Early motor development, early visual attention and functional outcome in children
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CHAPTER 1

GENERAL INTRODUCTION
AND OUTLINE OF THE THESIS

Marit M. Hitzert
General introduction and outline of the thesis

In recent decades, major advances have been made in neonatal intensive care which have led to increased survival of preterm infants. Surviving preterm infants, however, have a higher risk of developing cerebral palsy, and more than 50 percent will develop cognitive, learning, and behavioral difficulties. Several perinatal factors may pose a threat on the developing brain. Prenatally, exposure to toxic substances such as environmental pollutants may have a detrimental impact on cognitive and motor development. Postnatally, neonatal diseases and drug exposure may interfere with the development of the neonatal brain. With the increased survival of this group of high-risk infants, one of the most challenging tasks in neonatal intensive care is to develop strategies to reduce long-term morbidity, and especially, to prevent abnormal brain development.

Brain development

The development of the fetus’s central nervous system (CNS) starts with the formation of the neuronal tube. Neuroepithelial cells in the wall of the neural tube differentiate into numerous types of neurons and glial cells. At approximately two months of gestation, neurons in the ventricular and subventricular zones start to proliferate, which results in an excess production of neurons. After the proliferation stage, between three and five months of gestation, neurons migrate from their sites of origin to the loci within the central nervous system. The cortical subplate plays a crucial role during this migration process as it guides afferent axons to their final destination in cortical or subcortical structures. Once axons reach their target areas, refinement of the nascent neural circuits occurs by complex processes involving synaptogenesis and selective elimination (pruning) of neurons and synapses. During approximately the same period, glial cells enter the CNS where they proliferate and differentiate into astrocytes, oligodendrocytes, and microglia. Although the main architecture of the brain is achieved at approximately five months of gestation, the brain continues to develop well beyond adolescence.

Typically, these neurodevelopmental processes can be broadly classified into two mechanisms: processes that require neuronal activity (activity-dependent processes) and processes that do not (activity-independent processes). It has been suggested that differentiation, cell type determination, and axonal guidance are genetically predetermined, and thus activity-independent. Together these processes are responsible for the gross connectivity in the brain. The shaping of these initial large-scale neuronal circuits into more precise and finely tuned circuits that are crucial to the many complex functions of the adult brain seems to rather rely on activity-dependent processes. These activity-dependent processes either arise from endogenously generated patterns of activity, i.e. generated by the nervous system itself without any sensory input, or from sensory-driven input, i.e. input from the external environment. An illustrative example of endogenously generated patterns of activity is the spontaneous movements of newborn infants, which are generated by central pattern generators in the spinal cord and brain stem. Sensory-driven input depends on afferent information provided by explorative behavior of which looking behavior is a good example. As infants up to six months
just begin to learn to make voluntary and controlled movements, they explore their surroundings largely by means of eye movements elicited by salient, attractive stimuli.\textsuperscript{14}

**Early motor development up to six months after term**

One of the most reliable methods to judge the integrity of the central nervous system of young infants is to assess the quality of their spontaneous motor repertoire, the so-called general movements (GMs).\textsuperscript{15} General movements can be observed in fetuses as young as ten weeks postmenstrual age,\textsuperscript{16} and are characterized by large variability in speed, amplitude, force, and intensity.\textsuperscript{17} The sequence of arm, leg, head, and trunk movements is complex with rotations superimposed on flexion and extension which make normal GMs look fluent and elegant.\textsuperscript{18} In preterm-born infants GMs continue in a similar pattern until the infant has reached term age.\textsuperscript{17} In the first weeks after term, GMs are referred to as writhing GMs. These movements are of smaller amplitude and slower speed compared to the GMs of preterm infants. Fast and large elliptical movements may occasionally break through, particularly in the arms, which create the impression of a writhing quality.\textsuperscript{17} At six to nine weeks after term, fidgety movements (FMs) gradually emerge and remain present until fifteen to twenty weeks, at which age intentional and antigravity movements appear and start to dominate the repertoire.\textsuperscript{17,19} Fidgety movements are defined as small, circular, and elegant movements of neck, trunk, and limbs, continuously present in all directions. Abnormal FMs resemble normal FMs but are exaggerated with regard to amplitude, speed, and jerkiness.\textsuperscript{19} Various other movements may co-occur with FMs, such as swiping arm movements, manipulation of hands, feet, clothing (fiddling), leg lifts, axial rolling, or trunk rotation.\textsuperscript{12,17}

Repeatedly, the assessment of GMs and FMs has proven to be an important functional indicator of brain dysfunction. A persistent pattern of cramped-synchronized movements and the absence of FMs were shown to be a valid predictor of future neurological impairment, specifically cerebral palsy.\textsuperscript{19,20} Abnormal FMs were found to be a marker of complex, minor neurological dysfunction (MND) at seven to eleven years, where the presence of normal FMs in conjunction with a normal concurrent motor repertoire is a marker of normal outcome at school age.\textsuperscript{21} In addition to the qualitative assessment of GMs or FMs, other qualitative and quantitative aspects of the spontaneous motor repertoire were demonstrated to have predictive value, especially of motor outcome.\textsuperscript{21,22} Although the predictive value of the early motor repertoire is studied most extensively for later motor outcome, there are indications that the qualitative assessment of GMs and FMs and other detailed motor patterns may also serve as predictors of later cognitive performance\textsuperscript{23,24} and behavioral problems.\textsuperscript{23,25}

**Risk factors during the perinatal period: prenatal exposure to polychlorinated biphenyls (PCBs), inborn errors of metabolism, and the use of corticosteroids**

Both the prenatal and postnatal periods are critical for the developing brain and, ultimately, for a child's health. Disruption of early neural activity, and thus disruption of the formation of stable, finely tuned neuronal networks, may have major consequences for later neurodevelopment. Risk factors that may have an impact on the integrity of the neonatal brain include perinatal
metabolic disturbances and exposure to environmental pollutants and drugs.

Worldwide, polychlorinated biphenyls (PCBs), a group of toxic industrial chemical compounds, are among the most ubiquitous environmental pollutants. Although in the Netherlands the production and use of PCBs has been banned by law since 1985, they continue to be present in the environment due to their strong resistance to chemical and biological degradation. During pregnancy, PCBs and their hydroxylated compounds (OH-PCBs) are transferred across the placenta to the fetus. El Majidi et al. investigated the impact of prenatal exposure to PCBs and OH-PCBs on cognitive and motor development in nine cohorts of children with inconsistent results.

Many inborn errors of metabolism are associated with neurological damage due to accumulating toxic metabolites. Molybdenum cofactor deficiency (MoCD) type A is a lethal metabolic disorder characterized by the accumulation of sulfite due to lack of sulfite oxidase. If untreated, infants with MoCD develop severe progressive neurological damage, eventually leading to their untimely death. Substitution therapy with the missing substance, cyclic pyranopterin monophosphate (cPMP), was considered a potentially effective treatment strategy as it prevents ongoing sulfite neurotoxicity. Based on observations in a few patients with MoCD who were treated experimentally with cPMP, timely diagnosis and treatment was considered crucial to limit neurological damage. In this thesis we report on a single patient with MoCD whom we treated experimentally with cPMP immediately after birth.

Bronchopulmonary dysplasia (BPD) is still a major cause of morbidity among survivors of severe preterm birth despite the widespread use of surfactant treatment, antenatal and postnatal glucocorticoids, and new ventilator strategies. As inflammation seems to be the primary mediator of injury in the pathogenesis of BPD, the role of systemic steroids as an anti-inflammatory agent was studied extensively and has proven to be effective. Since the introduction of steroids in the 1950s, dexamethasone is the most commonly used steroid for preventing and treating BPD. In the late 1990s, however, studies questioned the routine use of high doses of dexamethasone as there is an increased risk of neurodevelopmental impairment, especially motor impairment, in infants treated with dexamethasone. These new insights prompted the American Academy of Pediatrics to publish restrictive guidelines and to initiate the search for safer alternatives. An alternative steroid considered to be potentially safer because of its lower glucocorticoid activity was hydrocortisone. The first randomized controlled trial of hydrocortisone was published in 1972 and reported no effect on decreasing the severity of respiratory distress syndrome when using high doses (25 mg/kg per day on the first day of postnatal life). Although more recent studies with lower doses of hydrocortisone indicate no adverse effects on neurodevelopment, data on the effect of hydrocortisone on rates of survival without BPD are still in conflict. Another alternative treatment option is to lower the dexamethasone doses given to preterm infants. Lower dexamethasone doses may facilitate extubation, although its effect on neurodevelopment is still inconclusive. As yet, debate is ongoing about the optimal treatment strategy for preterm infants at risk of BPD.
Visual attention in the first half year of life

Only a few methods are available to measure cognition in early infancy. One of the most frequently used methods, at least in experimental settings, is to observe gaze shifts of young infants. In the first hours after birth, infants are already able to make small eye movements towards objects in their peripheral visual field. When observing the infant more closely, however, it becomes apparent that infants tend to stare at an object or location for long periods even if they are surrounded by several other attractive stimuli. It would seem that during the first weeks after birth infants have particular difficulties in shifting their gaze away from an object they are attending to – a phenomenon dubbed ‘sticky fixation’. At approximately three to four months of age the frequency and speed of gaze shifts to a stimulus in the periphery increases substantially. This improved ability to shift gaze away from a fixated stimulus is considered to be the result of increased cortical control over subcortical areas. A growing body of evidence suggests that the early gaze shifting abilities of both fullterm and preterm-born infants is associated with later cognitive performance. Preterm-born infants are exposed to the visual environment during a period when the brain is still developing rapidly. To date, it is unclear whether this extra visual exposure has a significant impact on early and later development.

Focus

This thesis focuses mainly on motor development, specifically the quality of GMs and a detailed assessment of concurrent movements and postures, of healthy fullterm and preterm infants during the early postnatal period. In clinical practice, the assessment of GMs is increasingly recognized as a useful diagnostic tool to predict the neurodevelopmental outcomes of preterm-born children. Additionally, the gaze shifting abilities of infants during their first year of life is an early, potential predictor of later cognitive performance. Therefore, detailed understanding of the effects of specific risk factors on early motor development and answers to the questions whether, and if so how, early motor development and gaze shifting abilities might serve as predictors of later outcomes, will expand our ability to identify, treat, and possibly prevent impaired neurodevelopment. Moreover, these insights will enhance our understanding of the complex interaction between neuronal networks involved in early motor development, early visual attention, and functional impairment at school age. We provide an overview of the thesis in Figure 1.
Figure 1. Overview of the thesis. (OH-)PCBs, (hydroxylated) polychlorinated biphenyls; MoCD, molybdenum cofactor deficiency.
Aims of the thesis
I. To investigate early motor development and the long-term neurodevelopmental outcomes of infants treated with postnatal corticosteroids.
II. To investigate early motor development in various groups at risk of abnormal neurological development. More specifically, to investigate whether prenatal background exposure to PCBs and OH-PCBs are associated with motor development in three-month-old infants. In addition, we describe the motor development and neurological outcome of an infant with molybdenum cofactor type A deficiency whom we treated experimentally with cPMP.
III. To investigate the interrelationship between early motor development, early visual attention, and neurodevelopmental outcomes up to school age in preterm-born and healthy fullterm-born children.

Outline

Part I. Early motor development and outcome after corticosteroids
In Chapter 2, we describe the effect of hydrocortisone and high-dose dexamethasone therapy in preterm infants on the quality of GMs until three months after term. In Chapter 3, we investigate the effect of low-dose dexamethasone on the quality of GMs until three months after term. In Chapter 4, we establish the functional outcome at school age, i.e. motor, cognitive, and behavioral outcomes of preterm-born children treated with high-dose dexamethasone.

Part II. Early motor development in various risk groups
In Chapter 5, we determine the impact of prenatal background exposure to polychlorinated biphenyls and their hydroxylated metabolites on early motor development. In Chapter 6, we report on the outcome, in particular with regards to GM quality, of an infant diagnosed with molybdenum cofactor type A deficiency whom we treated experimentally with cyclic pyranopterin monophosphate (cPMP).

Part III. Interrelationship between early motor development, early visual attention, and functional outcome
In Chapter 7, we describe the association between early motor development and early visual attention in preterm and healthy fullterm infants. In Chapter 8, we determine the predictive value of early motor development for functional outcome, i.e. motor, cognitive, and behavioral outcomes in healthy fullterm-born infants. In Chapter 9, we study the relation between early visual attention and functional outcome in preterm and fullterm infants. Finally, in Chapter 10, we discuss our findings in relation to the literature and we point out some future perspectives. Chapter 11 is a summary of our findings in English and Dutch.
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GENERAL INTRODUCTION AND OUTLINE OF THE THESIS
# EARLY MOTOR DEVELOPMENT AND OUTCOME AFTER CORTICOSTEROIDS

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