Infants at very high risk of cerebral palsy

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INTRODUCTION

1

Understanding the complexity of brain function is one of the most intriguing and challenging topics in science. More than 100 billion neurons and trillions of synapses within the human brain enable us to think, talk, move, touch, feel, interact and experience.[1] Knowledge about working mechanisms underlying such a multifunctional, complex system is gradually increasing, but we are still far from exact understanding. Many studies focused on subjects with brain damage to unravel the mystery of the working brain. Knowledge about atypical brain functioning, assists in understanding typical brain functioning.

In infancy, atypical brain development may result in neurodevelopmental disorders. The most common physical disability in pediatrics is cerebral palsy (CP). CP is defined as follows: 'Cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, behaviour, by epilepsy and by secondary musculoskeletal problems'.[2] CP affects about two children of every 1000 newborns and it is estimated that a total of 17 million people worldwide are diagnosed with CP.[3] Well known risk factors for CP are prematurity, low birth weight, congenital malformations, intrauterine infections, multiparity, placental abnormalities, and hypoxia around birth.[4] In about 80-90% of the infants with CP, brain abnormalities can be detected, varying in type and severity.[5,6] In the present thesis, I will focus on infants at high risk of CP and effects of early intervention. To introduce the topic, I will start from a historic perspective to share some thoughts about the developing brain and atypical brain development.

For a long time, it has been assumed that the younger the brain, the more plasticity it has. In the first half of the 20th century, Margaret Kennard studied effects of timing of brain injury in monkeys. After brain damage, the young brain had a better capacity for reorganization than the mature brain. Kennard provided the basics for theories about plasticity of the developing nervous system.[7] This led to the so-called 'Kennard principle', interpreted in the 1960's as: 'If you're going to have brain damage, have it early'.[8] However, it turned out to be not that simple. Besides timing of injury, several other factors were recognized to be important for determining neurodevelopmental outcome.[9] Therefore, in the beginning of the 21st century, a modified Kennard principle was proposed, based on more advanced scientific insights: 'If you're going to have brain damage, have as little of it as possible. Have it early, and have it on just one side. Be a girl, and come from a supportive family that lives near a good hospital'.[10]

In other words: not only timing of brain injury is important, but also the extent and localization of brain injury, and genetic, social and environmental factors. The multifactorial character of brain development raises multiple questions: in which way do threatening and protecting factors contribute to neurodevelopment, how to detect infants at risk and which possibilities do we have to intervene, in order to improve neurodevelopmental outcome?

I will first zoom in on several factors influencing brain development, on the basis of the above mentioned ingredients of the modified Kennard principle[10], with examples and knowledge from current literature. The term 'brain damage' is used, but it has to be interpreted as a broader concept of atypical brain development, as described in the definition for CP: 'non-progressive disturbances that occurred in the developing fetal or infant brain'.[2] After explaining factors associated with neurodevelopmental outcome, the outline of this thesis will be described.

'If you're going to have brain damage, …'

'…have as little of it as possible'

It makes sense: the greater the extent of brain damage, the higher the risk of worse outcome. In general, this statement holds true. For example, preterm infants are known to be at risk for developing haemorrhages in and around the ventricles. Intraventricular haemorrhages (IVH) are described in grades of severity, ranging from 1 to 4.[11] The higher the grade of IVH, the more at risk for neurodevelopmental disorders, such as CP, developmental delay and sensory problems the infant is.[12,13]

However, the relation between extent of brain damage and outcome is not a straight forward relation. Localization of brain damage is also important. For example, brain injury in temporal lobes is related with more unfavourable neurodevelopmental outcome than injury in frontal lobes.[14] Little damage of crucial brain parts may have major consequences for neurodevelopment. An example is the posterior limb of the internal capsule (PLIC), a relative small brain structure, but injury to the PLIC is strongly associated with later neurodevelopmental difficulties, especially unilateral CP.[15]

Extent and localization of brain lesions trigger some questions related to possibilities for intervention: do effects of intervention vary for different types and extent of brain lesions? Should interventions focus on specific localization of brain lesions? Until now, little is known about these issues.

'…have it early'

The 'best' timing of brain injury is a difficult question. Underlying assumption for the principle of 'the earlier the better' is based on plasticity of the brain. Brain plasticity creates more opportunities to regenerate and compensate, and a young brain is supposed to be more plastic. Contralateral hemispheres are able to take over certain functions of a damaged hemisphere in early development, which is not possible anymore in an adult brain.[16]

However, there seem to be critical or sensitive windows in brain development, during which injury may have more consequences than in other.[17,13] Briefly summarized, brain development can be described as follows. During fetal life, neurons are produced around the ventricles in the germinal layer. Neuronal proliferation starts a few weeks after

conception and the germinal layer is relatively large until 34 weeks gestational age (GA). Afterwards, it involutes and around term birth only microscopic rests are visible. Neurons start to migrate from the germinal layer to a transient zone, the subplate, and travel from the subplate to their final cortical destination. Once they reached their destination, neurons start to expand, forming dendrites and axons, to be able to make synapses to connect to and communicate with other neurons. Synapse formation starts in utero and continues lifelong, but the major part of the synapses evolve between 24 weeks GA and the first postnatal years. The transient subplate has its peak size between 24 and 32 weeks GA. It plays a very important role in neuronal differentiation and developing thalamocortical and corticothalamal pathways.[18,19,20,21]

Consequently, injury during specific phases of brain development, may have different effects on outcome. Infants born very preterm (i.e. before 32 weeks of gestation), are born during the phase of neural migration, in which the subplate has its peak size. The subplate is very vulnerable for threatening factors, such as hypoxic-ischemic events and infections, which can induce a systemic cascade with inflammatory response and pro-inflammatory cytokines.[22] Preterm born infants are susceptible for hypoxic events, due to immature vascularity and autoregulation problems, and infections, for example due to an antenatal and premature rupture of the membranes. Therefore, preterms are extra vulnerable for injury to the subplate and subcortical white matter, often resulting in periventricular white matter injuries and impaired neuronal migration. Periventricular white matter injuries are the most common cause for CP in preterm infants. Premature brain injury is often diffuse, and may result in motor and cognitive impairments.[23] If hypoxia occurs at term age and results in brain injury, it affects generally other areas than those affected in preterms, because brain development is in a more developed stage. Injury is often more selective. Cortical areas are generally involved, and other well-known structures which are often affected are basal ganglia, thalamus or brain stem, which may result in motor disabilities. In developed countries, hypoxia at term age results less often than at preterm age in severe, diffuse neurodisability.[24]

Brain development can also be influenced by environmental factors, such as chemicals, radiation, alcohol or smoking. Literature shows that effects on outcome of specific agents may also depend on specific time periods in which the developing brain has been exposed to the toxic agent. For example, ionizing radiation effects during pregnancy may have most consequences in the first trimester on cognitive and behavioural development, whereas it is related with later development of schizophrenia, if the mother was exposed in the second trimester. Alcohol seems to be most harmful in the second trimester of pregnancy.[21,25,26]

Therefore, same factors, such as infections, hypoxic-ischemic events or toxins, may influence the developing brain in distinct ways at different times. Injury during critical or sensitive periods in development may have other consequences than injury before or after such a time frame and 'the earlier the better' is not always the case.[21,27]

Plasticity of the brain and sensitive windows in brain development, are both used in principles of and thoughts about early intervention. In general, principles of plasticity are applied in practice, and intervention is preferably given as early as possible, although clear evidence is lacking for efficacy.[28] Also, specific interventions during critical time windows of brain development have been developed. An example is providing antioxidants for infants born preterm, to prevent neuronal dying by oxidative stress, which is still under investigation.[29]

'…have it just on one side'

If brain lesions appear just at one hemisphere, developmental outcome is in general better than if both hemispheres are affected. For example, in a cohort of 69 infants with periventricular venous hemorrhagic infarction (PVHI), a common brain lesion in preterms, infants with bilateral PVHI had significantly worse motor and cognitive outcome than infants who presented with unilateral PVHI.[30] In another study (EPIPAGE), a large cohort of 1902 preterm born infants was followed. Infants with bilateral cystic periventricular leukomalacia (cPVL), developed significantly more often CP, than infants who had unilateral cPVL.[31]

If one-sided brain damage is followed by CP, it usually results in unilateral CP. For unilateral CP, some interventions have been proven to be effective, such as the constrained induced movement therapy (CIMT).[32] As far as I know, no such clear intervention effects are known for children with bilateral CP. Therefore, infants with unilateral brain lesions are not only known to have better neurodevelopmental outcomes, but intervention may also have more effect than in infants with bilateral lesions.

'…be a girl'

Sex is known to influence developmental outcome. Boys more often develop CP than girls.[33,34,35] Male sex in combination with prematurity or low birth weight has also been associated with lower cognitive outcome.[36] Several explanations have been hypothesized for the higher biological vulnerability of boys: different types of brain organization, genetic disorders, or hormonal influences.[35,37] For interventional purposes, gender is not a factor to intervene on, as it is a fact, and until now, differences in outcome for boys and girls have not resulted in sex specific interventions.

'…come from a supportive family'

Even before conception, several maternal factors may influence later brain development. Well-known preconceptional factors which may influence neural development are for example maternal use of folic acid, to prevent neural tube defects[38], and mother's nutritional status. Both underweight and overweight of the mother are related to adverse developmental outcome.[39,40,41] Low socio-economic status is related to perinatal and infant

mortality, low birth weight, intrauterine growth restriction and preterm birth, probably mediated by other factors such as smoking during pregnancy. All factors are related to poorer neurodevelopmental outcome.[42] Poverty and low income are associated with different structural brain development, such as lower volumes of gray matter.[43]

In animal models, environmental enrichment has shown to be able to counteract partially effects of brain damage.[44] In humans however, experiments with environmental enrichment are more difficult to perform than in animals, because a control group without enrichment is unethical and interventions are often combinations of different ingredients, amongst others enrichment. From examples in poignant situations, such as neglected Romanian orphans, it is known that deprivation – i.e. lack of environmental enrichment - has disastrous consequences for development.[45] However, effects of the degree of environmental enrichment on infants with brain lesions in typical family conditions, are not yet clear. A small positive effect on motor outcome of environmental enrichment interventions for children with cerebral palsy, compared to standard care, was shown in a systematic review.[46]

During the last decades several initiatives to influence developmental outcome by improving caregiver-child interaction have been studied. One well known example of direct caregiver child contact is kangaroo care for preterm or low birth weight infants in the Neonatal Intensive Care Unit (NICU), in which frequent direct skin-to-skin contact of the mother with the child is promoted, together with breastfeeding and early discharge from the hospital. It may be an alternative to conventional care, but effects on long term outcome have to be further investigated.[47] In animal models, parent-infant interaction seems to mediate synaptic connections and may alter brain development through epigenetics.[48]

Nowadays, a shift from child focused to family centered care occurs in pediatrics.[49] Family centered care is based on principles that the family plays an essential role in child development, caregivers are experts about their children's needs, are constantly present, and family centered care should promote the role of families in shared decision making with the health care service systems around them, on the basis of equal partnerships, in which strengths and competencies of families are promoted. Family centered services are associated with higher caregivers' satisfaction and lower stress levels.[50] A combination of environmental enrichment and a family centered approach in preterm infants was associated with better cognitive and behavioural outcome in a recent retrospective study.[51]

'… and live near a good hospital'

The better the hospital and health care system, the more possibilities for prevention of complications, optimal detection of infants at risk, interventions and follow-up. Prematurity is a well-known risk factor for neurodevelopmental problems and nowadays, hospitals have more options in preventing preterm birth than in the past, for example by

pharmacological inhibition of uterine contractions.[52] Moreover, in case of imminent preterm labor, maturation of the unborn can be accelerated with glucocorticoids, which is related to better neurodevelopmental outcome.[53] After birth, high risk infants can be monitored clinically and with cerebral imaging techniques, to be able to detect possible brain damage or deviant development in an early stage. Brain imaging techniques developed from the 1970's onwards, starting with ultrasound and nowadays often combined with more and more sophisticated MRI's, being able to detect brain lesions more specific. Better detection of lesions may improve predicting later outcome.[54] Clinical observations and examination are also good predictive tools for later outcome, especially the evaluation of general movements. A combination of general movement assessment with MRI predicts in preterm infants the outcome of cerebral palsy best.[55]

After detection of infants at risk, intervention could be provided. Nowadays, provision of stem cells to repair certain effects of brain injury is under investigation. In animal models, it led to promising results.[56] Cooling the brain has been proven to be effective in term infants at risk for hypoxic encephalopathy, to reduce risk of mortality and morbidity.[57] Nowadays, it has been introduced in the regular care of academic centers. Hypothermia for preterms with hypoxia is under investigation.[58]

Interventions early after hospital discharge, often focus on large but relatively low risk groups, such as low birth weight or premature infants. Most of those infants will not develop severe neurodevelopmental problems.[59] Early intervention targeted on relatively low risk groups, showed most effect on cognitive outcome and less on motor outcome.[60] In very high risk infants, such as infants with brain lesions, knowledge about effects of early intervention is sparse and methodological quality of available studies is low in general. A mix of ingredients to compose an effective intervention program is suggested to be most effective.[61,62]

In conclusion

From the above described factors influencing brain development, it will be clear that neurodevelopment is multifactorial and complex. Actually, until now it seems to be impossible to describe in a 'statement', such as proposed by the modified Kennard principle, what the effects of specific factors are. Knowledge is growing, but far from complete.

Present thesis

Trying to unravel a little piece of the big brain puzzle, in this thesis the effects of early intervention in infants at very high risk (VHR) of CP are studied in two different projects: the Vroegtijdig Interventie (Early Intervention) Project (VIP) and the LEARN2MOVE 0-2-project (L2M0-2).

Interventions

Two types of early, post discharge, interventions are studied: 'COPing with and CAring for infants with special needs – a family centered programme' (COPCA) and Typical Infant Physiotherapy (TIP), i.e. standard physiotherapy as provided in the Netherlands.[63] Both interventions are provided by physiotherapists.

COPCA has two main elements: a family component and a neuromotor component. The family component is based on a family centered approach, in which each family is considered to be unique with its own competencies, and physiotherapists and families create equal partnerships. The neuromotor component is based on the Neuronal Group Selection Theory (NGST), which describes different phases in variability in motor development. In the primary phase, neuronal connections are created abundantly, resulting in a varied motor repertoire. In the secondary phase, infants learn by trial and error to select adaptive motor strategies in specific situations from the available motor repertoire. In case of brain injury, formation of neural connections is limited and therefore, the motor repertoire will show less variation. Featuring less available motor options, selecting adaptive strategies in specific circumstances becomes more difficult and takes more time.[64,65]

TIP is often a mix of several physiotherapeutic ingredients. Traditionally, infant physiotherapy was in the Netherlands based on principles of NeuroDevelopmental Treatment (NDT), which aimed to normalize and optimize muscle tone and posture as far as possible.[66] However, due to developments both within NDT and outside NDT including new theories about neuromotor development, contents of physiotherapy changed over the years. Nowadays, infant physiotherapy is often a combination of different physiotherapeutic elements, amongst others based on preferences and education of the physiotherapist.[67] Therefore, large heterogeneity exists in 'standard' or 'typical' infant physiotherapy.[63]

Intervention projects

The VIP-project included between 2003 and 2005 infants at very high risk for neurodevelopmental problems, based on definitely abnormal general movements around the corrected age of 3 months. Infants were randomly assigned to a three month period of intervention, either COPCA or TIP. Follow-up of the infants was until the corrected age of 18 months.

The L2M0-2 is part of the Dutch LEARN2MOVE project, in which effects of intervention for children with CP are studied.[68,69,70,71] L2M0-2 included in the years 2008-2014 infants between 0 and 9 months corrected age, based on very high risk of developing CP, due to either a severe brain lesion (cystic periventricular leukomalacia, parenchymal infarction or bleeding), perinatal asphyxia combined with brain abnormalities or a clinical presentation which made them suspect for developing CP. At baseline of the L2M0-2-project, it was not yet clear whether infants would develop CP, as CP usually cannot be reliably diagnosed

before the age of 18-24 months.[72,73] Infants received a one year intervention of either COPCA or TIP and follow-up was continued until the corrected age of 21 months.

Outcome measures

Primary outcome measure in both the VIP- and the L2M0-2-project was the Infant Motor Profile, a measure to asses motor function in infancy, both qualitative and quantitative.[74] Secondary outcome measures consisted in both studies of a large battery of neuromotor and cognitive outcomes.[75,71] In L2M, also measures specific for children with CP and family measures were included.

In both studies, a detailed process analysis was performed to give insight in actual contents of infant physiotherapy. Associations between contents of intervention and outcome were studied, in order to provide insight in actual working mechanisms of interventions.

Aim and outline of the thesis

Main aim of this thesis is to study effects of early intervention in infants at very high risk for CP and their families. Secondary aims are providing insight in VHR infant's developmental trajectories and factors that my influence the trajectories, to provide knowledge about interventional contents and developments over the years, and to assist the development of adequate measures for VHR-infants.

PART 1: Factors that may affect outcome in very high risk infants

Chapter 2 studies literature about outcome of VHR-infants with cerebral lesions in a systematic review. Main question is: what are the motor and cognitive sequelae of severe neonatal brain lesions? Additional questions addressed are influences of type and side of brain lesion, sex and socio-economic status on neurodevelopmental outcome. Chapter 3 analyses contents of conventional physiotherapy during the last decades in the Netherlands. It addresses the questions whether infant physiotherapy changed over the years and whether theoretical frameworks about infant development and family care have been implemented in practice.

Knowledge about VHR-infants' developmental trajectories and changes in infant physiotherapy over time, assists in understanding and interpreting outcome of intervention studies.

PART 2: Early intervention in very high risk infants

Chapter 4 addresses the effects of early intervention in the VIP-project, in which VHR-infants received a 3-month period of either COPCA or TIP. VHR-infants were included on the basis of definitely abnormal general movements. Motor outcome, measured by the IMP, was compared at RCT-level and related to contents of intervention. Research questions are 1) do infants, randomly assigned to COPCA or TIP, differ in motor outcome? and 2) are interventional elements related to motor outcome? Chapter 5 describes the study design of a second intervention study, L2M0-2, in which the effects of a one year period of either COPCA or TIP in VHR-infants are studied. Infants were included on the basis of either a severe brain lesion or clinically suspect for developing CP. Chapter 6 reports about infant and family outcome of the L2M0-2 study. Questions addressed are 1) do infants, after receiving COPCA or TIP, differ in neuromotor or cognitive outcome; 2) does family outcome differ after receiving COPCA or TIP and 3) are contents of intervention related to infant or family outcome?

Both the VIP- and the L2M-project study the same interventions, but study designs differ: in the L2M-project, infants at higher risk for CP are included and intervention duration is longer than in the VIP-project. Differences in study design may assist in answering questions about timing, dosage and target specific effects of early intervention.

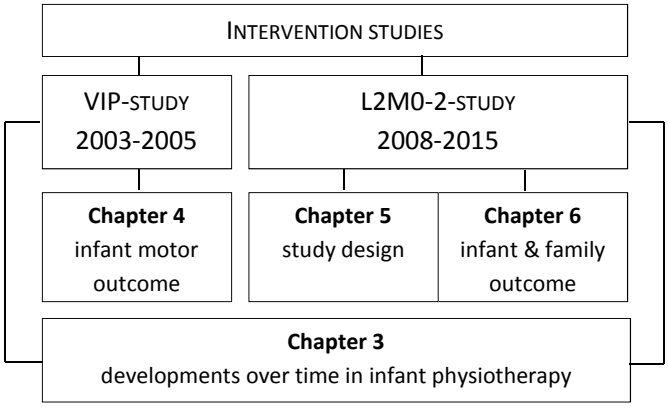

Figure 1. Overview of the intervention studies

PART 3: Measuring gross motor function in young infants with or at high risk of cerebral palsy

While designing and performing the intervention studies, various difficulties emerged in finding the best way measuring outcome in VHR-infants. To study effectiveness of early intervention, good measuring instruments are essential.

In Chapter 7, use of the Gross Motor Function Measure (GMFM) in infancy is discussed. Questions addressed are 1) what are the abilities of the GMFM to measure changes in gross motor function over time in comparison with other motor outcome measures; 2) what difficulties are encountered applying the GMFM in infancy and 3) whether adaptations of the instrument could be made to improve measuring gross motor function at early age in VHR infants. Chapter 8 discusses application of the classification system for severity of CP, the Gross Motor Function Classification System (GMFCS), in infancy. It addresses the question whether assisted mobility should be introduced in the GMFCS before the age of two years.

Developing good outcome measures for VHR-infants, assists in representing infant's actual level of functioning and measuring effects of early intervention.

GENERAL DISCUSSION

Finally, chapter 9 discusses the findings of the thesis and provides suggestions for future research.

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FACTORS THAT MAY AFFECT OUTCOME IN VERY HIGH RISK INFANTS

PART I