in term infants. After correction for preterm birth, the 50th percentile of preterm children was a few weeks earlier for many developmental items; for the same item the 90th percentile was some weeks later than in term children.

Discussion

After full correction in the first year, all items were achieved at aproximately the same age or slightly later by preterm compared with term children. Only some gross motor milestones at 6 and 12 months were reached a few weeks earlier. This is in accordance with the overestimation of motor scores found in other studies.[6,7] Without correction, all developmental milestones were reached later than in term children during the first year. Developmental delay would be suspected in half the preterm children at 6 months if chronologic age was used, but these children would be considered normal if corrected age was used. The children had no handicap at the age of 2 years, so the use of chronologic age would cause undue anxiety for parents and probably many over-referrals for stimulation programs.

At 2 years of age the development of pretem children was comparable or even earlier than in term children, even when chronologic age was used. It remains uncertain whether this is due to "catch-up" or whether it is the result of a wider variability of normal development at this age. Nevertheless, correction for preterm birth at this age is not necessary.

The difference between the 50th and 90th percentiles in preterm

children was greater than in term children. On the one hand, normal preterm children might reach developmental milestones early because of early extrauterine stimulation. This supports the view that development is not purely cerebral maturation but is also affected by environmental stimuli.[17] On the other hand, a slight delay in some of the preterm children, even when full correction is applied, is probably realistic. Although children with handicaps (including retardation) at the age of 2 years were excluded, the diagnosis of retardation was based on corrected age and some of the included children may have been mildly retarded when chronologic age was used. The percentage of children with mild neurologic abnormalities or mild language problems, which can be detected only at a later age, is expected to be higher in these children than in a normal population. Therefore slower development, even when it is comparable to that of term children after correction for preterm birth, might carry a higher risk of abnormal development.

Although the original epidemiologic survey was not designed to aswer the question of whether correction for preterm birth should be used, the variation in age of developmental assessment and the statistical method of stepwise isotonic regression gave us important information on this subject. Interobserver differences could not be excluded, because about 200 pediatricians participated in the study. Nevertheless, the developmental items used are incorporated in the child health developmental assessment that has been used for 10 years throughout the country, and they are easy to apply and easy to interpret. Therefore we assumed that the results were not biased by systematic errors.

We conclude that the comparison of developmental milestones in a large cohort of preterm children and in term children seems to support full correction for prematurity in the first year of life. In the second year of life, correction is no longer necessary.
Longer follow-up is needed to establish whether correction for preterm birth in the first year is indeed appropriate or whether it leads to unnecessary delay in the diagnosis of developmental disturbances.

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SUMMARY AND CONCLUSIONS

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Summary

In preterm infants, there is a higher than normal risk of severe neurological sequelae as well as of less severe but unequivocal neurodevelopmental disturbances interfering with normal life. Early detection of these neurodevelopmental disturbances is necessary because:

1.Early detection may help to estimate the long term effects of changes in perinatal treatment and thus helps to find possible ways of primary prevention.

2 Early detection gives the opportunity to offer remedial help to children with potential neurodevelopmental disturbances and thus offers a chance for secondary prevention.

The object of the present study was to evaluate some possibilities of early recognition of developmental disorders in very preterm infants. We performed specific investigations in the neonatal period in hospital-bound populations of very preterm infants, as well as routine clinical investigations in the neonatal period and early childhood in a large geographically-defined population of very preterm and/or very low birthweight infants.

In part I, we described the possible predictive value of biochemical (chapter 1) and Doppler-ultrasound (chapter 2) measurements in the neonatal period, the follow-up results of neonatal seizures (chapter 3) and neonatal neurological abnormalities (chapter 4), and the value of magnetic resonance staging of myelination shortly after term (chapter 5).

Serum creatine kinase (CK-BB) activity was studied in the first days of life in preterm infants. We found no relationship between increased serum CK-BB activity after birth and motor disabilities at 4 years of age. It was, however, related to mental delay in children without motor disabilities at 4 years of age. Therefore, this might prove to be an indicator of diffuse brain damage. Because one child with exceptionally high levels of CK-BB after birth appeared normal at 4 years, further investigations are still necessary to establish the worth of elevated CK-BB activity after possibly damaging events.

Blood-flow velocity patterns in the anterior cerebral artery were

studied in the first week of life in preterm infants. An increase in the peak systolic flow velocity (PSFV) and a significantly higher pulsatility index (PI) was found in children with major handicap at 2 years of age. End-diastolic flow and area under the velocity curve did not differ between normal and handicapped children. We postulated that the higher PI and PSFV values were caused by increased compliance of the vascular bed supplied by the anterior cerebral artery. This is possibly induced by congestion and oedema of the periventricular white matter due to ischaemic lesions, which also cause periventricular leukomalacia.

Neonatal seizures as well as neonatal neurological abnormalities are rare conditions when based on routine paediatric examination in a national year-cohort of very preterm and/or very low birthweight infants (5.4% and 14.2% respectively). Both conditions are associated with a very high mortality rate as well as a high handicap rate in survivors at 2 years of age. A normal outcome is not excluded by seizures or by mild neurological abnormalities; a normal outcome in infants with obvious neurological abnormalities in the neonatal period is, however, very unlikely.

The myelination stage of the central nervous system was studied by means of magnetic resonance imaging (MRI) in 26 preterm infants at 44 weeks postmenstrual age. The myelination stage showed a significant correlation with neurodevelopmental outcome at 1 year of age. Periventricular leukomalacia established with ultrasonography in the same infants, however, showed a better correlation to neurodevelopmental outcome. Ultrasonography can be applied even in ventilator-treated infants and gives earlier information on the existence of severe brain damage such as periventricular leukomalacia. MRI staging of myelination may prove to be a valuable tool in the prediction of neurodevelopmental outcome in patients with conditions that cannot be adequately monitored with ultrasonography.

In part II, we described the predictive value of neurological abnormalities in infancy (chapter 6) and some aspects of the developmental assessment of the Dutch child health care in the timely identification of neurodevelopmental problems (chapters 7 and 8).

Neurological abnormalities in the first 2 years were found in 33% of the examined very preterm or VLBW infants; these resolved in half of the cases. Children with transient neurological abnormalities had a high rate of other neurodevelopmental impairments, but this was only slightly less the case in children who were never found to be neurologically

abnormal. Since these results were based on routine clinical evaluations in a large epidemiological survey it is not unlikely that some under-recognition of neurological abnormalities exists as a result of large inter-observer variability.

We compared the results of the developmental assessment used in Dutch child health care (the Van Wiechen assessment) with the Bayley scales of mental and motor development in 117 preterm children at the age of 2 years (II,3). The correlation between the two assessments was not strong, but the relation of either of the assessments to outcome did not differ much. Both assessments had a good specificity leading to few over-referrals, but sensitivity was disappointingly low. Minor handicaps or disabilities due to mild retardation and language disorders were often not detected, and impairments such as minor neurological dysfunction, mild language delay or visual disturbances were almost never detected at 2 years of age, irrespective of which assessment was used.

To establish whether correction for preterm birth should be applied when development is assessed in very preterm children, we compared the age at which healthy fullterm children achieved milestones during the first 2 years with both corrected and chronological age in 'normal' very preterm children. In the first year, the 90th percentile was reached by very preterm children at the same age as fullterm children when full correction was applied. At 2 years of age, correction was no longer necessary. It was remarkable that the age difference between 50th and 90th percentile in preterm children was wider than in fullterm children.

Conclusions

Abnormal biochemical (elevated serum CK-BB activity) or abnormal Doppler-ultrasound findings shortly after birth did identify children with a higher risk of neurodevelopmental disturbances. Neurological abnormalities and seizures during the neonatal period also identified children with higher risks for neurodevelopmental disturbances. These parameters, therefore, may help in the search for possibly preventable causes of brain damage and can be used in the evaluation of changing perinatal management. MRI staging of myelination 4 weeks after term did not contribute to the already existing knowledge in this respect. Normal development could not be predicted by any of the investigations in the perinatal period; follow-up of all very preterm infants, therefore, is still mandatory.

Almost half of the preterm or VLBW infants showed neurological abnormalities in the first 2 years and/or at 5 years of age. A strong

relationship between neurological disturbances and other CNS problems was found in these infants (Veen et al. submitted). More detailed and standardized neurological examinations throughout the first years and extended at least until school age will probably prove to be the best strategy for the early recognition of neurodevelopmental disturbances in these very preterm infants.

The Van Wiechen assessment gave a fairly good estimate of the results a child will get on a full-scale developmental assessment. Major handicaps were identified mostly at an early age, but many minor handicaps or disabilities due to mild mental retardation, language disorders and minor neurological dysfunction were not detected by either the Van Wiechen developmental assessment in the first 2 years or the Bayley scales of mental and motor development. Longer follow-up is necessary to detect these disorders.

Correction for preterm birth seems logical in the first year; after correction, the age at which 'normal' preterm infants reached milestones was comparable to the age at which fullterm infants reached them. The use of chronological age may easily cause unnecessary anxiety for the parents. On the other hand, the wide range between the age at which 50% and 90% of the preterm children reached milestones might be the result of a relatively late development in children at risk for milder neurodevelopmental disturbances. Further study is necessary to establish whether full correction in the first year will cause under-recognition of developmental disturbances. After the first year, correction should be abandoned.

We only know the outcome up until 5 years of age in these very preterm infants . It is certain that this is not the final answer to the question of outcome in very preterm or VLBW infants. Some of the neurological abnormalities may lessen in degree or disappear altogether when the child gets older. On the other hand, mild mental retardation, language disorders or behavioral disturbances may make it impossible for some of these children to stay in the normal education system when they get older. Furthermore, these children are still too young for anything definite to be said on possible learning disabilities. Follow-up well into school age is necessary in order to plan interventional strategies for these children in the future.

Perinatal medicine has been highly successful in the last decades. Mortality in very preterm infants is still decreasing and the majority of the surviving children is without severe handicaps. Concern about the cognitive and behavioral disturbances in these children, however, makes it

unacceptable that the care for them is discontinued when the baby goes home or when the toddler appears to be without handicap. It is imperative to dedicate ourselves to the ongoing care of these children well into childhood. Further researches into the extent of late developmental disorders as well as into the value of interventional therapies are necessary.

SAMENVATTING EN CONCLUSIES

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Samenvatting

Te vroeg geboren kinderen hebben, meer dan voldragen kinderen, kans op ernstige neurologische restverschijnselen zowel als op minder ernstige maar onmiskenbaar op het normale leven ingrijpende ontwikkelingsstoornissen. Vroege onderkenning van deze ontwikkelingsstoornissen is noodzakelijk omdat ten eerste vroege onderkenning het mogelijk maakt de effecten op lange termijn van veranderingen in de perinatale zorg vroeg vast te stellen; dit kan bijdragen tot het vinden van mogelijkheden voor primaire preventie. Ten tweede omdat vroege onderkenning het mogelijk maakt om vroegtijdig in te grijpen bij kinderen met een ontwikkelingsstoornis en zo kan bijdragen tot secundaire preventie.

Ons doel was een aantal mogelijkheden voor vroegtijdige onderkenning van ontwikkelingsstoornissen bij te vroeg geboren kinderen te onderzoeken. Hiervoor werd, naast specifieke onderzoeken in een kleine ziekenhuis gebonden populatie, ook meer algemeen kindergeneeskundig onderzoek gedaan in een vrijwel volledig jaarcohort van in nederland veel te vroeg en/of veel te klein geboren kinderen (het POPS onderzoek).

deel I

In deel I werd het onderzoek in de neonatale periode beschreven. Dit betrof biochemisch (hoofdstuk 1) en Doppler-ultrageluid onderzoek (hoofdstuk 2) en onderzoek naar de waarde van gradering van de myelinisatie van het centraal zenuwstelsel kort na de à terme datum (hoofdstuk 5) in groepen kinderen die in ons eigen ziekenhuis werden verpleegd. Daarnaast werd gekeken naar vóórkomen en gevolgen van convulsies (hoofdstuk 3) en neurologische afwijkingen (hoofdstuk 4) in een groot epidemiologisch onderzoek.

In hoofdstuk 1 werd de serum creatine kinase (CK-BB) activiteit in de eerste levensdagen van te vroeg geborenen gerelateerd aan de uitkomst op twee- en vierjarige leeftijd. Een verhoogde CK-BB activiteit bleek niet samen te hangen met motorische handicaps, maar hing wel duidelijk samen met psychomotore retardatie bij kinderen zonder motorische stoornissen.Daarmee lijkt een verhoogde CK-BB activiteit een aanwijzing voor het bestaan van diffuse hersenbeschadiging.
Eén kind met een uitzonderlijk hoge CK-BB activiteit echter bleek op de leeftijd van 4 jaar een normale ontwikkeling te hebben. Verder onderzoek

is noodzakelijk om de waarde vast te stellen van de CK-BB activiteit na incidenten die mogelijk met hersenbeschadiging gepaard gaan.

In hoofdstuk 2 werden de bloeddoorstromingspatronen in de arteria cerebri anterior in de eerste levensweek van veel te vroeg geboren kinderen beschreven. Bij kinderen met een ernstige handicap op tweejarige leeftijd bleek de piek systolische flow snelheid (PSFV) verhoogd en bestond er een significant grotere pulsatility index (PI). De eind-diastolische bloedstroomsnelheid en de grootte van het gebied onder de stroomsnelheidscurve waren niet verschillend bij normale en gehandicapte kinderen. Waarschijnlijk worden de hogere PSFV en PI veroorzaakt door een toegenomen compliantie van het vaatbed dat wordt verzorgd door de arteria cerebri anterior. Dit kan het gevolg zijn van congestie en oedeem van de periventriculaire witte stof ten gevolge van ischemie, die ook periventriculaire leukomalacie veroorzaakt.

In hoofdstuk 3 en 4 blijkt dat zowel neonatale convulsies als neonatale neurologische afwijkingen relatief weinig werden gevonden bij routine kindergeneeskundig onderzoek in een grote epidemiologische studie (respectievelijk 5,4% en 14,2%). Beide problemen bleken samen te hangen met een zeer hoge sterfte en een hoog percentage handicaps bij de overlevende kinderen. Een normale ontwikkeling is zowel bij neonatale convulsies als bij lichte neonatale neurologische afwijkingen niet uitgesloten; bij ernstige neonatale neurologische afwijkingen is een normale ontwikkeling zeer onwaarschijnlijk.

In hoofdstuk 5 werd de myelinisatiegraad van het centrale zenuwstelsel bestudeerd met behulp van Magnetische Resonantie bij 26 prematuren op de leeftijd van 4 weken post terme. De myelinisatiegraad bleek significant samen te hangen met de psychomotore ontwikkeling op de leeftijd van 1 jaar. Bij dezelfde kinderen echter bleek een veel sterkere relatie te bestaan tussen de psychomotore ontwikkeling en een met echografisch onderzoek aangetoonde periventriculaire leukomalacie. In tegenstelling tot het MR onderzoek kan echografisch onderzoek aan het bed en zonodig ook bij beademde patiënten plaats vinden. Dit geeft veel eerder betrouwbare informatie over het bestaan van ernstige hersenbeschadiging zoals periventriculaire leukomalacie.

deel II

In deel II werd de predictieve waarde van neurologisch onderzoek bij

zuigelingen en peuters beschreven evenals enkele aspecten van het ontwikkelingsschema dat in de Nederlandse jeugdgezondheidszorg wordt gebruikt (het van Wiechen schema).

In hoofdstuk 6 werd het vóórkomen van neurologische afwijkingen in de eerste levensjaren beschreven. Bij 33% van de ernstig pre- en/of dysmature kinderen uit het POPS onderzoek werden in de eerste twee levensjaren neurologische afwijkingen gevonden. Deze afwijkingen bleken in de helft van de gevallen van voorbijgaande aard. Kinderen met voorbijgaande neurologische afwijkingen in de eerste levensjaren bleken op de leeftijd van 5 jaar vaak andere ontwikkelingsstoornissen te hebben. Bij kinderen, bij wie in de eerste levensjaren geen neurologische afwijkingen werden gevonden, bleken lichte afwijkingen nauwelijks minder vaak voor te komen. Ernstige problemen kwamen bij deze kinderen wel minder frequent voor. Een zekere onder-rapportage van neurologische afwijkingen ten gevolge van grote interobserver variatie in dit epidemiologische onderzoek lijkt overigens wel waarschijnlijk.

In hoofdstuk 7 werden de uitkomsten van het van Wiechen schema vergeleken met de uitkomsten van volledig ontwikkelings-psychologisch onderzoek met behulp van de Bayley ontwikkelingsschalen bij 117 te vroeg geboren kinderen op de leeftijd van 2 jaar. De onderlinge samenhang tussen de twee onderzoeken was niet erg sterk, maar de voorspellende waarde voor de uitkomst op 5 jarige leeftijd bleek bij beide vrijwel gelijk. Beide onderzoeken hadden een goede specificiteit en gaven weinig aanleiding tot overdiagnostiek. Bij beide onderzoeken bleek echter de sensitiviteit teleurstellend laag. Lichte handicaps of stoornissen ten gevolge van lichte psychomotore retardatie, spraak-taal stoornissen of lichte neurologische stoornissen werden vaak nog niet opgemerkt. Lichte afwijkingen op deze gebieden die geen aanleiding tot een handicap gaven werden vrijwel nooit op de leeftijd van 2 jaar vastgesteld, onafhankelijk van welk onderzoek werd gebruikt.

In hoofdstuk 8 werd onderzocht of het nodig is correctie voor de vroeggeboorte toe te passen bij het beoordelen van de psychomotore ontwikkeling van veel te vroeg geboren kinderen. Hiertoe werden de leeftijden waarop gezonde voldragen kinderen ontwikkelingsmijlpalen behaalden vergeleken met zowel de gecorrigeerde als de kalenderleeftijd waarop "normale" veel te vroeg geboren kinderen deze mijlpalen behaalden. In het eerste levensjaar bleek de p90 van de te vroeg geboren kinderen

vergelijkbaar met de p90 van de voldragen kinderen wanneer volledige correctie werd toegepast. Op tweejarige leeftijd was correctie niet langer nodig. Opmerkelijk was dat het verschil tussen de p50 en de p90 bij de te vroeg geboren kinderen veel groter was dan bij de voldragen kinderen.

Conclusies

Biochemische afwijkingen (verhoogde CK-BB activiteit) of afwijkende hersenbloeddoorstroming kort na de geboorte kunnen inderdaad kinderen identificeren die een verhoogde kans lopen op ontwikkelingsstoornissen. Neurologische afwijkingen of convulsies in de neonatale periode identificeerden eveneens kinderen met een hoger risico. Deze onderzoeken kunnen dus gebruikt worden bij het zoeken naar mogelijk te voorkomen oorzaken van hersenbeschadiging en bij de evaluatie van de perinatologische behandeling. MR onderzoek om de myelinisatiegraad van het centraal zenuwstelsel vast te stellen droeg niet bij tot de al bestaande kennis in dit opzicht. Zekerheid over een normale ontwikkeling kon echter geen van de genoemde onderzoeken in de neonatale periode geven. Follow-up blijft daarom voor alle veel te vroeg geboren kinderen noodzakelijk.

Bij bijna de helft van alle veel te vroeg of veel te klein geboren kinderen in het POPS onderzoek werden neurologische afwijkingen gezien in de eerste twee jaar en/of op de leeftijd van vijf jaar. Er bestond een duidelijke samenhang tussen deze neurologische afwijkingen en andere psychomotore ontwikkelings problemen, ook wanneer de neurologische afwijkingen van voorbijgaande aard waren. Gedetailleerd en gestandaardiseerd neurologisch onderzoek op verschillende tijdstippen zeker tot aan de schoolleeftijd is waarschijnlijk de beste waarborg voor de vroege onderkenning van ontwikkelingsstoornissen bij deze veel te vroeg geboren kinderen.

Het van Wiechen schema geeft een redelijke indicatie van de resultaten die een kind bij volledig ontwikkelings-psychologisch onderzoek zal halen. Ernstige handicaps werden over het algemeen vroeg geïdentificeerd, maar lichtere handicaps ten gevolge van psychomotore retardatie, spraak-taal stoornissen
of lichte neurologische afwijkingen werden noch met het van Wiechen schema noch met het Bayley onderzoek ontdekt. Langere follow-up is noodzakelijk om ook deze stoornissen aan het licht te brengen.

Correctie voor prematuriteit bij het beoordelen van de ontwikkeling van te vroeg geboren kinderen lijkt redelijk in het eerste levensjaar: na correctie worden mijlpalen op vergelijkbare leeftijd gehaald als door gezonde voldragen kinderen. Gebruik van de kalenderleeftijd kan tot onnodige ongerustheid aanleiding geven. Wel moeten we rekening houden met de veel grotere spreiding tussen p50 en p90 leeftijd bij de te vroeg geboren kinderen in vergelijking met op tijd geboren kinderen. Dit kan betekenen dat prematuren zich wat sneller ontwikkelen als er niets bijzonders is, terwijl zich onder de zich relatief wat trager ontwikkelende kinderen veel kinderen met lichte en nog niet herkende ontwikkelingsstoornissen bevinden. Nader onderzoek naar deze mogelijkheid moet nog worden verricht.

Tot nu toe weten wij slechts de uitkomst tot vijf jaar van deze veel te vroeg geboren kinderen. Het is zeker dat dit niet een definitief antwoord geeft op de vraag hoe te vroeg geboren kinderen zich ontwikkelen. Een deel van de neurologische afwijkingen kan minder ernstig worden of zelfs geheel verdwijnen bij het ouder worden. Anderzijds kunnen lichte psychomotore retardatie, spraak-taal stoornissen of gedragsstoornissen het voor een deel van de kinderen onmogelijk maken zich in het normale onderwijs te handhaven. Bovendien zijn deze kinderen nog zo jong dat eventuele leerstoornissen bij hen nog niet kunnen worden vastgesteld. Follow-up tot een eind in de school leeftijd is noodzakelijk om eventuele interventiestrategieen te kunnen plannen.

Perinatologie is in de afgelopen decennia zeer succesvol geweest, de sterfte onder zeer vroeg geboren kinderen neemt nog steeds af en het merendeel van deze kinderen overleeft zonder ernstige handicap. Niettemin blijven er zorgen bestaan ten aanzien van cognitieve en gedragsstoornissen. In het licht van deze problemen is het onaanvaardbaar dat de zorg voor deze kinderen ophoudt wanneer zij naar huis ontslagen worden of wanneer op de peuterleeftijd blijkt dat er geen ernstige handicaps bestaan. Follow-up tot in de schoolleeftijd en waar nodig begeleiding en behandeling zou voor alle veel te vroeg geboren kinderen gegarandeerd moeten zijn. Nader onderzoek naar het vóórkomen van late ontwikkelingsstoornissen en naar de waarde van interventieprogramma's om deze problemen te voorkomen is dan ook noodzakelijk.

Acknowledgements

When completing this thesis I want to express my gratitude to
-the authors and co-authors, without whom it would not even have started.
-the parents, who kept visiting the out-patient clinic and finally welcomed me home when their children were five years old and the children from whom more cooperation was asked as they grew older.
-the paediatricians from the POPS project: Thea van Zeben-van der Aa who collected the two year data and Martina Ens-Dokkum, Anneke Schreuder and Sylvia Veen who performed and analyzed the five year assessment.
-Ronald Brand who did all statistical analysis and made me understand most of what was done.
-Lou Hermans who did the illustrations and Ineke Haasnoot, Mirjam Silverentand and Ina Kloosterboer who offered secretarial help.
-Penny Mooyaart-McGregor who corrected the English of the summary.
I am very grateful for the climate I could work in and I want to thank
-My colleagues Margot van de Bor, Frank van Bel, Diny van Zoeren-Grobben and Monique de Haan for their continuous support and the time they offered me, and especially Howard Berger, who kept telling me that life without research is not worth living.
-Annelies Koningsveld- den Ouden and Lia Bruines-Simons, who took care of my children whenever I was not there.
-Evert van Rijssel, who never expected less than an equal.

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