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Functional development at school age of newborn infants at risk

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Chapter 13

SUMMARY IN ENGLISH

NEDERLANDSE SAMENVATTING

DANKWOORD

ABOUT THE AUTHOR

LIST OF PUBLICATIONS

ABBREVIATIONS

AUTHORS AND AFFILIATIONS

ELISE ROZE

Summary in English

The main goal of this thesis was to establish the functional outcome of newborn infants with perinatal risk factors of adverse outcome. The functional outcome indicates the motor, cognitive, and behavioral skills and abilities that are relevant for functioning in daily life. To this end, we studied the impact of risk factors ranging from prenatal exposure to environmental pollutions to neonatal systemic diseases and overt brain lesions on long-term, school age outcome.

In Part 1 we studied the functional outcome of infants exposed prenatally to environmental pollutants. We found that transplacental transfer of polybrominated flame retardants was associated with the development of children at school age. Brominated flame retardants correlated with worse fine manipulative abilities, worse attention, better coordination, better visual perception, and better behavior. Chlorinated organohalogens correlated with less choreiform dyskinesia. Hydroxylated polychlorinated biphenyls correlated with worse fine manipulative abilities, better attention, and better visual perception. The wood protective agent correlated with worse coordination, less sensory integrity, worse attention, and worse visuomotor integration. Because of the widespread use of these compounds our findings cause serious concern (**Chapter 2**).

In Part 2 we determined the functional outcome of newborn infants with brain injury. We found that in 54 preterm infants born <37 weeks of gestation with periventricular hemorrhagic infarction (PVHI), mortality occurred in 30%. Of the survivors, 66% developed cerebral palsy, which was mild in 21 children (Gross Motor Function Classification System (GMFCS) levels I and II) and moderate to severe in 4 (levels III and IV). Use of inotropics and maternal intrauterine infection were independent predictors for mortality (odds ratio (OR) 31.2, 95% confidence interval (CI) 2.6-373, $p < .01$ and OR 12.2, 95% CI 1.2-127, $p < .05$ respectively). In survivors, only the most extended form of PVHI was associated with the development of cerebral palsy (OR > 4.7, $p < .005$), but not with severity of cerebral palsy. Cystic periventricular leukomalacia and concurrent grade III germinal matrix hemorrhage were associated with more severe cerebral palsy. We concluded from

this study that in preterm infants with PVHI, mortality occurred despite optimal treatment and was associated with circulatory failure and maternal intrauterine infection. In survivors, motor development was abnormal in 66%, but functional abilities were good in the majority. Extension and localization of the PVHI were not clearly related to functional outcome (**Chapter 3**).

We then studied the functional outcome at school age of preterm infants with PVHI. Of 38 infants, 15 (39%) died. Twenty-one of 23 survivors were included in the follow-up. Four were neurologically normal, 1 had minor neurological dysfunction, 13 had unilateral spastic cerebral palsy (CP), and 3 bilateral CP. Coordination, associated movements and fine manipulative abilities were affected most according to the neurological examination. The GMFCS was level I in 7 children, level II in 7 children, level III in one child, and level IV in 2 children. The Manual Ability Classification System score was normal in 4 children, level I in 8 children, level II in 7 children, and level III in 2 children. The mean and median total intelligence quotient (IQ) was 83 (range 55-103, standard deviation (SD) 11). Visual perception was normal in 88%, visuomotor integration was normal in 74% and verbal memory was normal in 50% of the children. Behavior was normal in 53% and executive functions were normal in 65% and 29% (parents and teachers). Characteristics of the PVHI were not related to functional motor outcome and intelligence. Posthemorrhagic ventricular dilatation was a risk factor for poorer total and performance intelligence and abnormal fine manipulative abilities. We concluded from this study that the majority of surviving preterm children with PVHI had CP with limited functional impairment at school age. Intelligence was within 1 SD of the norm of preterm children without lesions in 60% to 80% of the children. Verbal memory, in particular, was affected. Behavioral and executive function problems occurred slightly more than in preterm infants without lesions. The functional outcome at school age of preterm children with PVHI was better than previously thought (**Chapter 4**).

We also studied the outcome of 82 term-born infants with seizures that required two or more anti-epileptic drugs (AEDs) and determined whether treatment efficacy and/or the underlying disorder were related to neurological outcome. We found that 47 infants (57%) had status epilepticus. The number of AEDs was not related to

neurological outcome. Treatment with three or four AEDs as opposed to two showed a trend towards an increased risk of a poor outcome, *i.e.* death or CP, (OR 2.74; 95% CI 0.98-7.69, $p=.055$). Failure to achieve seizure control increased the risk of poor outcome (OR 6.77; 95% CI 1.42-32.82, $p=.016$). Persistently severely abnormal aEEG background patterns also increased this risk (OR 3.19; 95% CI 1.90-5.36, $p<.001$). In a multivariate model including abnormal aEEG background patterns, failure to achieve seizure control nearly reached significance towards an increased risk of poor outcome, (OR 5.72, 95% CI 0.99–32.97, $p=.051$). We found no association between seizure aetiology and outcome. We concluded from this study that in term-born infants with seizures that required two or more AEDs outcome was poorer if seizure control failed. The number of AEDs required to reach seizure control and seizure aetiology had limited prognostic value (**Chapter 5**).

We then describe an advanced magnetic resonance imaging (MRI) technique, diffusion tensor imaging, to assess diffusion characteristics of the corticospinal tracts in 20 newborn infants with focal neonatal ischemic brain lesions compared to 21 healthy term controls. Conventional MRI was able to predict normal motor development ($n=9$) or a unilateral spastic cerebral palsy ($n=6$). In children who developed a mild motor asymmetry ($n=5$), conventional MRI predicted a unilateral spastic cerebral palsy in 2 and normal motor development in 3 infants. The asymmetry indices for tract volume, fractional anisotropy, apparent diffusion coefficient and radial diffusivity showed a significant difference between controls and infants who developed a unilateral spastic cerebral palsy and radial diffusivity also showed a significant difference in asymmetry index between controls and infants who developed a mild asymmetry. We concluded from this study that conventional MRI was able to predict subsequent normal motor development or unilateral spastic cerebral palsy following focal injury in newborn infants. Measures of radial diffusivity obtained from diffusion tractography may offer additional information for predicting a subsequent asymmetry in motor function (**Chapter 6**).

In Part 3 we determined the functional outcome of preterm and term-born infants with systemic diseases in the neonatal period and we studied the role of inflammation on development at school age. First, we determined motor, cognitive,

and behavioral outcome at school age of children that had either necrotizing enterocolitis (NEC) or spontaneous intestinal perforation (SIP). We included 52 of 65 survivors for follow-up. At mean age 9 years we found that 68% of the children had borderline or abnormal scores on the Movement Assessment Battery for Children (versus 45% of controls). Their mean total intelligence quotient (IQ) was 86 ± 14 compared to 97 ± 9 in the controls. Additionally, attention and visual perception were affected ($p < .01$ and $p = .02$). In comparison to controls, surgically treated children were at highest risk for adverse outcome. In conclusion, we found that at school age the motor functions and intelligence of many children with NEC or SIP were borderline or abnormal and, specifically, attention and visual perception were impaired. We stated that children with NEC or SIP form a specific risk-group for functional impairments at school age even though the majority did not have overt brain pathology (**Chapter 7**).

We then determined the motor, cognitive, and behavioral outcome at school age of preterm children with late-onset sepsis compared to matched controls. 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 more often compared to controls (0.61 SD, 95% CI 0.04-1.17, $p = .033$ and 0.94 SD, 95% CI 0.32-1.62, $p = .011$, respectively). Multiple episodes of sepsis and gram-negative sepsis were risk factors for worse cognitive outcome. We concluded that 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 (**Chapter 8**).

Finally, we established the outcome at school age of newborn infants with intestinal obstructions treated surgically during their first days of life. Of 44 children, three (7%) died. Twenty-seven survivors (66%) were included for follow-up (median gestational age 36.7 weeks, birth weight 3000 grams). Motor outcome was abnormal (<5th percentile) in 22% of the children. This was worse than the reference population ($p < .01$). Scores on selective attention were abnormal in 15% of the children ($p < .01$). Other cognitive functions were not affected. Lower birth weight and intestinal

perforation were risk factors for poorer motor outcome ($r^2=0.53$) while intrauterine growth restriction was a risk factor for poorer selective attention ($r^2=0.366$). We concluded that children treated surgically for intestinal obstructions in the neonatal period had an increased risk for poor motor functioning and selective attention at school age. Low birth weight, IUGR, and intestinal perforation were risk factors for adverse outcomes. We recommended to closely follow the motor and attentional development of these children (**Chapter 9**).

The final part of the thesis focused on developmental processes and the association between various developmental domains in preterm-born and term-born children (Part 4). First, we described developmental trajectories of 77 healthy term-born children until school age. We found that the mean absolute difference in standardized motor scores over all time points was 1.01 SD. Only the explained proportions of variance of maternal socioeconomic status (SES) and verbal intelligence were significant for sustained attention and verbal memory ($r^2=0.104$, $p=.030$ and $r^2=0.074$, $p=.027$ respectively). The children's scores on early motor tests added little value for their motor and cognitive development at school age. We concluded that in healthy children the stability of motor development from birth until school age is low. Maternal SES and verbal intelligence rather than the infants' scores on early motor tests signified added value for complex cognitive functions at school age (**Chapter 10**).

In the final chapter we established the neuropsychological profiles at school age of a cohort of very preterm-born children compared to term-born controls. We found that at mean 8.8 years, 55% of preterm children had suspect-abnormal neuropsychological outcomes in multiple (≥ 2) domains, versus 25% of the controls (OR 3.67, 95% CI 1.90-7.06). In preterm children with multiple impairments, verbal memory, attention, and performance IQ were mostly affected. No typical pattern of co-occurrence of neuropsychological impairments was specific to preterm children, except for those that included low performance IQ (OR 5.43, 95% CI 1.75-16.81). The higher the number of suspect-abnormal neuropsychological domains, the worse the academic achievement ($p<.01$). We concluded from this study that a majority of preterm children had multiple neuropsychological impairments. Low

performance IQ was characteristic of profiles including multiple neuropsychological impairments in preterm children but not in controls. We speculated that differences in neuropsychological profiles between preterms and controls may reflect an altered organization of brain structures in preterm children (**Chapter 11**).

The studies as reported in this thesis provided insight in to what extent certain risk factors from the perinatal period have an impact on functional outcome at school age. The proposed pathophysiological mechanisms were different for the various risk factors and they were often complex and multifactorial. Environmental pollutants mainly interfere with normal brain development by affecting hormone systems involved in synaptogenesis and myelination of neurons. They led to a mild effect on long-term outcome within the normal range. In preterm-born children with systemic disease, neuroinflammation is at the basis of disruption of normal development whilst in preterm-born children with overt types of brain lesions both local destruction of tissue and diffuse white matter injury may have played a role in the functional impairments we found at school age. Based on the findings of this thesis, we advocate that newborn infants with a complicated neonatal period should be followed up closely until school age. We recommend to include measures of motor, intellectual, neuropsychological and behavioral functioning in a follow-up program. Adequate follow-up of newborn infants could lead to the early identification of functional impairments so as to identify opportunities for early intervention.