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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