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Functional impairments at school age of preterm born children with late-onset sepsis

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ABSTRACT

Background: Late-onset sepsis is a relatively common complication particularly of preterm birth that affects approximately a quarter of very low birth weight infants.
Aim: We aimed to determine the motor, cognitive, and behavioural outcome at school age of preterm children with late-onset sepsis compared to matched controls.
Study design and subjects: A prospective case–control study that included preterm infants (gestational age<32 weeks and/or birth weight<1500 g) admitted to our Neonatal Intensive Care Unit in 2000–2001 with a culture-proven late-onset sepsis, and controls matched for gestational age.
Outcome measures: At school age we assessed motor skills, intelligence, visual perception, visuomotor integration, verbal memory, attention, executive functioning, and behaviour.
Results: At 6–9 years, 21 of 32 children with late-onset sepsis (68%) had borderline or abnormal motor outcome with most problems in fine motor skills. Their total IQ was 89 compared to 98 in controls. In addition, verbal memory and attention were affected compared to controls (0.61 standard deviations (SD), 95% confidence interval (CI) 0.04–1.17, $p=0.033$ and 0.94 SD, 95% CI 0.32–1.62, $p=0.011$, respectively). Multiple episodes of sepsis and gram-negative sepsis were risk factors for worse cognitive outcome.
Conclusions: At school age, a majority of preterm children with late-onset sepsis had motor problems. Their IQ was considerably lower than matched controls, and memory and attention were specifically impaired. Outcome at school age of preterm children with late-onset sepsis was worse than previously thought.

1. Introduction

Late-onset sepsis is still a common complication in preterm infants admitted to the neonatal intensive care unit despite a variety of strategies to prevent infection. Among very low birth weight infants (<1500 g), who are highly susceptible to infection, around 25% develop one or more episodes of late-onset sepsis [1]. Gram-positive bacteria, particularly coagulase-negative staphylococci (CoNS), are the most common pathogens leading to late-onset sepsis [1]. Mortality in preterm infants with late-onset sepsis is about 20% [1].

During the early neonatal period the brain and its white matter are vulnerable to inflammation and changes in cerebral blood flow that can follow from late-onset sepsis. Previous studies have indeed shown a relation between sepsis and white matter abnormalities in preterm infants [2,3]. These abnormalities contribute to the risk of neurodevelopmental impairments among preterm infants with late-onset sepsis. An earlier study reported that approximately 30% of children with neonatal sepsis have motor impairments at 2 years of age, while even more children may develop cognitive impairments [4]. It is unknown whether these impairments are persistent throughout school age, and whether specific cognitive deficits that may further hamper school performance, are present [5].

The first aim of our study was to determine the motor, cognitive, and behavioural outcome at school age of children with late-onset sepsis compared to control children of similar gestational age. Our second aim was to identify sepsis-related risk factors for adverse outcome.

2. Methods

2.1. Patients

We retrospectively included preterm infants (gestational age <32 weeks and/or birth weight <1500 g) from the Neonatal Intensive Care Unit (NICU) of the University Medical Center Groningen, who

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; AVLT, Auditory Verbal Learning Test; BRIEF, Behaviour Rating Inventory of Executive Function; BPD, bronchopulmonary dysplasia; CBCL, Child Behaviour Checklist; CoNS, coagulase-negative staphylococci; CP, cerebral palsy; GA, gestational age; GMFCS, Gross Motor Function Classification System; GMH–IVH, germinal matrix haemorrhage–intraventricular haemorrhage; IQ, intelligence quotient; Movement ABC, Movement Assessment Battery for Children; NEC, necrotizing enterocolitis; NEPSY, Neuropsychological Assessment; NICU, neonatal intensive care unit; OR, odds ratio; PVL, periventricular leukomalacia; Q–Q plot, quantile–quantile plot; SNAP, Score for Neonatal Acute Physiology; TEA-Ch, Test of Everyday Attention for Children; WISC, Wechsler Intelligence Scale for Children.

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had been admitted between November 2000 and December 2001 and were diagnosed with late-onset. Late-onset sepsis was defined as a positive blood culture occurring 96 h or more after birth. We also included control infants from our NICU. For every 2 infants with late-onset sepsis we selected 1 control infant. These control infants were born in the same period and matched for gestational age. We did not include infants, as either cases or controls, in whom the diagnosis of late-onset sepsis was suspected, but not confirmed by positive blood cultures. Infants with major congenital malformations or syndromes were also not included.

During the study period, a total of 249 infants with gestational age <32 weeks and/or birth weight <1500 g were admitted to our NICU. After database search, 51 infants with late-onset sepsis (20%) were included in the study. Of 51 infants with late-onset sepsis, 10 (20%) died in the neonatal period. A total of 41 survivors with late-onset sepsis remained. Of these, 3 children were excluded since they were diagnosed with neurofibromatosis I, Bartter syndrome and Fallot's tetralogy. Two sets of parents could not be traced. We then included 18 control infants born in 2000 and 2001 from our NICU for follow-up, since we aimed to include 1 control for every 2 infants with late-onset sepsis. After inviting the parents and children for follow-up, it appeared that 4 sets of parents declined the invitation to participate. The final number of included children is thus 32 children with late-onset sepsis (78%) and 18 control children.

2.2. Perinatal and neonatal risk factors

We reviewed the medical charts of the patients for neonatal and sepsis-related characteristics. We used the Score for Neonatal Acute Physiology Index, second version (SNAP-II), to compare newborn illness severity in the late-onset sepsis group with the control group. The SNAP-II is validated to predict risk of in-hospital morbidity. This physiology-based score uses 6 routinely available vital signs and laboratory results from the first 24 h after birth [6]. The higher the total score, the more severe the infant's illness.

2.3. Follow-up

The parents of the eligible patients were asked to bring their children to an extension of the routine follow-up program for the research study. It entailed the assessment of motor performance, cognition, and behaviour at the age of 6 to 9 years. Parents gave their written informed consent to participate in the follow-up program and to publication of the results. The total duration of the examination was approximately 2.5 h including breaks. Incomplete assessments and test scores obtained when a child was too tired or uncooperative, as assessed by the experimenter, were excluded. The study was approved by the Medical Ethical Committee of the University Medical Center Groningen.

2.4. Motor outcome

On the basis of the reports of the routine follow-up program we determined the presence or absence of cerebral palsy (CP) following Bax' criteria [7]. In case of CP, gross motor functioning was scored using the Gross Motor Function Classification System (GMFCS). This is a functional, five level classification system for CP based on self-initiated movement with particular emphasis on sitting (truncal control) and walking [8]. Higher GMFCS levels indicate more functional impairments.

To assess the children's motor outcome we administered the Movement Assessment Battery for Children (Movement ABC), a standardised test of motor skills for children [9]. This test yields a score for total movement performance based on separate subscores for manual dexterity (fine motor skills), ball skills, and static and dynamic balance (coordination). The higher the score, the poorer the performance.

2.5. Cognitive outcome

Total, verbal, and performance intelligence were assessed using a short form of the Wechsler Intelligence Scale for Children, third edition, Dutch version (WISC-III-NL) [10,11].

In addition, we assessed visual perception and visuomotor integration with the subtests 'geometric puzzles' and 'design copying' of the NEPSY-II (Neuropsychological Assessment, second edition), a neuropsychological test battery for children [12]. In geometric puzzles, the child is asked to match two shapes outside a grid with shapes on the inside. In design copying, the child is asked to reproduce geometric drawings of increasing complexity. Visuomotor integration involves the integration of visual information with finger–hand movements.

We assessed verbal memory using a standardised Dutch version of the Rey's Auditory Verbal Learning Test (AVLT) [13]. This test consists of five learning trials with immediate recall of fifteen words (tested after each presentation) and a delayed recall trial followed by a recognition trial.

We measured selective attention and attentional control with the subtests 'map mission' and 'opposite worlds' of the Test of Everyday Attention for Children (TEA-Ch) [14]. Selective attention refers to a child's ability to select target information from an array of distracters. Attentional control refers to the ability to shift attention flexibly and adaptively.

To obtain information on attentional functioning in daily life, the parents filled out an Attention Deficit Hyperactivity Disorder (ADHD) questionnaire containing 18 items on inattention, hyperactivity, and impulsivity [15].

Finally, the parents filled out the Behaviour Rating Inventory of Executive Function (BRIEF) to assess executive functioning involved in well-organised, purposeful, goal-directed, and problem-solving behaviour [16]. Examples of executive functioning are the ability to inhibit competing actions towards attractive stimuli, the flexibility to shift problem-solving strategies if necessary, and the ability to monitor and evaluate one's own behaviour.

2.6. Behavioural outcome

To obtain information on the children's behavioural and/or emotional competencies and problems, the parents completed the Child Behaviour Checklist (CBCL) [17]. The CBCL consists of one total scale and two subscales, i.e. internalizing problems (withdrawn behaviour, somatic complaints, and anxious and/or depressed scales) and externalizing problems (delinquent and aggressive behaviour scales).

2.7. Statistical analysis

We classified the intelligence quotients (IQs) into 'normal' (IQ≥85), 'borderline' (IQ 70–85) and 'abnormal' (IQ<70). We used the percentiles on the standardization samples of the Movement ABC and cognitive tests to classify raw scores into 'normal' (>P15), 'borderline' (P5-P15) and 'abnormal' (<P5). For the ADHD questionnaire, BRIEF and CBCL we used a similar classification following the criteria in the manual. Visual inspection of the histograms and quantile–quantile (Q–Q) plots were used to determine which outcome measures were normally distributed. We then used the Student's t, Mann-Whitney U, and Chi^2 tests where appropriate, to compare the outcome measures of the study group with the control group and to relate disease characteristics to outcome. We used backward logistic regression analyses to calculate the odds ratios (OR) for worse outcome when comparing the children with late-onset

sepsis to the controls. Patient demographics that were different in the sepsis group compared to the controls ($p<.10$) were entered as potential confounders in the logistic regression model. Throughout the analyses $p<.05$ was considered to be statistically significant. SPSS 16.0 software for Windows, (SPSS Inc, Chicago, IL) was used for all the analyses.

3. Results

Table 1 shows an overview of the patient demographics of the 32 infants with late-onset sepsis and the 18 controls. There were no significant or nearly significant differences in demographics between the groups, therefore none of these characteristics were entered as potential confounders in the logistic regression model for the prediction of outcome.

Eight children (25%) had more than one episode of sepsis. Thirty children had a gram-positive blood culture (n = 27 coagulase-negative Staphylococci and n = 4 Staphylococcus aureus). Four children had a gram-negative blood culture caused by Enterobacter cloacae in 2 infants, by Klebsiella pneumoniae in 1, and by Klebsiella oxytoca in 1. Thus two children had both a gram-positive and a gram-negative blood culture. None of the children had a fungal sepsis.

3.1. Motor outcome

The mean age at follow up was 8.4 years (range 6.8 to 9.1 years). Of 32 children with late-onset sepsis, 5 developed CP (16%). Their functional impairments were limited to GMFCS level I in 1 child and level II in 2 children. Two children had more severe functional impairments with GMFCS level III and IV. In the control group none of the children developed CP.

Mean scores on the Movement ABC are shown in Table 2. The two children with severe CP could not be assessed by the Movement ABC because the tasks were too difficult for them. Children with late-onset sepsis showed significantly worse fine motor skills, and a trend towards a worse total Movement ABC score.

Table 3 shows the motor outcome classified into three different groups: normal (p>15), borderline (p5–p15) and abnormal (<p15). This is graphically shown in Fig. 1. The two children with severe CP were included in the category 'abnormal'.

As it is apparent from Table 3, 68% of the children with late-onset sepsis obtained a borderline or an abnormal total score on the Movement ABC, with an OR for borderline and abnormal outcome of 3.30. In accordance with analyses of the mean scores, most problems were found in fine motor skills (OR 5.46).

3.2. Cognitive and behavioural outcome

Eight children (25%) with late-onset sepsis required special education compared to none of the children in the control group ($p=.026$). Table 2 shows the mean scores on the cognitive and behavioural measures. For two children with late-onset sepsis, the

Table 1
Patient demographics.

	Late-onset sepsis (n = 32)	Controls (n = 18)	p-value+
Males/females	22/10	9/9	.16
Gestational age (weeks)	28.9 (25.7–33.4)	28.9 (25.7–33.6)	.74
Birth weight (g)	1010 (600–1690)	1122 (640–1455)	.81
Very Low Birth Weight (VLBW)	n = 29 (91)	n = 18 (100)	.25
IUGR (<P10)	n = 12 (38)	n = 5 (28)	.35
Apgar at 5 minutes	8 (5–10)	9 (1–10)	.67
SNAP-II score	14 (5–40)	19 (5–31)	.26
Asphyxia	none	none	#
Ventilatory support (IPPV or HFO)	n = 29 (91)	n = 14 (78)	.20
Inotropics	n = 5 (16)	n = 4 (22)	.41
Cerebral pathology			
Mild GMH–IVH[1]	n = 9 (29)	n = 4 (22)	.48
Severe GMH–IVH[1]	n = 1 (3)	none	.66
Cystic PVL	none	none	#
Noncystic PVL[3]	n = 18 (56)	n = 8 (44)	.38
Late-onset morbidity			
Retinopathy of prematurity[2]	n = 1 (3)	none	.64
Bronchopulmonary dysplasia	n = 9 (28)	n = 4 (22)	.46
Meningitis	n = 2 (6)	none	.41
Necrotizing enterocolitis	n = 2 (6)	n = 2 (11)	.46

Data are given as median (minimum–maximum) or as numbers (percentage). None of the patient demographics were significantly different between the groups. # Could not be determined due to absence of the demographic in both groups. + p-values derived from chi[2] and Mann-Whitney U tests.
Abbreviations: IUGR- intrauterine growth restriction; IPPV- intermittent positive pressure ventilation; HFO- high frequency oscillation; GMH–IVH- germinal matrix haemorrhage–intraventricular haemorrhage; PVL- periventricular leukomalacia; SNAP- Score for Acute Neonatal Physiology.
[1] Mild GMH–IVH was defined as grade I and II, severe GMH–IVH as grade III and periventricular hemorrhagic infarction.
[2] Retinopathy of prematurity grade III and worse.
[3] Defined as periventricular echodensities present for more than 1 week.

Table 2
Motor, cognitive, and behavioural outcome in preterm born children with late-onset sepsis versus controls.

	Late-onset sepsis (n = 30)[a]	Controls (n = 18)	p-value+
Motor outcome (n = 47)[b]			
Movement ABC Total	13 (10, 1.5–39)	8 (6,5–18)	.073*
Fine motor skills	6 (4, 0–15)	3 (3, 0–8)	.039**
Ball skills	3 (3, 0–10)	3 (3, 0–8.5)	ns
Coordination	4 (5, 0–10)	2 (2, 0–6.5)	ns
Cognitive outcome (n = 48)			
Total intelligence[c]	89 (14, 55–118)	98 (8, 82–110)	.012**
Verbal intelligence[c]	91 (15, 55–128)	102 (14, 81–128)	.015**
Performance intelligence[c]	87 (15, 55–118)	95 (10, 80–113)	.060*
Visual perception (n = 37)[d]	57 (25, 0.1–98)	61 (27, 5–95)	ns
Visuomotor integration (n = 47)[d]	56 (37, 2–100)	66 (30, 5–100)	ns
Verbal memory (n = 47)[d]	32 (26, 0.8–86)	50 (28, 2–88)	.033**
Delayed recall (n = 46)[d]	29 (24, 0.1–90)	49 (33, 6–98)	.048**
Recognition (n = 47)[b]	29 (1, 27–30)	29 (2, 21–30)	ns
Selective attention (n = 47)[d]	33 (27, 0.1–84)	47 (31, 2–98)	ns
Attentional control (n = 47)[d]	20 (20, 0.1–63)	45 (33, 1–84)	.011**
Behavioural outcome			
Total behavioural problems (n = 48)[e]	53 (12, 25–75)	56 (9, 38–71)	ns
Internalizing problems (n = 48)[e]	52 (13, 33–78)	57 (11, 39–70)	ns
Externalizing problems (n = 48)[e]	49 (11, 33–70)	53 (9, 34–60)	ns
ADHD symptoms (n = 40)[b]	15 (14, 0–52)	18 (17, 0–53)	ns
Executive functioning (n = 46)[d]	46 (31, 4–95)	50 (22, 3–97)	ns

Data are given as mean (standard deviation, range). ns; not significant ($p>.1$).
+ p-values derived from Student's t and Mann-Whitney U tests, *$p<.10$, **$p<.05$.
[a] Two children with late-onset sepsis had severe functional impairments and could not be tested as a result.
[b] Raw scores.
[c] Intelligence quotients.
[d] Percentiles.
[e] T-scores.

Table 3
Outcome of preterm born children with late-onset sepsis classified into normal, borderline, and abnormal versus controls.

	Children with late-onset sepsis (n = 32)			Controls (n = 18)			OR (95% CI)[a]	OR (95% CI)[b]
	Normal	Borderline	Abnormal	Normal	Borderline	Abnormal		
Motor outcome (n = 49)								
Movement ABC Total	10 (32)	9 (29)	12 (39)	11 (61)	2 (11)	5 (28)	3.30 (0.98–11.07)*	1.64 (0.47–5.79)
Fine motor skills	10 (32)	10 (32)	11 (36)	13 (72)	3 (17)	2 (11)	5.46 (1.52–19.58)***	4.40 (0.85–22.77)*
Ball skills	18 (58)	4 (13)	9 (29)	12 (67)	3 (17)	3 (17)	1.44 (0.43–4.85)	2.05 (0.47–8.83)
Coordination	15 (48)	6 (19)	10 (32)	13 (72)	3 (17)	2 (11)	2.77 (0.79–9.67)	3.81 (0.73–19.87)
Cognitive outcome								
Total intelligence *(n = 50)*	18 (56)	9 (28)	5 (16)	17 (94)	1 (6)		13.22 (1.57–111.74)**	#
Verbal intelligence	17 (53)	11 (34)	4 (13)	15 (83)	3 (17)		4.41 (1.07–18.27)**	#
Performance intelligence	16 (50)	11 (35)	5 (16)	14 (78)	4 (22)		3.50 (0.95–12.97)*	#
Visual perception (n = 39)	22 (88)		3 (12)	13 (93)	1 (7)		1.77 (0.17–18.86)	#
Visuomotor integration (n = 49)	21 (68)	5 (16)	5 (16)	16 (89)	1 (6)	1 (6)	3.81 (0.73–19.87)	3.27 (0.35–30.48)
Verbal memory *(n = 49)*	18 (58)	6 (19)	7 (23)	16 (89)	1 (6)	1 (6)	5.78 (1.13–29.61)**	4.96 (0.56–44.10)
Delayed recall *(n = 48)*	19 (63)	4 (13)	7 (23)	13 (72)	5 (28)		1.51 (0.42–5.37)	#
Recognition *(n = 49)*	26 (84)	3 (10)	2 (7)	13 (72)	2 (11)	3 (17)	0.50 (0.12–2.04)	0.35 (0.05–2.29)
Selective attention (n = 49)	21 (68)	4 (13)	6 (19)	16 (89)	1 (6)	1 (6)	3.81 (0.73–19.87)	4.08 (0.45–37.00)
Attentional control *(n = 49)*	15 (48)	5 (16)	11 (36)	13 (72)	2 (11)	3 (17)	2.77 (0.79–9.67)	2.75 (0.65–11.62)
Behavioural outcome (n = 48)								
Total behavioural problems	21 (70)	3 (10)	6 (20)	12 (67)	2 (11)	4 (22)	0.86 (0.25–3.00)	0.88 (0.21–3.64)
Internalizing problems	20 (67)	3 (10)	7 (23)	9 (50)	3 (17)	6 (33)	0.50 (0.15–1.63)	0.61 (1.67–2.22)
Externalizing problems	23 (77)	3 (10)	4 (13)	14 (78)	2 (11)	2 (11)	1.07 (0.26–4.31)	1.23 (0.21–7.51)
ADHD symptoms *(n = 40)*	23 (92)		2 (8)	13 (87)		2 (13)	#	0.57 (0.07–4.50)
Executive functioning *(n = 46)*	24 (83)	4 (14)	1 (3)	15 (88)	1 (6)	1 (6)	1.56 (0.27–9.10)	0.57 (0.03–9.7)

Data are given as number (percentage). Normal was defined as < P15, borderline as P5–P15 and abnormal < P5, with regard to intelligence, normal was defined as IQ > 85, borderline as IQ 70–85 and abnormal as IQ < 70. OR- odds ratio; CI- confidence interval, *p < .10, **p < .05, ***p < .01, # Could not be determined due to absence of borderline or abnormal controls. [a] ORs for borderline and abnormal outcome, [b] ORs for abnormal outcome.

neuropsychological tests were too difficult because of very low intellectual development. The children with late-onset sepsis had significantly lower total and verbal IQs than controls. In addition, verbal memory was worse in children with sepsis than in the controls (0.61 SD, 95% confidence interval (CI) 0.04–1.17). This was also the case for attentional control (0.94 SD, 95% CI 0.32–1.62, Table 2). The incidence of behavioural problems was comparable between the groups. Table 3 shows the cognitive and behavioural outcome classified in normal, borderline, and abnormal. The children of whom the neuropsychological functions could not be assessed were included in the category 'abnormal'. Total IQ was borderline or abnormal in 44% of the children with late-onset sepsis compared to 6% in the controls with an OR of 13.22. In addition, we found that of the 18 children with normal total IQs, still 9 had problems in attention or memory.

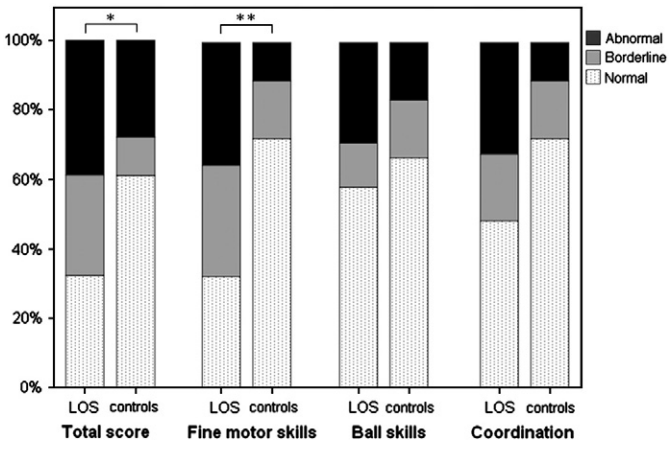

Fig. 1. Motor outcome according to the Movement ABC in preterm born children with late-onset sepsis compared to controls. LOS- late-onset sepsis. *p < .10, **p < .05.

The ORs confirmed the analyses of the mean scores, apart from attentional control for which the OR was not significant.

3.3. Disease characteristics in relation to outcome

Subsequently, we determined whether certain disease characteristics of children with late-onset sepsis were related to their outcome at school age. The disease characteristics concerned were multiple episodes of sepsis, whether gram-negative or gram-positive pathogens caused late-onset sepsis, and the children's postmenstrual age at development of late-onset sepsis.

Children who had more than one episode of sepsis had significantly lower IQs than children with a single episode (79 versus 92, $p = .02$). They also showed worse attentional control ($p = .03$) and visual perception ($p = .02$). The mean verbal IQ in children with gram-negative pathogens was 16 points lower compared to children who only had gram-positive pathogens (77 versus 93, $p = .042$) and showed a trend towards worse total IQ (78 versus 91, $p = .085$). The scores on attentional control were also lower in children with gram-negative pathogens ($p = .037$). There was no association between the postmenstrual age at development of late-onset sepsis and outcome.

4. Discussion

This study demonstrated that motor outcome at school age of a majority of preterm infants who survived late-onset sepsis was either borderline or abnormal. On average, their intelligence was 9 points lower than matched control children without late-onset sepsis. In addition, attention and verbal memory were specifically impaired, while visual perception, visuomotor integration, and executive functioning were not affected. The incidence of behavioural problems was comparable between the groups. Within the group of children with late-onset sepsis, more than one episode of sepsis and sepsis caused by gram-negative bacteria were risk factors for worse outcome.

Late-onset sepsis remains a significant neonatal complication that affects up to 16,000 VLBW infants annually in the United States alone [1,18]. To the best of our knowledge this is the first study that established the functional outcome at school age of children with late-onset sepsis. Our study showed that at a mean of 8.4 years of age, 39% of children with late-onset sepsis had abnormal Movement ABC scores. This is higher than the previous findings of Stoll et al. in a large cohort study (n = 6314) on early outcome in extremely low birth weight infants (<1000 g) with either early or late-onset sepsis. They found that at 2 years of age, 27% of children with sepsis had an abnormal (<70) Psychomotor Developmental Index score of the Bayley Scales of Infant Development [4].

Regarding cognition, we found that the IQs of our study group were considerably lower than in the controls. Moreover, at school age 44% had IQ scores below 85, which is an approximate cut-off point for being able to attend regular education in the Netherlands. In the controls this was only 6%. Stoll et al. found that 37% of children with sepsis had an abnormal (<70) Mental Developmental Index (MDI) score of the Bayley Scales of Infant Development at 2 years of age, compared to 22% in the controls [4].

Our study included infants of <32 weeks of gestational age and late-onset sepsis, while the study by Stoll et al. included only extremely low birth weight infants of lower gestational ages than our study. It thus appears that the motor and cognitive impairments as found in preterm infants with late-onset sepsis at school age are worse than previously reported. At school age, outcome can be determined more reliably due to higher test validity and behaviour of the children that fits the testing situation better. Moreover, at school age more subtle cognitive deficits may come to light since school is more demanding which could make compensation strategies more difficult to use.

In addition to lower intelligence, we also found poorer attentional control and verbal memory. These specific cognitive deficits, which have not been identified previously, can further hamper school performance. Poor attention and verbal memory, for example, may both affect learning. One could speculate that these impairments are attributable to lower IQs, especially verbal IQ, which may have had an influence on verbal memory. We also found children with normal IQs, however, who had problems with attention and verbal memory. It thus appears that sepsis-induced brain disruptions in particular have a negative impact on the development of networks in the brain involved in these functions.

It is likely that the functional impairments as found in our study are the result of a multifactorial process leading to brain injury in which inflammatory mediators play an essential role. The preterm brain and its white matter are highly vulnerable to damage by inflammation and ischemia [19]. During infectious episodes, the brain is exposed to pro-inflammatory cytokines released by microglial cells. These cytokines inhibit proliferation of neuronal precursor cells and contribute to damage to the pre-oligodendrocytes, which play an important role in myelination of the brain [20,21]. Ischemia of brain areas can result from hypotension which is associated with sepsis. Recently, it was postulated that the presence of systemic cytokines may be related to a disturbance in cerebrovascular autoregulation and diminished cerebral blood flow [21,22]. In addition to the role of pro-inflammatory cytokines, the injurious effects of microglial activation also relate to the release of reactive oxygen and nitrogen species in infants with sepsis [23]. Finally, sepsis and the subsequent increase in cytokines are related to the development of germinal matrix haemorrhage–intraventricular haemorrhage (GMH–IVH), particularly in infants with early-onset sepsis [24]. In our series GMH–IVH was already present before the late-onset sepsis occurred. However the slightly increased number of GMH–IVH among infants with late-onset sepsis versus controls, although not significant, may have worsened neurodevelopmental outcome. It has been postulated that brain injury in the setting of systemic inflammation not only leads to destruction of tissue but may also lead to altered brain development, even though the exact mechanisms have yet to be uncovered [20].

Our secondary aim was to identify sepsis-related risk factors for adverse outcome. In our study, multiple episodes of sepsis were related to worse cognitive outcome. Progressive white matter injury which follows from recurrent infection may be responsible for this finding [25]. Additionally, a gram-negative sepsis was related to worse cognitive outcome even though it was found only in four children. Previous studies already showed that infants with a gram-negative sepsis are often more severely ill, have a higher mortality rate, and may have a different immune response than infants with gram-positive infections [26,27].

A limitation of this study was the relatively small study and control group. Since this was a single centre study, generalizability to other centres needs to be established. Moreover, not all the tests were completed by all the children due to unwillingness to cooperate because the tasks were too difficult. This was particularly the case in the sepsis group. Outcome in the sepsis group may thus have been even slightly worse than we reported. We included fewer control children than children with late-onset sepsis in the study since we were particularly interested in the outcome of children with late-onset sepsis and therefore used standardised tests. We included the control children to take into account the degree of prematurity. We aimed at including control children that were as similar as possible in neonatal characteristics compared to the study group, which is also apparent from the clinical characteristics and SNAP scores of the children, to rule out the potential role of other risk factors for adverse outcome. The strengths of this study are that we examined in great detail a broad range of motor and cognitive skills and behavioural aspects that might limit functional abilities at school age compared to matched control children.

The functional impairments at school age as identified in the present study were worse than one would expect based on previous outcome studies at 2 years of age. We believe that in children with late-onset sepsis the focus of attention should be on early identification of children at risk for functional impairments so as not to miss opportunities for intervention. In addition, preventive measures beyond antibiotics should be considered to prevent brain pathology. Previous quality improvement studies showed that it may be possible to reduce infection rates and to improve the outcome of neonatal care by implementation of preventive measures [28,29]. More research is needed to determine the exact pathophysiological mechanisms responsible for the neurodevelopmental impairments in children with late-onset sepsis. In particular, the question why certain children do and others do not exhibit significant functional impairments at school age. Differences in neuroprotective capacities of the brain, but also differences in environmental aspects during childhood, may play a role.

Conflict of Interest Statement

All authors declare that they have nothing to disclose, financially or otherwise. There is no conflict of interest. This study is not the result of a clinical trial.

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References

[1] Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: The experience of the NICHD Neonatal Research Network. Pediatrics 2002;110(2):285–91.

[2] Shah DK, Doyle LW, Anderson PJ, Bear M, Daley AJ, Hunt RW, et al. Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term. J Pediatr 2008;153(2):170–5.

[3] Graham EM, Holcroft CI, Rai KK, Donohue PK, Allen MC. Neonatal cerebral white matter injury in preterm infants is associated with culture positive infections and only rarely with metabolic acidosis. Am J Obstet Gynecol 2004;191(4):1305–10.

[4] Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 2004;292(19):2357–65.

[5] Hack M, Taylor HG, Drotar D, Schluchter M, Cartar L, Wilson-Costello D, et al. Poor predictive validity of the Bayley Scales of Infant Development for cognitive function of extremely low birth weight children at school age. Pediatrics 2005;116 (2):333–41.

[6] Richardson DK, Corcoran JD, Escobar GJ, Lee SK. SNAP-II and SNAPPE-II: Simplified newborn illness severity and mortality risk scores. J Pediatr 2001;138(1):92–100.

[7] Bax M, Goldstein M, Rosenbaum P, Leviton A, Paneth N, Dan B, et al. Proposed definition and classification of cerebral palsy, April 2005. Dev Med Child Neurol 2005;47(8):571–6.

[8] Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39:214–33.

[9] Smits-Engelsman BCM. Movement Assessment Battery for Children. The Netherlands: Swets & Zeitlinger, Lisse; 1998.

[10] Kort W, Compaan EL, Bleichrodt N, Resing WCM, Schittekatte M, Bosmans M, et al. WISC-III NL Handleiding. Amsterdam: NIP dienstencentrum; 2002.

[11] Gregoire J. Comparison of three short forms of the Wechsler intelligence scale for children - third edition (WISC-III). Eur Rev Appl Psychol 2000;50(4):437–41.

[12] Korkman M, Kirk U, Kemp SL. NEPSY II. Clinical and Interpretative Manual. San Antonio, TX: PsychCorp. A Brand of Harcourt Assessments; 2007.

[13] van den Burg W, Kingma A. Performance of 225 Dutch school children on Rey's Auditory Verbal Learning Test (AVLT): parallel test-retest reliabilities with an interval of 3 months and normative data. Arch Clin Neuropsychol 1999;14(6): 545–59.

[14] Manly T, Anderson V, Nimmo-Smith I, Turner A, Watson P, Robertson IH. The differential assessment of children's attention: the Test of Everyday Attention for Children (TEA-Ch), normative sample and ADHD performance. J Child Psychol Psychiatry 2001;42(8):1065–81.

[15] Scholte EM, van der Ploeg JD. ADHD-vragenlijst (AVL) handleiding. Houten, The Netherlands: Bohn Stafleu Van Loghum; 2004.

[16] Gioia GA, Isquith PK, Guy SC, Kenworthy L. BRIEF—Behavior Rating Inventory of Executive Function: professional manual. Odessa (FL): Psychological Assessment Resources; 2000.

[17] Achenbach TM, Edelbrock C. Manual for the Child Behavior Checklist: 4–18 and 1991 profile. Burlington, Univ. of Vermont: Department of Psychiatry; 1991.

[18] Hamilton BE, Martin JA, Ventura SJ. Births: Preliminary Data for 2007. Hyattsville, Maryland: National Center for Health Statistics; 2009.

[19] Adams-Chapman I, Stoll BJ. Neonatal infection and long-term neurodevelopmental outcome in the preterm infant. Curr Opin Infect Dis 2006;19(3):290–7.

[20] Malaeb S, Dammann O. Fetal inflammatory response and brain injury in the preterm newborn. J Child Neurol 2009 Sep;24(9):1119–26.

[21] Volpe JJ. Postnatal sepsis, necrotizing entercolitis, and the critical role of systemic inflammation in white matter injury in premature infants. J Pediatr 2008;153(2): 160–3.

[22] Yanowitz TD, Potter DM, Bowen A, Baker RW, Roberts JM. Variability in cerebral oxygen delivery is reduced in premature neonates exposed to chorioamnionitis. Pediatr Res 2006;59(2):299–304.

[23] Khwaja O, Volpe JJ. Pathogenesis of cerebral white matter injury of prematurity. Arch Dis Child Fetal Neonatal Ed 2008;93(2):F153–61.

[24] Heep A, Behrendt D, Nitsch P, Fimmers R, Bartmann P, Dembinski J. Increased serum levels of interleukin 6 are associated with severe intraventricular haemorrhage in extremely premature infants. Arch Dis Child Fetal Neonatal Ed 2003;88(6):F501–4.

[25] Glass HC, Bonifacio SL, Chau V, Glidden D, Poskitt K, Barkovich AJ, et al. Recurrent postnatal infections are associated with progressive white matter injury in premature infants. Pediatrics 2008;122(2):299–305.

[26] Stoll BJ, Gordon T, Korones SB, Shankaran S, Tyson JE, Bauer CR, et al. Late-onset sepsis in very low birth weight neonates: a report from the National Institute of Child Health and Human Development Neonatal Research Network. J Pediatr 1996;129(1):63–71.

[27] Blanco A, Solis G, Arranz E, Coto GD, Ramos A, Telleria J. Serum levels of CD14 in neonatal sepsis by Gram-positive and Gram-negative bacteria. Acta Paediatr 1996;85(6):728–32.

[28] Horbar JD, Rogowski J, Plsek PE, Delmore P, Edwards WH, Hocker J, et al. Collaborative quality improvement for neonatal intensive care. NIC/Q Project Investigators of the Vermont Oxford Network. Pediatrics 2001;107(1):14–22.

[29] Kilbride HW, Wirtschafter DD, Powers RJ, Sheehan MB. Implementation of evidence-based potentially better practices to decrease nosocomial infections. Pediatrics 2003;111:e519–33.