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ORIGINAL PAPER

Outcome of extremely low birth weight survivors at school age: the influence of perinatal parameters on neurodevelopment

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Abstract Extremely low birth weight (ELBW) is associated with impaired neurodevelopmental outcome in infancy. Information on the long-term cognitive and neurological consequences of ELBW is scarce. We aimed to identify the perinatal and neonatal factors of ELBW infants associated with adverse cognitive and neurological outcome at school age. A regional cohort of 135 ELBW infants born between 1993 and 1998 was prospectively evaluated at 3, 6, 12, and 18 months postmenstrual age and at yearly intervals up to age 10 years. The comprehensive follow-up programme for high-risk infants included neurological examinations and psychometric evaluations. According to the overall results of these tests, children were classified as either being normal or having minor or major impairment. At a mean age of 8.4 (SD: 1.6) years, 43% of children had survived without any impairment. Minor impairment was diagnosed in 39% and major impairment in 18% of assessed children. The proportion of disabled school children rose with decreasing gestational age. The following neonatal complications were significant risk factors for developing major or minor impairment at school age: an increase in head circumference <6 mm per week (OR 4.0, 95% CI: 1.1–14.8), parenteral nutrition ≥6 weeks (OR 2.5, 95% CI: 1.1–6.0), and mechanical ventilation >14 days (OR 2.3, 95% CI: 1.0–5.1). High-grade intraventricular haemorrhage (IVH) and/or PVL (OR 13.3, 95% CI: 4.0–44.9), neonatal seizures (OR 5.2, 95% CI: 1.2–22.4) and bowel perforation, and/or necrotizing enterocolitis (OR 4.4, 95% CI: 1.1–17.0) were significant risk factors for developing major impairment. In spite of the relatively large proportion of normal children, ELBW remains an important risk factor for neurodevelopmental impairment at school age. Thus, measures to prevent complications such as necrotizing enterocolitis, cerebral haemorrhage, and undernutrition remain important goals for neonatal intensive care.

Keywords Extremely low birth weight infant · Child development/complications · Developmental disabilities · Follow-up studies

Abbreviations

BPD	bronchopulmonary dysplasia
CP	cerebral palsy
CTG	cardiotocography
CRIB	clinical risk index for babies
ED	expected date of delivery
ELBW	extremely low birth weight
IVH	peri- and intraventricular haemorrhage
NEC	necrotizing enterocolitis
NICU	neonatal intensive care unit
OR	odds ratio
PDA	patent ductus arteriosus
PVL	periventricular leukomalacia
RDS	respiratory distress syndrome

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Introduction

The survival rate of extremely low birth weight (ELBW) infants has improved considerably during the last 3 decades [10]. In the late 1970s, the survival rates of preterm infants with a birth weight below 1,000 g were about 30% [32]. These figures increased to >70% in the 1990s [20, 38, 39]. Specific improvements of neonatal care, for instance surfactant therapy and antenatal steroids, have contributed to these successes. As mortality decreased during the last decade, questions have arisen relative to the long-term morbidity of these children [17, 18, 25, 46, 47]. Studies that followed up infants for longer time periods reported higher incidences of disability [12, 14, 28].

Assessments of the long-term follow-up of ELBW infants are essential for the continuous improvement of perinatal and neonatal care. Of paramount importance is the neurodevelopmental outcome of these children. Many studies have been published that present data on outcomes at the age of 1 or 2 years [23, 42, 46, 47], while less information is available with respect to the cognitive and neurologic consequences of ELBW at school age or later [2, 8, 14, 19]. It is doubtful that final follow-up testing of ELBW completed before school age will yield reliable results for the ultimate neurodevelopmental outcome [44].

More than 10 years ago, we started a follow-up programme for high-risk infants who had received neonatal care at our institution. The programme provides paediatric assessments at regular intervals and multidisciplinary care, if required. An important feature is a comprehensive neurodevelopmental and neuropsychological evaluation. In the present report, we describe the mortality, morbidity and neurodevelopmental outcome at school age of ELBW infants enrolled in our programme. The aim is to identify the perinatal and neonatal factors associated with adverse cognitive and neurological outcomes.

Methods

Study population and survival

Between January 1993 and December 1998, 200 infants with a birth weight below 1,000 g were treated at our level III neonatal intensive care unit (NICU). Three children were born with lethal malformations and died during the neonatal period. Of the remaining 26 children (13%) who died, 10 did so on the 1st day. Nine of ten first-day deaths occurred in infants born at a gestational age below 26 weeks (Table 1).

One hundred seventy-three infants were discharged home, and two of these children died at the age of 1 and 7 years. Of the 171 surviving children, 135 (79%) were prospectively assessed at our outpatient clinic at regular intervals. Thirty-six children (21%) were lost to follow-up (10 of these had moved to an unknown address, and 26 children did not attend beyond 6 years of age). The 36 children lost to follow-up had a tendency to a higher birth weight [847 vs. 793 g, p not significant (NS)] and to a

Table 1 Survival and disability to school age

	Gestational age						
	<24	24	25	26	27	≥28	Total n (%)
Live births (*n*)	10	19	49	36	21	62	197*
Died (*n*)	6	5	7	1	2	5	26 (13%)
Day 1 (*n*)	3	3	3	0	0	1	10 (38%)
Days 2–7 (*n*)	1	2	1	0	0	0	4 (15%)
Days 8–28 (*n*)	1	0	1	1	2	1	6 (23%)
After day 28 to discharge (*n*)	1	0	2	0	0	1	4 (15%)
Post discharge (*n*)	0	0	0	0	0	2	2 (8%)
Lost to follow-up (%)	0 (0%)	2 (14%)	8 (19%)	7 (20%)	4 (21%)	15 (26%)	36 (21%)
Assessed	4	12	34	28	15	42	135
Survived normal (*n*)	1	5	9	14	9	20	58
% of assessed children	25	42	26	50	60	48	43
Survived with minor impairment *(n)*	1	4	16	9	6	17	53
% of assessed children	25	33	47	32	40	40	39
Survived with major impairment *(n)*	2	3	9	5	0	5	24
% of assessed children	50	25	26	18	0	12	18

Normal: normal neurological evaluation, IQ >84 and no neurodevelopmental deficits. Minor impairment: one or more of the following problems: subnormal cognitive abilities (IQ 70–84), gross and fine motor activity deficits, disorders of language development, visual and auditory defects, attention deficit disorders, and abnormal socio-emotional development. Major impairment: one or more of the following problems: cerebral palsy (CP), intellectual disability (US: mental retardation) with an IQ <70, blindness, deafness, and/or intractable epilepsy.

*Three children with lethal congenital abnormalities were excluded

higher gestational age (27.3 vs. 27.0 weeks, p=NS) and a lower rate of grade III or IV intraventricular haemorrhage (IVH) or periventricular leukomalacia (PVL) (3 vs. 13%, p=0.08) than the study patients, indicating a potentially better prognosis than the study group. There were no differences between groups with respect to perinatal parameters and NICU care.

Neonatal care

The NICU at Children's Hospital Auf der Bult delivers tertiary care for 12 obstetric departments or hospitals in Hannover with approximately 10,000 deliveries per year. Between January 1993 and December 1998, we treated 200 extremely low birth weight (ELBW) infants with a body weight below 1,000 g at delivery.

During the neonatal period, high-resolution (7 MHz) cranial ultrasonography was performed routinely at the following time points: on the 1st or 2nd day, during follow-up at weeks 1, 2, 4, and 8, and when the child was scheduled for discharge home. Peri- and intraventricular haemorrhages (IVH) were classified into four grades of severity according to Papile et al. [29]. Periventricular leukomalacia (PVL) was diagnosed if periventricular echodensities or cysts were observed on cranial ultrasound scans [9].

All infants were examined routinely by echocardiography during the 1st 2 weeks for the presence of patent ductus arteriosus (PDA). Children received indomethacin if the PDA produced haemodynamic derangements, and in case of treatment failure PDA ligation was performed. Surfactant replacement therapy was initiated if symptoms and/or radiologic changes were suggestive of surfactant deficiency.

Sepsis was defined as a positive blood culture with clinical infection requiring antibiotic treatment for at least 5 days. Mild/moderate bronchopulmonary dysplasia (BPD) was defined as oxygen treatment (>21%) for at least 28 days and oxygen dependency <30% at 36 weeks postmenstrual age. Severe BPD was defined as persisting oxygen requirement (≥30%) and/or positive pressure ventilation or nasal continuous positive airway pressure at 36 weeks postmenstrual age [24].

For the present analysis, a total of 105 different parameters on clinical status and medical interventions were prospectively evaluated and documented in patient charts.

Assessment of outcomes of survivors

All surviving children (n=171) were offered care in our high-risk infant follow-up programme. Repetitive examinations by experienced paediatric neurologists were performed at a postmenstrual age of 3, 6, 12, and 18 months and at yearly intervals from ages 2 to 8 years. A final assessment was performed at the age of 10 years.

At each assessment the child received a standardised neurological evaluation with a modified Touwen test [40]. At the age of 4 and 6 years, clinical psychologists conducted psychometric evaluations using the Kaufman Assessment Battery for children (K-ABC), German version [27], or the Snijders-Oomen Non-Verbal Intelligence Test (SON-R 2 1/2–7), German version [36]. At the age of 10 years, the child's intelligence quotient (IQ) was determined using the Hamburg-Wechsler Intelligence Test for Children, HAWIK III [37]. Subtests of K-ABC [27] and HAWIK III [37] were used to assess the speech development of the child.

Each child was classified as being normal or having minor or major impairment according to the overall results of these tests. Major impairment was present if the child had one or more of the following problems: cerebral palsy (CP), intellectual disability (US: mental retardation) with an IQ <70, blindness, deafness, and/or intractable epilepsy. Children with minor impairment showed less severe deviations from normal development. These cases had one or more of the following problems: subnormal cognitive abilities (IQ 70–84), gross and fine motor activity deficits, disorders of language development, visual and auditory defects, attention deficit disorders, and abnormal socio-emotional development. Children with normal development had a normal neurological evaluation, an IQ >84, and no neurodevelopmental deficits.

Statistics

SPSS for Windows (SPSS Inc., release 12.01, 11 November 2003) was used as a database and for statistical analyses. Fifty perinatal and postnatal variables were correlated with the outcomes at school age. The Mann-Whitney U-test was used for continuous data and the Pearson's chi-square test for categorical data. All tests were two-sided. The level of statistical significance was set at $p<0.05$ for all tests, and variables that differed significantly between groups were entered into the regression analyses. A logistic regression model with forward-selection to adjust for potential confounding variables was used to determine the importance of specific parameters on outcome at school age. The multiple regression analyses were repeated omitting variables that no longer reached significance ($p<0.05$). Models included maternal age, gestational age, birth weight, sex, rupture of membranes more than 24 h before delivery, CTG, inborn/outborn, minimum body temperature, mode of delivery, antenatal antibiotic and steroid use, postnatal surfactant and steroid use, umbilical cord blood pH, mean arterial pressure, APGAR score, CRIB score, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), intraventricular haemorrhage (IVH), hydrocephalus, periventricular leukomalacia (PVL), neonatal

seizures, culture-proven sepsis, duration of mechanical ventilation, oxygen supplementation, duration of parenteral nutrition, central venous catheters, postnatal weight gain, and increase in head circumference after birth. Adjusted odds ratios (OR) with 95% confidence intervals were calculated using the logistic regression model. Odds ratios were determined for (1) normal development vs. any impairment and for (2) major impairment vs. normal development or minor impairment. Data presented are with means and standard deviations in brackets, if not stated otherwise.

Results

Of the 200 ELBW infants born within a 6-year period, 135 were prospectively evaluated up to school age.

Obstetric history and perinatal management

Most children (n=96, 71%) were delivered in 1 of 12 hospitals in Hannover and the surrounding area, 1 child was born at home, and 38 children were delivered at our unit. Of the infants, 84% were delivered by Caesarean section. The mean birth weight of all children was 793 (122) g, and the mean gestational age was 27.0 (1.9) weeks. Of the mothers, 72% had been given antenatal corticosteroids for neonatal RDS prophylaxis. Seventy-nine per cent of mothers were of German nationality.

Neonatal morbidity

The mean duration of postnatal hospital care was 125 (50) days, and 65 (30) of these days were spent in the NICU. Eighty-seven per cent of infants required mechanical ventilation, 46% developed > grade I respiratory distress syndrome (RDS), and 41% received surfactant treatment. Mean durations of mechanical ventilation, oxygen therapy (>30%), and parenteral nutrition were 19, 5, and 45 days, respectively.

Early signs of chronic lung disease (i.e., the requirement of oxygen, typical radiologic abnormalities, or persistent symptoms of RDS during days 7 to 27) developed in 63% of children, whereas only 10% of infants progressed to definitive mild or moderate bronchopulmonary dysplasia (BPD) [24]. None of the children fulfilled the criteria of severe BPD, defined as the need for ≥30% oxygen and/or positive pressure ventilation at 36 weeks postmenstrual age.

Intraventricular haemorrhages (IVH) of any degree (grades I–IV) occurred in 32% and haemorrhages of grade III or IV in 13% of infants. The mean gestational age of children with cerebral haemorrhages was 26.1 (1.4) weeks, and this was significantly lower than that of children without IVH [27.4 (2.0) weeks]. Grade III/IV bleedings occurred in a larger proportion of preterms of gestational ages below 25 weeks. Sixty per cent of cerebral haemorrhages were diagnosed by day 2 and 92% by day 5. During follow-up, a total number of 11 children developed hydrocephalus. Seventy-three per cent (8 of 11) of children with grade IV and 50% (2 of 4) of children with grade III haemorrhage developed hydrocephalus (of whom 60% required a ventriculoperitoneal shunt). Periventricular leukomalacia was diagnosed in two infants, of whom one developed hydrocephalus. Twelve children (9%) had neonatal seizures, and in seven cases this was due to intraventricular haemorrhage (grade IV IVH: n=4; grade II IVH: n=1; grade I IVH: n=2).

Patent ductus arteriosus (PDA) was observed in 46% of infants and required surgery in 16% of these cases, whereas 84% of affected preterms were successfully treated with indomethacin. Culture-proven sepsis was also a frequent complication and occurred in 43% of infants. Other medical complications were retinopathy that required treatment (10%) and pneumothorax (5%). Enterostomy was required by 16% (n=21) of infants because of necrotising enterocolitis (n=8) or bowel perforation without NEC (n=8), and 5 infants required surgery due to functional bowel obstruction.

Anthropometry at the expected date of delivery

At the expected date of delivery, all children had a body weight below the 10th percentile for sex and age [43], and 91% of girls and 97% of boys had a body weight below the 3rd percentile [mean weight: males 2,029 (336) g, females 2,007 (427) g]. Length was also considerably reduced [mean: males 43.6 (2.5) cm, females 43.4 (3.0) cm], and 97% of male and 84% of female infants had a length below the 3rd percentile. The situation was better for head circumference, which was within the normal range in 50% of children, and mean values for males were 32.5 (1.8) cm, and for females 31.8 (1.9) cm [43].

Neurodevelopmental assessments at school age

The mean age at the most recent evaluation was 8.4 (1.6) years. Up to that assessment, 43% of children had survived without any impairment (Table 1). Minor impairment was diagnosed in 39% and major impairment in 18% of assessed children.

Neurosensory and physical outcomes

In the subgroup of 24 children with major impairment, cerebral palsy was diagnosed in 12 and mental retardation in 19 children (9% and 15% of assessed children, respectively). Seven of the 24 children with major impairment had both CP and mental retardation, and the 5 children who had

hydrocephalus requiring a ventriculoperitoneal shunt were in this group. Six children suffered from seizures and one child had central blindness, while none of the infants developed bilateral blindness after retinopathy of prematurity. Other complications such as deafness, short bowel syndrome, or oxygen dependence after 36 weeks postmenstrual age were not observed in our cohort.

Children with major impairment showed the following deficiencies: subnormal cognitive function only (no CP): n=12; subnormal cognitive function and tetraparesis: n=5; subnormal cognitive function and diparesis: n=2; diparesis without mental impairment: n=3; hemiparesis without mental impairment: n=2. With one exception, all children with major impairment required special education.

Association between risk factors and outcomes

A number of neonatal complications were associated with outcome at school age. For example, 67% of patients with major cerebral haemorrhages (IVH grade III or IV, parenchymal haemorrhage) or PVL developed major impairment, compared to only 10% of children without major cerebral haemorrhages or PVL. Other adverse prognostic factors were mechanical ventilation >14 days (28 vs. 6%), parenteral nutrition >41 days (28 vs. 11%), a patent ductus arteriosus (26 vs. 11%), and NEC or bowel perforation (47 vs. 14%). With respect to growth and nutrition, major impairment was associated with abnormally low weight gain (<100 g per week) and a subnormal increase in head circumference until the expected date of delivery (<6 mm per week). Female infants had a better prognosis with respect to neurodevelopmental outcome. Only 12% of female, but 24% of male infants had major impairment at a mean age of 8.4 years, although this difference was not statistically significant.

Bowel perforation and/or NEC was associated with a substantial increase in risk for subsequent impairment (odds ratio, OR, for major impairment vs. normal development or minor impairment at school age: 4.4, 95% CI: 1.1–17.0) (Fig. 1). Only 2 of the 15 surviving infants with NEC or bowel perforation were assessed “normal” at school age. The largest odds ratio (OR: 13.3; 95% CI: 4.0–44.9) was found if cranial ultrasound showed either grade III or IV IVH, parenchymal bleeding, or periventricular leukomalacia. The odds ratio for neonatal seizures was 5.2 (CI: 1.2–22.4). In contrast, no influence ($p>0.05$) on the outcomes of major impairment vs. normal development or minor impairment was found for gestational age, weight at birth, being a multiple birth, being SGA, being outborn, being hypothermic or requiring surfactant.

Multiple step-wise logistic regression revealed factors that were significantly associated with adverse outcomes (abnormal vs. normal, Table 2). The three significant associations referred to complications during NICU care (increase in head circumference <6 mm per week, parenteral nutrition >41 days, and mechanical ventilation >14 days). Neither obstetric nor neonatal variables such as weight, gender, or APGAR score had any significant effect.

Nutrition during NICU care had a significant impact on development until school age (Fig. 2). Children who needed parenteral nutrition beyond day 41 had a significantly increased risk of being neurodevelopmentally abnormal (OR: 2.5, 95% CI: 1.1–6.0), and of the 54 patients in this group, only 12 (22%) turned out to develop normally.

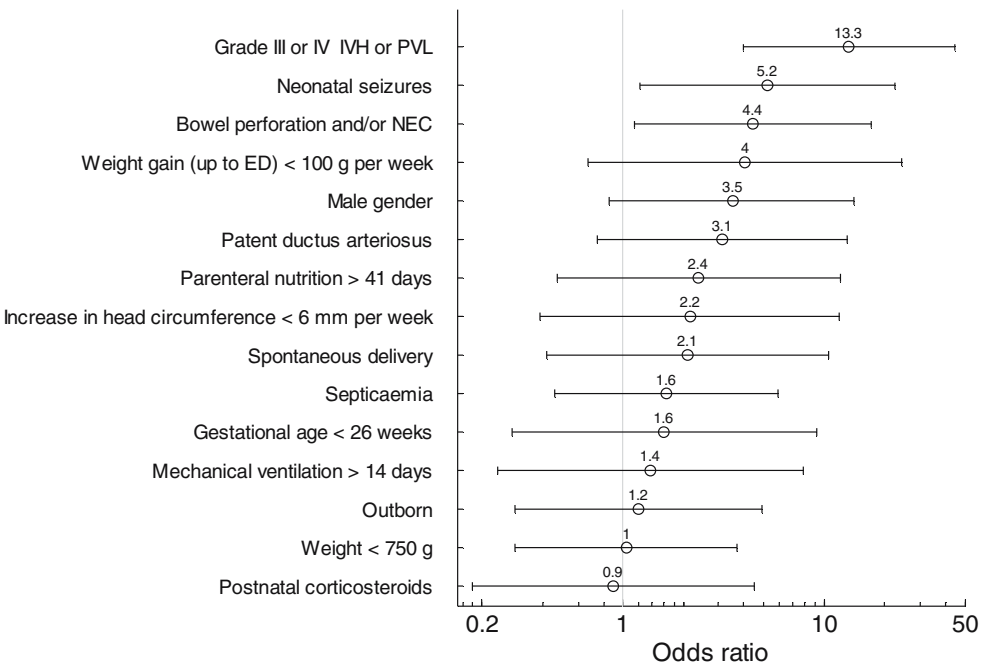

Fig. 1 Logistic regression for major impairment vs. normal development or minor impairment at school age, adjusted odds ratios, and 95% confidence intervals (data presented on a logarithmic scale)

Table 2 Perinatal factors and outcomes at school age

Perinatal risk factor Outcome at school age	n	Normal n (%) Normal	Minor impairment n (%) Abnormal	Major impairment n (%)	Odds ratio abnormal vs. normal
All children	135	58 (43)	53 (39)	24 (18)	
Obstetric variables					
Outborn	97	40 (41)	39 (40)	18 (19)	1.60 (0.55–4.65)
No RDS prophylaxis	36	15 (42)	12 (33)	9 (25)	1.14 (0.41–3.17)
Spontaneous delivery	21	7 (33)	6 (29)	8 (38)	1.14 (0.27–4.56)
Gestational age <26 weeks	50	15 (30)	21 (42)	14 (28)	1.13 (0.31–4.11)
Single birth	91	39 (43)	35 (38)	17 (19)	0.98 (0.38–2.51)
Paediatric variables					
Male gender	63	23 (36)	25 (40)	15 (24)	1.60 (0.61–4.21)
APGAR score at 10 min <5	5	2 (40)	2 (40)	1 (20)	1.31 (0.10–17.7)
Body temperature <36°C at NICU admission	46	16 (35)	20 (43)	10 (22)	1.24 (0.48–3.20)
Weight <750 g	51	17 (33)	23 (45)	11 (22)	1.20 (0.42–3.41)
APGAR score at 5 min <5	17	8 (47)	7 (41)	2 (12)	0.50 (0.10–2.63)
SGA (<10th percentile)	36	15 (42)	17 (47)	4 (11)	0.33 (0.09–1.22)
NICU care and complications					
Increase in head circumference <6 mm per week	35	6 (17)	20 (57)	9 (26)	3.98 (1.07–14.8)*
Parenteral nutrition >41 days	54	12 (22)	27 (50)	15 (28)	2.52 (1.06–6.01)*
Grade III or IV IVH or PVL	18	4 (22)	2 (11)	12 (67)	2.46 (0.52–11.7)
Mechanical ventilation >14 days	71	20 (28)	31 (44)	20 (28)	2.31 (1.04–5.10)*
Patent ductus arteriosus	62	20 (32)	26 (42)	16 (26)	1.63 (0.61–4.36)
Bowel perforation and/or NEC	15	2 (13)	6 (40)	7 (47)	1.59 (0.23–11.1)
Surfactant	56	21 (38)	23 (41)	12 (21)	1.54 (0.59–4.01)
Postnatal corticosteroids	27	5 (18)	14 (52)	8 (30)	1.44 (0.34–6.19)
Neonatal seizures	12	3 (25)	3 (25)	6 (70)	1.43 (0.26–7.66)
Weight gain (up to ED) <100 g per week	80	25 (31)	37 (46)	18 (23)	1.00 (0.37–2.71)
Septicaemia (culture proven)	58	24 (41)	21 (36)	13 (22)	0.97 (0.38–2.50)
Grade I or II IVH**	26	10 (38)	12 (46)	4 (15)	**

Normal: normal neurological evaluation, IQ >84 and no neurodevelopmental deficits. Minor impairment: one or more of the following problems: subnormal cognitive abilities (IQ 70–84), gross and fine motor activity deficits, disorders of language development, visual and auditory defects, attention deficit disorders, and abnormal socio-emotional development. Major impairment: one or more of the following problems: cerebral palsy (CP), intellectual disability (US: mental retardation) with an IQ <70, blindness, deafness, and/or intractable epilepsy

*$p<0.05$, **18 children with grade III or IV IVH excluded

When comparing these children with the whole cohort, they were of shorter gestational age (26.0 vs. 27.6 weeks) and lower birth weight (729 vs. 832 g), and received mechanical ventilation for a much longer period (29 vs. 12 days). Also, ventricular haemorrhage (19 vs. 10%) and PDA (56 vs. 39%) developed more frequently than in other children, suggesting that infants receiving long-term parenteral nutrition represent a high-risk group for subsequent impairment. Nevertheless, parenteral nutrition >6 weeks was identified as an independent risk factor by stepwise logistic regression.

An increase in head circumference <6 mm per week, parenteral nutrition >41 days, and mechanical ventilation >14 days were the only factors associated with a significantly increased risk for not being normal at school age. High-grade IVH and/or PVL, neonatal seizures as well as duration of parenteral nutrition were significant risk factors for developing major impairment.

Discussion

In this regional cohort of 135 ELBW children born between 1993 and 1998, we found high rates of neurodevelopmental abnormalities at school age. The proportion of children with impairment was inversely related to gestational age. Twenty-eight per cent of infants born at a gestational age of <26 weeks, but only 12% of the more mature infants, showed major impairment at a mean age of 8.4 years. There was, however, a considerable proportion of children assessed normal (43% for the total cohort), even in the least mature group.

In order to determine the predictive value of pre- and postnatal risk factors for impairment at school age, we analysed obstetric and paediatric parameters and evaluated neonatal intensive care and medical complications. Of the obstetric and the paediatric variables, only gestational age below 26 weeks was identified as a risk factor for any impairment, although this was not significant by logistic

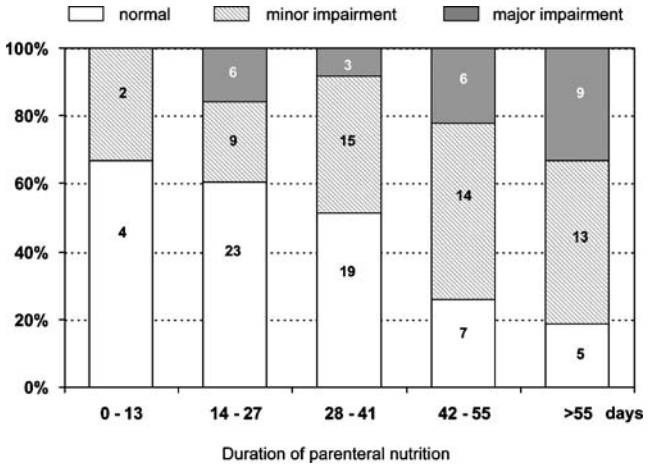

Fig. 2 Duration of parenteral nutrition as a risk factor for adverse outcome at school age. Children were grouped according to their outcome at school age (normal, minor, or major impairment). The numbers in the bars denote the number of children in the respective group. The shorter the duration of parenteral nutrition, the larger the proportion of children with normal outcome

regression analysis. A birth weight below 750 g or below the 10th percentile was not associated with a significantly higher risk, which is in accordance with data from other authors [1, 4].

A number of neonatal complications proved to be important for neurodevelopmental outcome at school age. As has been shown previously [23, 33, 35], necrotizing enterocolitis (NEC) and/or bowel perforation had detrimental effects in the majority of children, since only 2 of 15 infants were assessed "normal" at school age. An earlier paper reported that 33% of necrotizing enterocolitis survivors had significant neurodevelopmental impairment at 20 months' corrected age [45]. The NICHD Neonatal Research Network found in 124 surgically treated infants that NEC was associated with significant growth delay and adverse neurodevelopmental outcomes at 18 to 22 months' corrected age, with significantly impaired mental and psychomotor development as well as abnormal neurodevelopmental indices [23]. These children also had significantly decreased growth parameters at 2 years of age compared to children without NEC. In contrast, the researchers observed no increased risk for impairment in the 121 infants who were managed medically. Despite modern medical and surgical treatment, NEC remains a serious disorder in premature infants with considerable impact on later child development.

We identified mechanical ventilation beyond 2 weeks of age as an additional risk factor (OR: 2.3, 95% CI: 1.0–5.1) for any impairment at school age. Only 28% of these 71 infants developed normally. The use of postnatal steroids was not identified as a risk factor by logistic regression. Contrary to our results Australian authors found an OR of 21.0 for severe impairment at 3 years of age in children who had received postnatal steroids [5]. Furthermore, dexamethasone treatment started within the 1st 4 days of life was associated with an increased risk of abnormal neurodevelopment including cerebral palsy [21]. In our NICU, the use of postnatal steroids was reserved for babies who were not successfully weaned from mechanical ventilation at 2 weeks of age [7]. The 27 children who received postnatal steroids were significantly more premature (gestational age: 25.4 vs. 27.4 weeks), were signficantly longer on mechanical ventilation (33 vs. 15 days) or on parenteral nutrition (55 vs. 43 days), and were more frequently male (67 vs. 42%). In addition, IVH 3/4, PVL (30 vs. 9%) or neonatal seizures (15 vs. 7%) occurred more frequently than in children who had not received postnatal corticosteroids. Each of the aforementioned parameters is associated with a higher risk for impaired development.

Some studies have shown the association between inadequate early nutrition and impaired long-term developmental outcome. Poor postnatal growth in preterm infants was associated with increased levels of motor and cognitive impairment at 7 years of age [6]. Ehrenkranz et al. [11] reported a significantly better development at 18 to 20 months of age in ELBW infants with a sufficient postnatal weight gain. In the present study, growth parameters were also associated with impairment at school age, i.e., a weight gain below 100 g per week during NICU care, and a rise in head circumference of below 6 mm per week. Head circumference correlates closely with intracranial volume during infancy and can be used as a predictor of cerebral volume [16]. Consequently, decreased head growth during the neonatal period may be a predicitor for abnormal development during infancy.

A major reason why children do not grow adequately is inadequate energy intake. For normal intrauterine growth, the foetus requires about 140 nonprotein calories per kilogram body weight and day and 3–4 g protein/kg/day [22]. If these requirements are not met during NICU care, the infant will not grow. We found a significant negative linear correlation between the duration of parenteral nutrition and the weekly increase in head circumference, suggesting that the nutritional requirements for normal brain growth were possibly not met during long-term parenteral feeding. In the years of the study, some newborn ELBW infants received only glucose electrolyte solutions during the 1st days of life and were then switched to small amounts of breast milk or Alfare, a partially hydrolysed formula with a comparatively low caloric content (66 kcal/100 ml). Current recommendations are to provide early total parenteral nutrition, which should ideally start in the 1st hours after birth. Small enteral feedings on the 1st or 2nd day of life will help to "prime" the gut and to stimulate normal gastrointestinal tract activity [13]. In critically ill VLBW infants, small early enteral feedings resulted in a greater weight gain by 1 month of life [15, 41]. However, caution is required not to advance feeding volumes too

quickly, since a daily increase by 20 ml/kg/day up to 140 ml/kg/day was associated with a higher incidence of NEC in some studies [3]. In a recent study, the introduction of a standardised feeding regimen substantially reduced the incidence of NEC by 87% and thereby one of the major risk factors for impaired neurodevelopment [30].

Similar to previous publications [18, 20], severe abnormalities on cranial ultrasound, i.e., grade III or IV IVH and PVL, were significant risk factors for major impairment at school age in our cohort (OR: 13.3, 95% CI: 4.0–44.9 compared to children without major impairment). In recent articles, the consequences of grade I or II IVH in ELBW infants have been a matter of considerable debate. Patra et al. [31] reported that these children had significantly poorer neurodevelopmental outcomes at 20 months than ELBW infants with normal cranial ultrasounds. Conversely, according to a study by Sherlock et al. [34], neurodevelopmental outcomes at 8 years of age did not differ significantly between children with or without grade I or II IVH. A tendency towards poorer neurodevelopmental outcomes at school age was observed in our cohort of ELBW infants with grade I or II IVH, however, without statistical significance.

The current cohort was a regional sample, and we were able to prospectively evaluate the outcomes of most ELBW infants treated at our unit. Only a small proportion of families declined follow-up or could not be reached. Infants who dropped out had a significantly lower proportion of grade III or IV IVH or PVL than children in the present study, which would suggest a better rather than a worse prognosis of excluded infants. Therefore, we have no evidence that our sample was biased for lower risk.

One of the drawbacks in our study was that the paediatric neurologist and other staff performing the follow-up examinations were not blinded. During the repeated long-term assessments, they became aware of the medical history and the clinical course of the children. We have no indication, however, that this may have biased the results at school age. Another potential problem is the lack of a comparison group of normal children. The reference values for neurodevelopmental tests are based on samples of children who grew up many years ago. Over time, there has been a change in performance of children on these test scales [26]. The proportion of normal children in our study may therefore be an overestimate in relation to normal children of the same age.

In summary, we found high rates of neurodevelopmental impairments in a regional cohort of ELBW infants born between 1993 and 1998. The proportion of disabled children rose with decreasing gestational age; only one in three children born before 26 weeks of gestation had no evidence of cerebral palsy or intellectual disability at school age. Neonatal complications were important risk factors for major impairment at school age, particularly NEC, severe IVH/PVL, or prolonged mechanical ventilation beyond day 14. Parenteral nutrition of 6 weeks or longer was also a major risk factor and showed a negative correlation with weekly growth in head circumference as a determinant of brain growth. Thus, measures to prevent complications such as NEC, cerebral haemorrhage, and undernutrition remain important goals for NICU care.

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