Infants at very high risk of cerebral palsy

a challenging population

Tjitske Hielkema

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INTRODUCTION

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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.

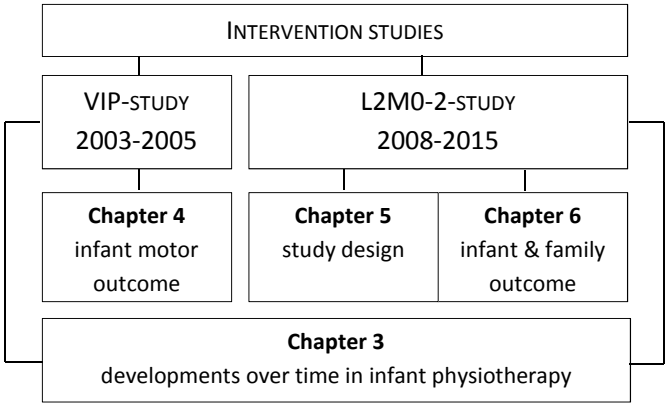

Figure 1. Overview of the intervention studies

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

MOTOR AND COGNITIVE OUTCOME AFTER SPECIFIC EARLY LESIONS OF THE BRAIN - A SYSTEMATIC REVIEW

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ABSTRACT

The aim of this systematic review was to study motor and cognitive outcome in infants with severe early brain lesions and to evaluate effects of side of the lesion, sex, and social economic status on outcome. A literature search was performed using the databases Pubmed and Embase. Included studies involved infants with either cystic periventricular leukomalacia (cPVL), preterm, or term stroke (i.e. parenchymal lesion of the brain). Outcome was expressed as cerebral palsy (CP) and intellectual disability (mental retardation). Median prevalence rates of CP after cPVL, preterm, and term stroke were 86%, 71%, and 29% respectively; of intellectual disability 50%, 27%, and 33%. Most infants with cPVL developed bilateral CP, those with term stroke unilateral CP, whereas after preterm stroke bilateral and unilateral CP occurred equally often. Information on the effects of sex and social economic status on outcome after specific brain lesions was very limited. Our findings show that the risk for CP is high after cPVL, moderate after preterm stroke, and lowest after term stroke. The risk for intellectual disability after an early brain lesion is lower than that for CP. Predicting outcome at individual level remains difficult; new imaging techniques may improve predicting developmental trajectories.

WHAT THIS PAPER ADDS

- Severe brain lesions in preterm infants are associated with a high risk for cerebral palsy (median prevalence >70%); the risk is highest in infants with cystic periventricular leukomalacia (median prevalence 86%).
- About 30% of infants with term stroke is diagnosed with cerebral palsy.
- An early lesion of the brain is in 27-50% (median prevalence) of infants associated with intellectual disability.

It is well established that infants with a prenatal, perinatal, or neonatal lesion of the brain are at risk for neurodevelopmental disorders. In general, infants with the most extensive lesions are at highest risk for neuromotor disabilities, such as CP, and cognitive impairments.[1] However, some infants with an extensive brain lesion develop quite well, whereas some infants in whom brain imaging showed the presence of only a relatively small or no lesion may develop severe neurodevelopmental problems.[2] Little is known on the neurodevelopmental sequelae of specific brain lesions. In addition, it has not been systematically studied whether an early lesion of the brain affects the motor and cognitive domains similarly. Neither is it clear whether the child's sex and social class affect the developmental sequelae of a lesion. In general, male sex and low social class are associated with a higher risk of adverse outcome,[2–4] but whether these factors modify the developmental effect of a lesion of the brain is uncertain.

The aim of this systematic review is to assess developmental outcome in infants with the following specific lesions of the brain: cystic periventricular leukomalacia (cPVL) and neonatal stroke. For the latter lesion, we differentiated between lesions occurring at preterm age and those occurring around term age.[5] Outcome will be specified as CP, including unilateral and bilateral forms, and as impaired cognitive outcome, expressed as intellectual disability (mental retardation). Specific attention will be paid to a potentially modifying effect of sex, social class, and the side of the lesion.

METHOD

A literature search was performed to identify studies published from 1970 to April 2014. Electronic databases searched were PubMed and Embase. Reference lists in original studies and reviews were examined for appropriate articles. For details of the search string see Table 1.

Inclusion criteria for the studies were: a follow-up at least until the age of 18 months; brain imaging was available (cranial ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI); outcome expressed in either CP or a developmental or intelligence quotient; peer-reviewed articles with full text published in English, German, or French. Studies were excluded if they dealt with traumatic brain injury or severe congenital disorders, if they were review studies or retrospective imaging studies in children with clinical problems, or if they included fewer than three participants. For studies that described outcome of infants with various types of brain lesion, we studied outcome for each lesion group separately.

For the definition of cPVL we followed de Vries et al.[6] If a study did not use the classification of de Vries et al, we determined whether the lesions reported resembled grade 2 or higher cPVL according to de Vries et al. Studies were excluded if imaging information was insufficiently detailed for such classification, or if lesions were milder. Haemorrhagic

or ischaemic parenchymal lesions of the brain with a preterm origin will be referred to as 'preterm stroke'; neonatal parenchymal lesions occurring at or within 28 days after term age will be referred to as 'term stroke'. For the definition of stroke we used the American Heart Association/American Stroke Association Expert Consensus Document.[7] This consensus document is mainly based on adult stroke. Preterm parenchymal lesions usually have a different origin than term or adult stroke. In preterm infants, intracerebral lesions often originate from haemorrhages caused by impaired drainage of the veins in the white matter. For brevity's sake, we labelled both haemorrhagic and ischaemic parenchymal lesions as 'stroke' and differentiated between preterm and term origin. Therefore, both preterm and term parenchymal lesions are described as stroke, notwithstanding their different pathophysiology. Cognitive outcome was classified as intellectual disability if developmental quotient or IQ was under 70.

Table 1: Search string and key words

Brain lesion		Outcome		Study group
leukomalacia OR (periventricular OR parenchymal OR cerebral AND cysts) OR (cerebral OR brain OR cortical OR parenchymal OR periventricular) AND (stroke OR ischemia OR hemorrhage OR bleeding OR infarction OR lesion) OR (sinovenous AND thrombosis) OR (cerebrosinovenous AND thrombosis) OR (intraventricular AND (bleeding OR hemorrhage)	**AND**	motor AND outcome OR cognition OR (motor AND development) OR (cognitive AND development) OR (cerebral AND palsy)	**AND**	infant OR neonate OR newborn OR infancy

RESULTS

The literature search resulted in 3818 unique hits (see Figure 1). After screening titles and abstracts, 111 articles were left that reported some aspect of developmental outcome for infants with cPVL and 238 for infants with preterm or term intraparenchymal haemorrhage or infarction. Eventually, 29 articles on cPVL (28 with outcome CP, 11 reported on intellectual disability (mental retardation), 23 articles on preterm stroke (22 with outcome CP, 13 with outcome intellectual disability (mental retardation), and 18 articles on term stroke (15 with outcome of CP; 9 with outcome of intellectual disability (mental retardation) met our inclusion criteria.

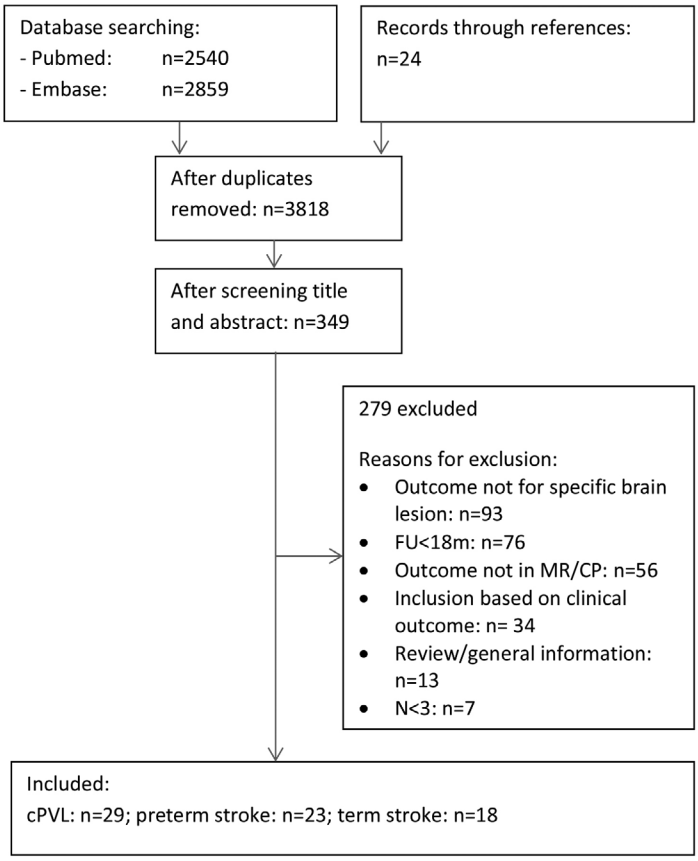

Figure 1: Literature search for outcome

Cystic periventricular leukomalacia

Most of the infants with cPVL developed CP, that is, CP was diagnosed in 474 out of the 607 (78%) infants assessed (median 86%; range in the 28 studies 52–100%; see Fig. 2).[8–35] In studies that presented the severity of the lesion in terms of the grades of periventricular leukomalacia according to de Vries et al. (n=8), the prevalence of CP was higher in infants with a grade 3 and 4 lesion (95% (110/116) and 78% (7/9) respectively) than in infants with grade 2 periventricular leukomalacia (59% (67/113)). Note that studies on infants with grade 1 periventricular leukomalacia were excluded from the review. Fifteen out of the28 studies classified CP into unilateral or bilateral forms; 92% of the infants with cPVL who were diagnosed with CP had the bilateral form (232/253). Ten studies (n=266) reported whether cPVL was unilateral (n=65; 24%) or bilateral (n=201; 76%). Of the infants with bilateral cPVL, 81% developed CP (163/201); of those with unilateral cPVL, 42% (27/65) developed CP. Five

studies (n=59; 18 unilateral cPVL, 41 bilateral cPVL) specified whether CP was unilateral or bilateral. Four of the 18 infants with unilateral cPVL developed a unilateral CP (two contralateral, two not specified); seven infants developed a bilateral CP and seven infants did not develop CP. Thirty-nine of the 41 infants with a bilateral cPVL developed a bilateral CP, two did not develop CP.

Eleven studies reported on cognitive outcome (Figure 2);[8–11,13,14,16,19,21,22,26,27,36] the overall rate of children diagnosed with intellectual disability was 47% (106/224; range of individual studies 25–100%; median 50%). Five studies reported the sex of the infants with cPVL (n=51); 30 (59%) were male. Four studies reported outcome per sex (n=27; 21 males, six females): 20 males and six females developed CP. The search string did not reveal studies that addressed social status in relation to outcome in infants with cPVL.

Preterm stroke

Sixty-two percent (297/479) of infants with preterm stroke was diagnosed with CP (median 71%; range 25–100%; see Fig. 2).[8,16,26,29,37–53] Thirteen studies (n=132) classified CP as unilateral or bilateral; half (66/132=50%) of the infants developed a bilateral CP. Six studies (n=127) described the localization of the lesion in terms of unilateral (106/127=83%) or bilateral distribution (21/127=17%). Five of the latter studies also reported outcome for unilateral (n=87) and bilateral (n=19) lesions separately. Twentyseven of the 87 (31%) infants with a unilateral brain lesion developed a unilateral CP; 28 (32%) developed a bilateral CP and 32 (37%) had no CP. Twelve of the 19 infants with a bilateral brain lesion developed a bilateral CP; three developed a unilateral CP and four had no CP. In three studies (n=22), outcome was described per side of the lesion. Eight infants had a right-sided brain lesion: one developed a unilateral left-sided CP, one a unilateral rightsided CP, and four a bilateral CP; two infants had no CP. Thirteen infants had a left-sided brain lesion, five developed a unilateral right-sided CP, five a bilateral CP, and three had no CP.

Cognitive outcome varied largely (Figure 2):[8,16,26,37–42,44,46,49,54] 25% (57/231) of the infants developed intellectual disability, with a range from 0% to 100% (median 26.5%). Three studies (n=98) described cognitive outcome for unilateral and bilateral lesions separately. Twenty-nine of the 79 infants with a unilateral lesion had intellectual disability (37%); 17 of the 19 infants with a bilateral lesion had intellectual disability (89%).

Four studies reported the sex of the infants (n=97); 59 infants (61%) were male. Three studies reported outcome per sex (n=12): 7/8 of the male infants developed CP and 4/4 female infants. No studies reported relations between social status and outcome for infants with preterm stroke.

Term stroke

Of the term infants with neonatal stroke, 34% (range 7–83; median 29%) developed CP (102/296; see Fig. 2).[52,55–68] Eleven studies (n=204) classified CP (n=61) as unilateral (58/61=95%) or bilateral (3/61=5%).

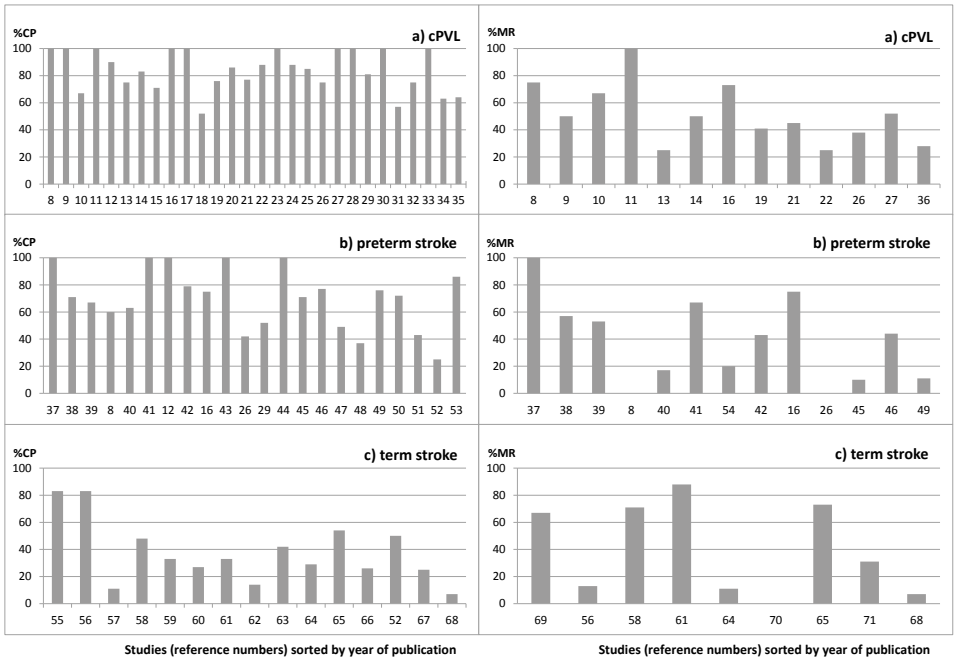

Figure 2: Outcome (percentages CP (Cerebral Palsy) and MR) (Mental Retardation) for infants with a) cPVL, b) preterm stroke and c) term stroke

Fourteen studies described whether brain lesions were unilateral (n=253; 88%) or bilateral (n=36; 12%). The unilateral lesions were more left-sided (n=173; 68%) than right-sided. Seven studies (n=57; n=47 unilateral, n=10 bilateral lesion) described outcome in left-or right-sided CP per side of the lesion. Nine of the 32 infants with a left-sided brain lesion developed a unilateral, right-sided CP; one developed a unilateral left-sided CP; 22 had no CP. Six of the 15 infants with a right-sided brain lesion developed a unilateral, left-sided CP; one developed a bilateral CP; eight had no CP. Thus, children with CP on the basis of a unilateral brain lesion usually had unilateral CP (16/17). Two of the six infants with a bilateral lesion had right-sided CP and four infants had no CP.

Nine studies reported on intellectual disability after term stroke.[56,58,61,64,65,68–71] The prevalence of intellectual disability was 0% to 88% (median 32.5%). Overall, 61 out of 174 infants (35%) were diagnosed with intellectual disability.

Twelve studies provided information about sex (n=191); 57% of the infants was male. Six studies (n=65) reported motor outcome per sex: 12/42 (29%) males and 13/33 (39%) females developed CP. Another six studies (n=94) described cognitive outcome for males and females; 8/59 (14%) males and 6/35 (17%) females had intellectual disability. One study[64] (n=26) reported about social class by means of maternal educational level; educational level was not related to outcome.

DISCUSSION

Our systematic review indicated that cPVL is followed by median high rates of CP (86%), preterm stroke with lower rates of CP (71%), and term stroke with the lowest rates (29%). Also highest median rates of intellectual disability were observed in infants with cPVL (50%). About a quarter of the infants with preterm stroke and about one-third of the infants with term stroke developed intellectual disability. It should be noted, however, that fewer studies reported cognitive outcome than motor outcome. This may be due to the difficulty measuring cognitive outcome in children with a severe brain lesion; it is easier to assess whether a child developed CP than to measure the developmental quotient or IQ of a child with severe impairments, as motor and speech impairments may interfere with cognitive testing.

Infants with cPVL are at very high risk for CP, usually a bilateral form; this is especially true for the infants with grades 3 and 4 cPVL.[25,72,73] The reported prevalence of CP in children with grade 4 cPVL seemed lower than that in children with grade 3 cPVL. This may be a chance finding as the number of infants with cPVL grade 4 was very small (n=9; grade 3: n=116). Alternatively, surviving after grade 4 cPVL may be an indication of 'fitness' and may be associated with relatively better outcome. The risk for intellectual disability after cPVL is substantially less than the risk for CP. However, the absence of intellectual disability does not automatically imply the absence of cognitive impairment. CPVL may result in specific cognitive impairments such as impaired perception attention deficit and impaired social cognition, with or without a reduction in overall IQ.[73] Nevertheless, the finding that, in infants with cPVL, intellectual disability occurred less often than CP is interesting, as early intervention in infants at risk for developmental problems has a stronger effect on cognitive than on motor development.[74] It is conceivable that in infants with cPVL the potential for functional improvement also mainly pertains to the cognitive domain – the domain that predicts later functioning in daily life.[75,76]

Outcome after perinatal stroke is primarily affected by the age at the insult: the risk for CP after preterm stroke is about twice as high as the one after term stroke. Only a minority of infants with perinatal stroke develop intellectual disability (one out of four infants with preterm stroke; one out of three infants with term stroke). Here, the same caveat as above is valid: the absence of intellectual disability does not preclude the presence of specific

cognitive impairment. The difference in outcome for preterm and term stroke may be attributed especially to the neural substrate of lesion. In our review, preterm stroke denoted preterm parenchymal lesions and periventricular haemorrhagic infarction, caused by impaired drainage of the veins in the white matter. The latter is frequently accompanied by hydrocephalus and periventricular leukomalacia and often results in damage of the periventricular and subplate zone. This zone plays a pivotal role in the development of the cortex.[5,77] The localization of term stroke in general resembles that of adult stroke, with focal or cortical involvement, usually without involvement of the periventricular zone. It is less often associated with CP. In addition, the sequelae in terms of the type of CP differed for unilateral preterm and term stroke. After preterm stroke half of the children who were diagnosed with CP had a unilateral form, the other half had a bilateral form. After term stroke, children diagnosed with CP in general (94%) had a unilateral form, a minority (6%) a bilateral CP. Conceivably, the higher prevalence of bilateral CP after preterm stroke, results from a different pathophysiology and suggests that preterm stroke often is an expression of a more general encephalopathy, similar to the one associated with cPVL.[77] If a unilateral lesion resulted in unilateral CP, the contralesional side usually was the most affected side. However, occasionally the ipsilesional side was the most affected side. This was observed both after preterm stroke and term stroke. It should be mentioned that we only included infants with stroke who had imaging before the age of 28 days. Unnoticed stroke during pregnancy and asymptomatic perinatal stroke are common causes of later CP, but are usually not diagnosed in an early stage[78] and are therefore beyond the scope of our study. The asymptomatic early strokes may have been missed especially in term infants, who – in contrast to preterm infants – do not receive standard neuroimaging.

In preterm infants no differences in the prevalence of right-sided and left-sided lesions were reported. However, in term infants perinatal stroke occurs more often on the left side than on the right side. It has been hypothesized that this difference is due to an asymmetry of the vascularity of the middle cerebral artery and the hemisphere it serves.[79,80]

Golomb et al.[81] reported that males are more affected by perinatal arterial ischaemic stroke and cerebrosinovenous thrombosis than females. This corresponds to the slight surplus of males in our cases with preterm and term stroke. The few studies that provided information on outcome per sex did not suggest the presence of a clear sex difference. Specification of outcome per social status was virtually absent, with the study of Westmacott[70] being the exception to the rule. This is disappointing as social economic status is known to have a large impact on development in general, and may be considered as a potential effect modifier of outcome.[4] In addition, it may be an effect modifier that may be affected by intervention.

One of the strengths of our study is the systematic search and presentation of results. To the best of our knowledge it is the first study that provides an overview of motor and

cognitive outcome of infants with a specific early lesion of the brain, from the 1970s onwards. Followup was at least until the age that CP can be diagnosed, that is, 18 months; however, follow-up at 18 months is relatively short for a good interpretation of cognitive outcome. The relatively low age of 18 months may have caused an underestimation of intellectual disability in our study, particularly since the literature indicates that, especially in very preterm infants, cognitive problems are a major problem.[82] The time period involved in our review is long, extending over almost 40 years. During that period, neonatal care improved substantially,[83] which might have affected the outcome after an early lesion of the brain. However, Figure 2 does not suggest the presence of a time trend. This may reflect that better neonatal care not only improved developmental outcome, but also resulted in higher survival rates of infants with lower gestational age and birthweight, well known risk factors for developmental disorders.[84] Another consequence of the long study period is that brain lesions were diagnosed with a variety of imaging techniques (ultrasound, CT, conventional MRI), resulting in heterogeneity in diagnostics – a limitation of our study. It is conceivable that during the next decade, the application of novel imaging techniques will assist in the prediction of outcome of specific lesions. In fact, first steps have been taken already; for example, lesions of the posterior limb of the internal capsule, shown on MRI, are a relatively good predictor of adverse outcome.[85] Another limitation of our study is a possible overlap between study populations, for example, this may be the case for the studies from the Hammersmith Hospital[8,32,60,62,64] and those of de Vries et al.[9,16,19,24,26,29,34,35,47,63,68] If overlap was clear, we excluded one of the overlapping studies, that is, the one that provided least details.

The focus on infants with severe brain lesions is another limitation; it often resulted in small numbers per study, which were often small subgroups of larger studies. Background characteristics, such as social economic status and sex, were generally described for the larger study group, but not for the subgroups of infants with a specific lesion of the brain.

In conclusion, infants with cPVL have a high risk for CP, infants with preterm stroke a moderate risk, and those with term stroke the lowest risk. The risk for intellectual disability after an early lesion of the brain is less than that for CP. Novel imaging techniques in combination with improved knowledge about the developmental trajectories of infants with an early lesion of the brain may help to predict and interpret outcome. A better predicting of outcome is an essential tool in family counselling and the planning of intervention. Therefore, we suggest that future research addresses the significance of novel imaging and developmental trajectories in infants with an early lesion of the brain in order to improve prediction of outcome in individual infants.

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CHANGES OVER TIME IN CONTENTS OF INFANT PHYSICAL THERAPY: A QUANTITATIVE, OBSERVATIONAL STUDY

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ABSTRACT

Aims: Pediatric physical therapy (PPT) gradually implements novel concepts on family and development. Aim of our observational longitudinal study is to evaluate changes over time in standard PPT for infants at risk for neurodevelopmental disorders.

Methods: PPT-sessions in two time periods (2003-2005 (n=22) and 2008-2014 (n=16)) were video-recorded and analyzed quantitatively in five categories: neuromotor, educational and communication actions, position and situation. Differences in percentages of time spent on therapeutic actions between periods were tested with Mann Whitney U- and Hodges Lehmann's-tests.

Results: No significant changes appeared in main categories of neuromotor actions. Time spent on not-specified educational actions towards caregivers (median from 99% to 81%, p=0.04) and not-specified communication (median from 72% to 52%, p=0.002) decreased. Consequently, time spent on specific educational actions (caregiver training and coaching; median from 1% to 19%, p=0.04) and specific communication (information exchange, instruct, provide feedback; median from 21% to 38%, p=0.007) increased. Position changed only minimally: time spent on transitions – i.e. change of position – decreased slightly over time (median from 7% to 6%, p=0.04). Situation did not change significantly over time.

Conclusions: Neuromotor actions in PPT remained largely stable over time. Specific educational actions and communication increased, indicating larger family involvement.

INTRODUCTION

Pediatric physical therapy (PPT) is developing. Over the years, novel concepts and theories have been implemented. Traditionally, concepts of motor development were mainly based on maturational theories, in which the central nervous system is supposed to control motor development in a predetermined way.[1] Gradually, more environmental influences were acknowledged and incorporated in theories and practice. A theory in which environment plays a major role is the Dynamic Systems Theory.[2] This theory explains development by a process in which different components interact with each other resulting in changes, which are the starting point for future changes. Another neuromotor theory, the Neuronal Group Selection Theory[3,4], incorporates both influences from the central nervous system and the environment. According to this theory infants first develop a varied motor repertoire by creating networks between the billions of available neurons in the brain; subsequently infants learn to select strategies from the motor repertoire that are adaptive to the specifics of the condition. Based on animal studies, encouraging enriched environments are incorporated in several early intervention programs, to optimize use of the neuroplasticity of the brain.[5,6]

Concurrent with changes in the concepts of motor development, the application of the International Classification of Function for Children and Youth (ICF-CY)[7] encouraged two shifts over time: one from a focus on body functions and structures towards activities and participation, the other from a child centred approach to a more context focused and family centred approach.[8,9] Family centred care involves partnerships between professionals and families, in which caregivers are recognized as the decision makers for their child.[10]

Developments in theories about neuromotor development and the increasing focus on family and function, induced changes in intervention over the years. This may be illustrated by the changes that occurred in the widely used approach of NeuroDevelopmental Treatment (NDT).[11,12] Originally – in the second half of last century – it was based on maturational theories and aimed to optimize and normalize movements and muscle tone. But during the years and due to the fact that the approach was developed as a living concept, new neuroscience insights were incorporated and led to a more functional approach, aiming to transfer motor activities into daily life activities.[13] Others created context therapy on the basis of dynamic systems theory in combination with a family centered approach.[14] During the last two decades also novel types of early intervention have been developed that discarded the maturational developmental theories. Cases in point of novel early intervention programs are the COPCA-intervention (COping with and CAring for infants with special needs – a family centered approach[15] and the GAME-program (Goals, Activity and Motor Enrichment).[16] The COPCA-program is based on the theoretical framework of the NGST combined with a family centred approach.[15] The GAME-program uses principles of environmental enrichment together with frequent, goal-oriented task practice in the

critical early period of brain development.[16] The described conceptual changes in theory and practice, imply that contents of PPT nowadays differ from that in the past. However, the contents of PPT largely remains a 'black box'[17] and little is known about possible changes across time.

In the last decades, we have been involved in two early intervention studies, which compared the effect of the COPCA-program with that of standard – or typical - physical therapy (typical infant physical therapy – TIP).[18,19,20] In order to understand the actual contents of the interventions we videotaped the intervention sessions. As the studies occurred in different time periods (2003-2005 and 2008-2013), the video material allowed us to study changes over time in typical infant physical therapy. Therefore, the aim of the current observational study is to explore changes across time in PPT by comparing quantitatively the contents of TIP in both intervention studies. Knowledge on changes in standard PPT will improve our interpretation of intervention studies, in which recently developed interventions are often compared with standard care. We hypothesize that developmental changes in PPT over time would be associated with 1) a decrease in the use of hands-on neuromotor actions (NDT-techniques), in line with developments with more focus on environment and context, together with the shift from a focus on body functions and structures towards activities and participation; and 2) an increase in family centeredness, fitting into the development from child centred towards more family centred care.

METHODS

Participants

Participants are infants enrolled in the Vroegtijdige Interventie (Early Intervention) Project (VIP; 2003-2005)[18,19] or the LEARN2MOVE 0-2 years project (L2M; 2008-2014).[20] Both projects were approved by the medical ethic committee of the University Medical Center Groningen (UMCG) and registered in the Dutch trial register, under NTR361 and NTR1428 respectively.
In the VIP-project, infants admitted to the neonatal intensive care unit of the UMCG between March 2003 and May 2005 presenting with definitely abnormal general movements at 10 weeks corrected age (CA) (indicating a high risk for developmental disorder) were included after informed consent of the caregivers. The L2M-project included between November 2008 and December 2013 infants between 0 and 9 months CA at very high risk for cerebral palsy (CP), based on imaging of the brain (cystic periventricular leukomalacia, preterm or term parenchymal lesion), asphyxia with abnormalities on brain imaging or clear neurological dysfunction suspect for the development of CP. Caregivers gave informed consent. Infants were recruited from 12 hospitals in the Northern part of the Netherlands and around Amsterdam.

Exclusion criteria for both intervention projects were the presence of a severe congenital disorder or an insufficient understanding of the Dutch language of the caregivers. Infants were randomly assigned to either TIP or COPCA after informed consent of the caregivers. In the present study, we focus only on the infants who received TIP, i.e. the infants who received standard physical therapy care (VIP-project: n=25; L2M-project: n=20).

Characteristics of the infants are presented in Table 1. Inherent to the difference in design of the studies, significantly more infants presented with a severe brain lesion in the L2M-project than in the VIP-project (p<0.001) and consequently, more CP was diagnosed in the children of the L2M-project (p=0.033).

Table 1: Characteristics of the infants

	VIP-project (n=22)	L2M-project (n=16)
Sex		
▪ Male: n (%)	10 (45)	10 (62)
▪ Female: n (%)	12 (55)	6 (38)
Gestational age		
▪ Median (weeks)	30	30
▪ Range	25-39	26-41
Birthweight		
▪ Median (grams)	1243	1440
▪ Range	635-3460	820-5400
Brain lesion		
▪ No severe brain lesion: n (%)	19 (86)	2 (12)
▪ Severe brain lesion*: n (%)	3 (14)[a]	15 (88)[a]
Maternal education		
▪ Low or middle: n (%)	12 (55)	10 (63)
▪ High: n (%)	10 (45)	6 (37)
Paternal education		
▪ Low or middle: n (%)	16 (80)	5 (44)
▪ High: n (%)	4 (20)	8 (50)
▪ Missing: n (%)	0 (0)	1 (6)
Maternal age at birth		
▪ Median (years)	33	34
▪ Range	22-39	17-41
Age infant at PT-video		
▪ Median (months)	5.1	5.2
▪ Range	3.3-7.5	2.8-8.0
Infants diagnosed with CP at 18 or 21 months CA		
▪ CP: n (%)	5 (23)	7 (44)
▪ No CP: n (%)	17 (77)	7 (44)
▪ Unknown (%)	0 (0)	2 (12)

CA = Corrected Age; CP = Cerebral Palsy; L2M = LEARN 2 MOVE; n = Number; PT = Physiotherapy; TIP = Traditional Infant Physiotherapy; VIP = Vroegtijdig Interventie Project (Early Intervention Project); *Periventricular leukomalacia (PVL) grade 3 or 4, parenchymal hemorrhage/infarction or ischaemic cerebral lesions; a = difference between VIP and L2M: Chi-square test, p<0.001

Intervention in the VIP-project was provided between 3 and 6 months CA; in the L2M-project intervention was applied for one year, starting after inclusion. In both projects, physical therapy was usually provided at home (90%); the frequency depended on the pediatrician's advice and the physiotherapist's findings. Median duration of PPT-sessions in both projects was 32 minutes (ranges: VIP 12-51; L2M 17-63).

Measures and procedure

Both projects are follow-up studies in which infants underwent regular neuromotor tests. The last measurement (in VIP: 18 months CA; in L2M: 21 months CA) included assessment of the presence or absence of CP, based on the Touwen Infant Neurological Examination.[21] In the VIP-project, PPT-sessions were videotaped at 4 and 6 months CA (median age 4.9 months, range 3.3-7.5). Three infants did not receive physical therapy on pediatrician's advice; therefore PPT-sessions had been recorded in 22 infants. In L2M, PPT-sessions were videotaped at 1, 6 and 12 months after inclusion. In order to exclude an effect of the infant's age on the comparison of VIP with L2M, we selected from the L2M videotapes only the sessions occurring between 2.5 and 8.0 months CA, resulting in a group of 16 infants (median age 5.2 months; range 2.8-8.0). Contents of the data of PPT-sessions of infants who had two videotaped PPT-sessions was largely comparable (tested with the Wilcoxon signed rank test). Therefore, data of both sessions were averaged, in order to have one set of data per infant for further analyses.

PPT-sessions of both VIP- and L2M-project were analyzed with a detailed observation protocol, the Groningen Observer Protocol version 2 (GOP 2.0; see appendix for a detailed description). GOP 2.0 differs slightly from the first version of GOP[15]: a) two additional therapeutic approaches were included, i.e., Vojta[22] and constrained induced movement therapy[23,24], to allow for an up to date and international application of the protocol; b) the category Self-Produced Motor Behavior was better specified and c) categories were reorganized, especially by lumping most neuromotor actions into the main category of 'neuromotor actions' resulting in five instead of eight main categories. Two observers (RFT and SJH) performed the analyses of the PPT-actions with help of The Observer version 11.5.[25] Time spent on specific PPT-actions was expressed by the percentage of time in relation to the total duration of the PPT-session. PPT-actions were scored as continuous variables in five main categories: neuromotor actions, educational actions, communication, position and situation. Within each category, actions were scored mutually exclusive. Actions which do not fulfill the criteria of one of these categories are scored as 'not specified' behavior within that category. Some PPT-actions are further specified by 'modifiers', specific sub-behaviors within a category.

Interobserver agreement for GOP 2.0 was determined by calculating intraclass correlation coefficients (ICC) of 10 independently assessed videos. Interobserver reliability

was good to excellent for all main categories (median ICC 0.945 (0.677-0.998)) and most of the modifiers (ICC 0.620-0.999). ICCs were moderate for three modifiers: sitting with minimal support (0.582); challenged to self-produced motor behavior (CSPMB) with large variation (0.480) and instructing with strict instructions (0.551); and poor for CSPMB with little variation (0.159) and CSPMB without challenge (-0.186). We did not include the two items with poor ICCs into the analyses.

Data analyses

We compared prevalence of PPT-actions in the two periods. PPT-actions that were observed in less than five infants or observed in less than 2% of time in each of the infants studied were excluded from the analyses.

SPSS version 20 was used for statistical analyses. Non-parametrical Mann Whitney U Tests and Chi-square tests were used to test differences in distribution and between baseline characteristics respectively, as the data were not normally distributed. A p-value of 0.05 was used as cut-off for statistical significance, as the study aimed to explore possible changes across time. In view of the number of tested variables, the relatively high p-value as cut-off score was chosen because we were also interested in tendencies and trends. Hodge's Lehmann estimates of the difference of the medians are provided with 95% confidence intervals to estimate the size of the differences.

RESULTS

Two infants were lost to follow-up in the L2M-project due to family overload. In the VIP-project, none of the 22 infants receiving therapy were lost to follow-up.

Table 2 shows developments across time in contents of physical therapy. As we observed various changes over time in the modifiers (i.e. the details) of the communication items, we added these modifiers in the table. In the other main categories changes in modifiers were restricted to single behaviors; these are summarized in the text.

Each paragraph describes the developments across time in physical therapy contents, in which we compare contents of the VIP-project with that of the L2M-project. Numbers in brackets represent p-values and, when not provided in the tables, also information about median percentages and ranges. First differences in the main categories (e.g., neuromotor actions: facilitation) are reported, followed by a report on differences in modifiers (e.g., neuromotor actions: facilitation, with handling techniques). When it was conceivable that presence or absence of a difference in PPT-actions over time was partly explained by a higher number of children diagnosed with CP in the L2M-project, we added information on the association between that PPT-actions and CP.

Table 2: Changes over time in contents of infant physical therapy

PT-situation or action	VIP-project (2003-2005)	L2M-project (2008-2013)	MWU	Hodge's Lehmann diff between medians		
	Median (range)	Median (range)	p-value	Estimate	95% CI	
					Lower	Upper
Neuromotor action						
Facilitation	18.2 (2.5-37.4)	10.1 (0.0-29.2)	0.122	-4.0	-11.4	0.9
Sensory experience	2.4 (0.0-20.1)	4.1 (0.0-20.3)	0.549	0.7	-1.7	4.9
Passive motor experience	1.2 (0.0-21.7)	2.1 (0.0-18.7)	0.326	0.7	-0.6	2.2
SPMB	36.2 (17.5-64.4)	36.8 (15.1-69.7)	0.965	0.2	-9.4	9.7
CSPMB, infant is allowed to continue activity	26.7 (11.2-40.1)	22.8 (0.0-57.0)	0.804	1.0	-11.8	9.0
CSPMB, flows over into hands-on techniques*	8.5 (0.4-23.0)	10.3 (0.0-21.9)	0.737	1.0	-4.0	6.3
NS neuromotor action	3.6 (1.6-18.9)	7.0 (1.9-15.3)	0.069	2.3	-0.1	5.2
Educational actions toward caregiver						
Caregiver training	0.7 (0.0-47.5)	16.5 (0.0-60.1)	0.258	8.5	-0.1	18.8
Caregiver coaching	0.0 (0.0-11.7)	0.0 (0.0-41.7)	0.404	0.0	0.0	0.0
NS educational actions	99.0 (51.31-100)	81.3 (10.2-100)	**0.042**	-14.2	-24.4	0.0
Communication						
Information exchange	2.1 (0.0-8.4)	7.5 (2.3-18.0)	**0.001**	4.0	1.8	7.8
▪ About NDT	▪ 0.0 (0.0-1.3)	▪ 0.9 (0.0-5.1)	**0.002**	0.7	0.0	1.6
▪ About family issues	▪ 2.0 (0.0-7.6)	▪ 7.5 (1.3-14.0)	**0.002**	2.9	0.0	6.3
Instruct	1.5 (0.0-14.5)	6.3 (0.2-17.3)	0.056	3.1	-0.4	6.4
▪ Strict instruction	▪ 0.6 (0.0-12.5)	▪ 1.4 (0.0-14.9)	0.625	0.3	-1.5	1.7
▪ Multiple options	▪ 0.8 (0.0-5.0)	▪ 0.4 (0.0-8.2)	0.784	0.0	-0.6	0.7
▪ Giving hints	▪ 0.0 (0.0-2.3)	▪ 1.1 (0.0-15.1)	**0.009**	0.7	0.0	1.6
▪ Not specified	▪ 0.0 (0.0-0.3)	▪ 0.0 (0.0-0.0)	0.222	0.0	0.0	0.0
Provide feedback	13.7 (0.8-46.0)	22.0 (6.8-35.9)	**0.045**	6.8	0.3	14.2
▪ Share information	▪ 1.8 (0.0-7.3	▪ 7.9 (1.0-23.4)	**<0.001**	5.6	1.9	11.7
▪ Asks & listens to opinion of caregiver	▪ 0.1 (0.0-16.7)	▪ 0.6 (0.0-9.3)	0.192	0.4	0.0	0.9
▪ Evaluating the procedure	▪ 11.3 (0.8-24.0)	▪ 8.8 (2.4-26.0)	0.605	-1.2	-7.4	3.5
▪ Right/wrong	▪ 0.0 (0.0-1.6)	▪ 0.0 (0.0-1.5)	0.590	0.0	0.0	0.0
No communication	5.9 (0.74-18.4)	4.7 (0.0-27.3)	0.767	-1.0	-3.9	6.8
Not specified communication	72.2 (35.0-92.9)	52.0 (41.0-73.3)	**0.002**	-17.1	-28.1	-7.4
Position						
Supine	48.5 (23.5-87.7)	54.0 (2.9-79.6)	0.298	6.0	-6.1	15.7
Prone	20.1 (4.3-29.5)	13.9 (1.7-31.7)	0.089	-5.2	-10.7	0.5
Sitting	18.2 (0.0-30.7)	14.2 (0.2-57.8)	0.872	-1.5	-4.2	0.5
Transition	7.1 (3.6-19.5)	5.6 (1.1-16.1)	**0.042**	-1.9	-4.2	-0.1

Table 2: Changes over time in contents of infant physical therapy (Continued)

PT-situation or action	VIP-project (2003-2005)	L2M-project (2008-2013)	MWU	Hodge's Lehmann diff between medians		
	Median (range)	Median (range)	p-value	Estimate	95% CI	
					Lower	Upper
Situation						
Motor activity/play	97.6 (81.2-100)	94.3 (65.8-100)	0.312	-2.2	-12.2	0.9
Feeding	0.0 (0.0-1.5)	0.0 (0.0-32.7)	0.438	0.0	0.0	0.0
Bathing	0.0 (0.0-0.0)	0.0 (0.0-0.0)	1.000	0.0	0.0	0.0
Dressing	1.1 (0.0-18.9)	0.6 (0.0-29.7)	0.672	0.0	-1.6	0.8
Carrying	0.3 (0.0-2.3)	0.8 (0.0-9.3)	**0.042**	0.4	0.0	1.4
Changing diapers	0.0 (0.0-0.76)	0.0 (0.0-2.2)	0.988	0.0	0.0	0.0

P-values in bold represent significant differences. CI= Confidence interval; CSPMB = Challenged to self-produced motor behavior; diff = difference; L2M = LEARN2MOVE; MWU = Mann Whitney U test; NDT = neurodevelopmental treatment; NS=not specified; PT = Physical therapy; SPMB = Self-produced motor behavior; TIP = Typical Infant Physical Therapy; VIP = Vroegtijdig Interventie (Early Intervention) Project.
* For readability we abbreviated 'flows over into or is combined with facilitation, sensory or passive experience' into: 'flows over into hands-on techniques'

Neuromotor actions

Time spent with the main categories of neuromotor actions did not change over time. Neuromotor actions that occurred most frequently were self-produced motor behaviors of the infant, either as spontaneous actions of the infant, or elicited by a challenge of an adult person. The analyses of the modifiers yielded one change: in case of 'CSPMB with an overflow into or is combined with facilitation, sensory or passive experience, sensory experience techniques' were less often applied over time (in VIP 1.0% (0.0-15.1), in L2M 0.0% (0.0-4.8); p=0.048).

Educational actions towards caregiver

The most frequently occurring educational actions were not specified actions. These not specified educational actions towards caregivers decreased across time (Table 2, p=0.042); i.e., specified educational actions (the amount of caregiver training and caregiver coaching together; median from 1.0% to 18.7% , p=0.042) increased.

Communication

Not specified communication was the most frequent type of communication. Time spent on not specified communication decreased across time (p=0.002). Consequently, total time spent on specified communication (i.e. the sum of information exchange, feedback and instruction) increased significantly over time (from 20.9% to 37.5%, p=0.007). The

increases in the amount of information exchange and in the provision of feedback were also individually statistically significant (p=0.001 and p=0.045, resp.), the amount of instructing was more stable over time (p=0.056). The modifier analyses on the type of information exchange indicated that over the years more time was spent both on explanation about NDT (p=0.002) and on family issues (p=0.002). Also the type of instruction changed: in the second period more time was spent on giving hints (p=0.009). In addition, the modifier analyses on the type of feedback showed that in the second period more time was spent on sharing information (p<0.001).

Position

During the therapy sessions the infants were mostly in supine position. Treatment position remained large stable across time, with the exception of a small but significant decrease in the percentage of time spent on transitions, i.e. time spent on changing from one position to another (p=0.042). The analysis of the modifiers indicated two changes across time: 1) an increase in the time spent in prone position on the upper part of the caregivers' body (from 0.0% (0.0-7.3) to 0.6% (0.0-6.1), p=0.042) and 2) a decrease in time spent in prone position across the leg of the caregiver or therapist (from 0.6% (0.0-5.8) to 0.0% (0.0-5.4), p=0.042).

Situation

Virtually all therapy time was spent on motor activity and play, this was true for both periods. The only minor change over time that occurred was a small increase in the therapy time spent with carrying (p=0.042).

DISCUSSION

Our study indicated changes in PPT during the last decade. Sharing of information increased, with more information exchange, provision of feedback and education by means of a combination of training and coaching. The observed changes fit into caregivers needs for sharing information with professionals.[26,27] Interestingly, the type of neuromotor actions remained largely stable over time.

Both communication and educational actions towards the caregiver became more specific over time, i.e., not specified actions were partially replaced by caregiver training and coaching. It reflects more involvement of the caregivers and may indicate the intention to implement a family centred approach, with partnership with family members.[10] Our findings suggest that family involvement increased, but probably did not yet reach a full level of equal relationship, as the educational actions showed that time spent on training was much higher than the time spent on coaching and that the type of instruction was

most often strict. However, time spent on giving hints increased indicating that the type of communication changed.

We expected a decrease in hands-on techniques - i.e., neuromotor actions in the form of facilitation, sensory experience or passive experience - over time. Yet, appliance of neuromotor actions remained largely stable over time. The absence of changes in neuromotor actions may be explained by the higher number of infants with severe brain lesions in the L2M-project than in the VIP-project. Theoretically, it is conceivable that infants who are neurologically more affected and whose motor repertoire and possibilities are more restricted trigger therapists to use more often hands-on techniques. This in turn may have occluded a decrease in the application of hands-on techniques. However, our data indicated that the amount of time spent on hands-on techniques was similar for children diagnosed with CP and those without this diagnosis, which does not support this idea. As hands-on techniques are mainly focused on body functions and structures, the absence of a change in those actions suggests that we did not find the expected shift in neuromotor actions from body functions and structures towards activities and participation. Nevertheless, a minor shift towards activities and participation may be observed in the increase in time spent on daily activities like carrying, and the decrease in time spent on transitions. Moreover, in prone position an increase in the time spent on the caregivers body was observed, and a decrease in the time spent in prone across the caregivers or therapist's leg. These two changes may suggest a more affective and less technical approach of applying neuromotor techniques.

A major strength of our study is the detailed quantification of PPT-contents. To our knowledge, our study is the first in comparing contents of PPT-interventions over time. Contents of interventions in non-pharmacological health care are in general poorly reported.[28] In pediatric rehabilitation, recently an instrument has been developed to evaluate whether interventions for children with physical disabilities provide what they are supposed to do, the Pediatric Rehabilitation Observational Measure of Fidelity, by scoring frequencies.[29] In our opinion, our analyses with durations of PPT-actions describe more precisely the contents of PPT. Subjective interpretation was ruled out as far as possible, by providing a detailed protocol. Analyses were performed by two independent blinded observers, who had a good to excellent interobserver reliability, enlarging opportunities for replicability. Unfortunately, the videos were not assessed in random order, but sequentially. Yet, the fact that we did not find the motor action trend that we expected suggests that the analyses were relatively free from bias. Another limitation of the study is the small size of the samples, which may have resulted in underreporting of significant changes in less frequently occurring PPT-actions. Our study deliberately explored differences in many variables to pick up current trends, with the probability of chance capitalization. This implies that our results should be interpreted with caution; they call for reproduction in other studies. The different

inclusion criteria of both projects is another limitation: infants in the L2M-project had more often brain lesions and CP than those in the VIP-project. The higher proportion of CP in the L2M-project did however not explain the changes in PPT-actions over time. Because both intervention programs have been studied in the Netherlands, generalizability to other countries may be limited.

CONCLUSIONS

Our study sheds light on the contents and implementation of PPT, which is a prerequisite for the understanding of effective working components.[30] Moreover, insight in current interventions may help to develop and implement new interventions. The PPT community is aware that PPT is changing, probably as the result of developing insights in pediatric and rehabilitation care. Our study indicated that family involvement increased over time, signaling advances in the implementation of family centred care. However, we did not find a decrease over time in hands-on techniques, i.e., the neuromotor actions applied did not reflect a change in therapy focus from body functions and structures towards activities and participation. This means that the observed changes in our study sometimes corresponded to novel insights and theories, sometimes they did not. Thus, our findings disclose a gap between theory and daily practice. Awareness of this gap will facilitate the process of gap closure, so that in future interventions practice will match theory. Concordance between theory and practice is a cornerstone of the house of evidence based PPT interventions.

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APPENDIX

THE GRONINGEN OBSERVER PROTOCOL (GOP 2.0)

A standardized observation protocol for the classification of pediatric physical therapy actions

A. DEPENDENT VARIABLES

A.1 NEUROMOTOR ACTIONS

1.1 Behaviors

1.1.1 Facilitation techniques

All therapeutic hands-on actions of the physical therapist or caregiver aimed at guidance of movement or maintenance of the infant's posture by gently placing the hands on specific parts of the infant's body, thus providing the infant with sensorimotor experience and controlling movement output. Note that if the therapists also applies constraint of the best arm during facilitation, scoring of facilitation continues (i.e., it is not interrupted by 'constraint').

Modifier group:
Type of facilitation

1.1.2 Reflex locomotion

According to Vojta holding and pressure point techniques aim to provoke reflex locomotion. These techniques may be observed in two major forms: a) 'pure' Vojta like, i.e., consisting of actions that aim to fixate the infant in a defined starting position (holding) which may be followed by application of pressure on defined points of the body (pressure points). b) Vojta pressure point techniques which are applied in combination with handling.

Examples of holding:
- Supine, side lying, prone.
- Head turned with an arm and/or leg in a seemingly unnatural position.

Examples of pressure points:
- Points on the head, around the mouth, around the shoulder, elbow or wrist.
- Points on the thorax or pelvis.
- Points around the hip, knee and ankle.

Modifier group:
Type of reflex locomotion

1.1.3 & 1.1.4 Sensory experience; point & state event
All tactile and vestibular stimulation given to the infant during treatment – *without* the aim of facilitation, tapping, or passive motor experience. Sensory events are only scored when they are explicitly provided as a sensory stimulus. This implies that other activities involving sensory experience, such as spontaneous motility, being dressed or undressed, or being repositioned a few centimeters in order to obtain a better camera view, are not scored as sensory experience.

Examples of concrete PT/caregiver actions:
- Touching skin with toy.
- Touching to comfort or praise the infant.

Modifier group:
Aim of sensory experience

1.1.5 Passive motor experience
All handling techniques induced by the PT or the caregiver in which no activity of the infant is required in the performance of the actions.

Examples of concrete PT/caregiver actions:
- Passive movements of arms and/or legs.
- Repetitive movements of the upper arm towards (frontal) support surface.

1.1.6 Self-produced motor Behavior (SPMB), no interference with PT/CG
All actions during which the infant is given ample opportunities to explore toys or other aspects of the environment or his body, without interference from PT or caregiver.

Examples of concrete PT/caregiver actions:
- Placing an infant activity play center over the infant and letting the infant explore the effect of movements of arms, hands, legs, and feet. Note that this implies that the infant plays by itself and that nobody interferes or joins in, e.g., by shaking one of the rattles of the activity center. If the latter occurs CSPMB is scored.
- Infant is given opportunity for spontaneous exploration with or without toy.
- Postural challenges, infant spontaneously explores postural capacities.

1.1.7 SPMB in combination with constraint of one upper limb

All actions during with the infant is given ample opportunities to explore toys or other aspects of the environment or his body while one upper limb, i.e., the best performing limb, is being restrained to participate by a caregiver, PT or by a device such as a sling, towel or mitten.

When SPMB in combination with a constraint (SPMB+) is combined with a facilitation-technique, SPMB+ will change into facilitation when the constraint lasts for more than 10 seconds.

Modifier-group:
Type of constraint

1.1.8 Challenged to SPMB (CSPMB), infant is allowed to continue activity by him/herself

All actions in which the infant is challenged by toys or the face of the PT or caregiver to experience a variety of motor activity that is continued by the infant her/himself. Note that the neuromotor action CSPMB changes into 'Self-produced motor Behavior' if PT/CG has not renewed the challenge within an interval of 20 seconds. However, if in the latter case 'SPMB' lasts less than 10 seconds before it changes into challenging again, CSPMB is not interrupted by SPMB but continued.

Modifier-groups:
1. *Variation*
2. *Extent of challenge*

1.1.9 CSPMB in combination with constraint of upper limb, infant is allowed to continue by him/herself

All actions in which the infant is challenged by toys or the face of the caregiver to experience a variety of motor activity that is continued by the infant her/himself while one upper limb, i.e., the best performing limb, is being restrained to participate by a caregiver or by a device such as a sling, towel or mitten.

Modifier-groups:
1. *Variation*
2. *Type of constraint upper limb*
3. *Extent of challenge*

1.1.10 CSPMB, activity flows over into or is combined with facilitation, sensory or passive experience

All actions in which the infant is challenged by toys or the face of the PT or caregiver to experience a variety of motor activity that is followed by or combined with handling techniques, facilitation (with or without the help of support devices; pressure; tapping), sensory or passive experiences. The interval between the challenge and the handling techniques may be very short (starting virtually simultaneously) and may last maximally 20 seconds. If the time interval between challenging and therapeutic handling is longer than 20 seconds, 'CSPMB; infant is allowed to continue activity by her/himself' is scored. Note that the activity that is being challenged (for instance grasping Behavior) does not have to be directly related to the main aim of handling (for instance facilitation of rolling into prone). To indicate that a 'facilitation technique' starts while the challenge continues, in the category 'Educational actions towards the infant' an 'interference by PT/CG during treatment session' is scored as 'PT/CG corrects when infant fails'.

Modifier-groups:
1. Variation
2. Type of facilitation techniques, sensory, passive motor experience
3. Extent of challenge

1.1.11 Craniosacral therapy

Applying a gentle manual force to address somatic dysfunctions of the head and spinal cord, in particular aiming to mobilize the cranial structures. Craniosacral therapy is a hands on technique focusing on mobility in neck and spine. This aim is clear from the hand movements of the therapist.

1.1.12 Not specified neuromotor action

All therapeutic actions during the treatment session that cannot be classified into the ten defined categories.

Example:
o Changing the treatment situation.

1.2 Modifier groups

1.2.1 Type of facilitation

- *Handling:* Specific hands-on techniques to give the infant sensorimotor experience to improve the quality and repertoire of the infant's movements.

Examples of concrete PT/caregiver actions:

- In supine position or sitting: Shoulders function as key point: handling hands guide shoulders of the infant in protraction to control tone and to facilitate hand-hand contact and symmetry.
- In supine position: Proximal or distal leg functions as key point: the infant's hip is passively brought in semi-flexion while adducting the leg across the midline to facilitate head righting and rolling.
- In supine position: Pelvis functions as key point: the infant's pelvis is slightly lifted to elongate the extensor muscles of the trunk and to control tone; in this way hand-foot contact and symmetry are facilitated.
- In prone position: Shoulder functions as key point, the arms are placed in puppy position to facilitate head righting, midline orientation, and body-alignment.
- Sitting: Shoulder functions as key point: the shoulders are moved alternately forwards and backwards to dissociate and facilitate independent arm movements.

- *Pressure techniques:* All handling techniques that produce intermittent pressure to stimulate and gain control over muscle tone, posture, and movement. Pressure is scored when the observer is able to see that the hand which rests on the child exerts pressure. The presence of pressure should not be concluded on the basis of the Behavioral reaction of the child.

Examples of concrete PT/caregiver actions:

- Sitting: intermittent downward pressure on shoulders in the direction of the pelvis to facilitate extension of the trunk.
- Sitting: slight intermittent pressure movements on abdominal region in direction of the sacrum to facilitate contraction of the ventral muscles.

- *Tapping techniques, intermittent and sweep tapping*

1.2.2 Type of reflex locomotion

- Holding with pressure points
- Pressure points with handling
- Holding without pressure points
- Other

1.2.3 Aim of sensory experience

- Affective sensory experience
- Mixed affective and body awareness
- With the aim of body awareness

1.2.4 Type of constraint

- Caregiver/ PT
- Towel, mitten, etc.

1.2.5. Type of variation

During one activity variation is scored once; it represents the overall degree of variation during that activity. If the child during a specific activity is challenged to explore more than two strategies, the modifier of variation is scored as 'large' as long as 'CSPMB' continues.

- Little variation: All actions in which the infant is challenged by toys or the face of the PT or caregiver to explore one or two strategies to reach and grasp, to control posture, to roll, etc. This may also imply that the PT or caregiver presents objects in various directions, but does not provide the infant with ample opportunity to deal with the challenge.
- Large variation: All actions in which the infant is challenged by toys or the face of the PT or caregiver; the infant is challenged to explore more than two strategies to reach and grasp, to control posture, to roll, etc. This implies that the infant is offered ample time to deal with the various challenges, and that some challenges are offered multiple times.

1.2.6 Extent of challenge

- Minimal challenge (easy/too easy)
- Just at the verge of the infant's abilities (has to put some effort)

A.2 EDUCATIONAL ACTION

2. A Educational actions towards infant; Interference by PT/CG during treatment session

2.1.A Behaviors

2.1.A.1 PT/CG interferes with activities of infant

2.1.A.2 Not specified educational actions towards infant

2.2.A Modifier-groups

2.2.A.1 Type of interference

- PT/CG interrupts activities of infant after having given ample time
- PT/Caregiver interrupts activities of the infant, does not allow the infant time
- PT/Caregiver provokes reflex activity
- PT/CG corrects when infant fails

2.B EDUCATIONAL ACTION TOWARD CAREGIVER

2.1.B Behaviors

2.1.B.1 Caregiver training

All actions during which the PT instructs caregivers on how to handle the infant or how to use specific Vojta techniques with the aim being that caregivers can continue treatment strategies during daily-life activities and/or in the home environment. The PT (teacher) provides parents with references about what the therapist is doing or what a parent could do while the therapist treats the infant (hands-on).

Examples of concrete actions:

- o PT demonstrates therapeutic handling actions to caregiver.
- o PT demonstrates Vojta techniques to caregiver
- o PT demonstrates action to caregiver, variable options provided.
- o PT practices with caregivers teaching them how to continue some of the handling techniques in daily life at home.
- o PT practices with caregivers; he/she teaches caregivers how to continue some of the handling techniques in combination with some of the Vojta techniques in daily life at home
- o PT practices with caregivers; he/she teaches the caregivers how to perform reflex rolling and crawling in the home situation

2.1.B.2 Caregiver coaching

All actions during which the PT coaches the caregiver. Coaching aims to empower caregivers so that they can make their own educational decisions during daily-care activities in the home environment. The coach listens, informs, and observes (hands-off), while the caregiver is involved in daily routines with the child, including play, thereby creating a situation in which caregivers feel free to explore and discuss alternative strategies.

Examples of concrete actions:

- o PT patiently observes the parent and infant behavior.
- o PT provides a suggestion how the caregiver may challenge motor performances just at the limit of the infant's abilities.
- o PT provides a suggestion how the caregiver may provide as little postural support as possible – in order to challenge postural behavior of the infant.
- o PT observes while the caregiver tries to evoke pleasure in the infant.

2.1.B.3 Not specified educational action toward caregiver

A.3 COMMUNICATION

3.1 Behaviors

3.1.1 Information exchange

All communication between the PT and the caregiver that is related to the guidance of infant and family (includes imparting knowledge) and that is not directly related to the child's development. Impart knowledge implies communication that provides the caregiver with knowledge about the therapeutic actions that are performed.

Examples of concrete actions:
- o PT asks about the performance of an action.
- o PT explains the ins and outs of an action.
- o PT asks about understanding.
- o PT asks about ability of caregiver to perform an action; PT listens to caregiver's comments on actions.

Modifier group:
Type of exchange

3.1.2 Instruct

All communication in which the caregiver is given assignments, hints or strict directions regarding treatment strategies.

Examples of concrete actions:
- o PT assigns, gives advice what to do.
- o PT gives hints, provides a suggestion or clue in a very indirect way so that caregivers feel free to explore ample variable opportunities.
- o PT gives strict directions what to do.

Modifier group:
Type of instructing

3.1.3 Provide Feedback

All communication in which the treatment or the performances of infant and caregiver are evaluated.

Examples of concrete actions:
- o PT tells the caregiver what went right/wrong.
- o PT evaluates the procedure.
- o PT asks and listens to the opinion of the caregiver.
- o Caregiver and PT share information on infant development.

Modifier group:
Type of feedback

3.1.4 Not specified communication, e.g. communication with infant
3.1.5 No communication
No communication is scored if there is a silence for more than 5 seconds.

3.2 Modifier-groups
3.2.1 Type of exchange
- Regarding family history, NICU experiences, current situation or daily business
- Regarding principles of NDT: All communication that explains the background of the treatment strategies, including developmental education and family related items (includes imparting knowledge).

Examples of concrete actions:
- o Information on role of parents as member of the team, as co-therapist; PT informs the parent what they should or may do (extension of therapy).
- o PT explains handling in terms of typical movement patterns, typical development, posture, muscle tone, asymmetry/symmetry, and hand placing.
- o PT discusses the application of intervention strategies to daily routines in terms of handling.

- Regarding principles of VOJTA: All communication that explains the background of the treatment strategies, including developmental education and family related items (includes imparting knowledge).

Examples of concrete actions:
- o Information on role of parents as therapist in treatment according to Vojta: therapist as teacher, the PT informs the parent what to do during daytime (frequency and duration).
- o PT explains Vojta test and reflex locomotion in terms of holding the infant in a specific position, pressure on specific parts of the body, reflex rolling, reflex crawling.
- o PT discusses the frequency of application of Vojta techniques at home (e.g., number of times/day and duration).

- Regarding principles of COPCA: All communication that explains the background of the treatment strategies, including developmental education and family related items (includes imparting knowledge).

Examples of concrete actions:
- o Information on family function, individual lifestyle, family autonomy, raising children, coping with problems, role of siblings, and daily care.
- o Information on role of the coach: observing, listening, partners.
- o PT explains the need for variation, minimal support, exploration, trial and error, challenge, and patience.
- o PT explains the infant's need to explore.
- o PT explains means to stimulate speech and language development [communication].
- o PT discusses the application of the intervention to daily routines in terms of variation, exploration, motor challenge.

3.2.2 Type of instructing

Different types of instruction or rather in the way ideas are communicated can be distinguished. The distinction is based on the space of freedom created by the PT allowing the CG to discover and/or formulate own ideas and actions. Note that the *way* the information is provided does not determine the type of instruction. For example strict instructions may be phrased as a polite question.

- PT gives strict instruction on the best way to perform: only a single, explicitly formulated option is provided, e.g. "While bathing, the child should be sitting" or "Could you, please, have the child in sitting position during bathing?".
- Instruction about multiple ways to achieve best performance: more than one explicitly formulated option is provided, e.g. "While bathing, the child can either sit or lay in supine position".
- PT gives hints, provides a suggestion/clue (indirect): no explicitly formulated options are provided, the subject to be discussed is presented in an open way, encouraging the CG to generate options and ideas, e.g. "Could you think of different positions while bathing your child?".
- Not specified.

3.2.3 Type of feedback

- PT tells the caregiver what went right/wrong: only short comments without details, e.g. 'well done', 'good job'.
- PT evaluates the procedure: includes all communication on therapeutic actions and caregiving strategies which have been addressed during PT-sessions. E.g. how well the

child performs during treatment, how implementation in daily life works out or how the child reacts to different actions.
- PT asks and listens to the opinion of the caregiver: scored when the PT is interested in the CG's opinion, is interested to obtain more insight in the CG's point of view.
- Caregiver and PT share information on infant development: all information exchange involving the child's development that is not directly related to therapeutic actions or CG coaching.

A.4 POSITION

The position of the child is always scored except for situations in which the child is not visible. A new position (after a transition) starts when the child stays in the position for at least three seconds.

For exceptions and specific scorings of postures see Appendix I.

4.1 Behaviors

4.1.1. Supine	*Modifier groups:*	*1. Surface* *2. Lifting of the pelvis* *3. Adaptations*
4.1.2. Prone		
4.1.3. Side	*Modifier groups:*	*1. Surface*
4.1.4. Sitting		*2. Postural support*
4.1.5. Standing		*3. Adaptations*
4.1.6. Walking		
4.1.7. Transition	*Modifier group:*	*With or without handling*
4.1.8: Not specified position		

4.2 Modifier-groups

4.2.1.Lifting of the pelvis:
- With imposed pelvis lift
- Pelvis not lifted
- Pelvis lift not observable

4.2.2. Surface
- On flat surface
- On lap PT /CG
- On Bobath ball

- On Bobath roll
- Across leg/arm of PT/CG
- Saddle
- Maxicosi/buggy
- Baby chair
- Baby walker
- On dressing mattress
- Against upper part of CG/PT's body
- Other surface

4.2.3 Postural support:

Postural support can be offered by the CG/PT or the environment, e.g., a baby chair. Other examples of postural support by the environment are holding onto the table, leaning against the wall or leaning with one or two hand(s) on the ground.

- No postural support: PT or caregiver leaves it to the infant to adjust posture independently. "Hands-off."
- Minimal postural support: PT or caregiver provides as little support as possible in order to challenge postural Behavior of the infant performance just at the verge of the infant's abilities, The child has to "work" hard to maintain balance, which is for example visible in wobbling or swaying back and forth. The amount of support that is considered minimal is depending on the abilities of the child and varies between infants and situations. Note that if the infant is able to maintain the position itself, e.g., is able to sit independently on a flat surface, it is not possible to allude the score 'minimal' to the support provided. The latter support has to be classified as either clear or full support depending on the situation.
- Clear postural support: PT or caregiver provides support to such that minimal active involvement of the infant is required to adjust posture.
- Full postural support: PT or caregiver supports all parts of the body of the infant that play a role in postural adjustments. No active involvement of the infant is required.

4.2.4 Adaptive equipment, e.g., lying, seating, standing or walking devices

- No adaptive equipment
- Adaptive equipment

4.2.5 With or without handling

- With a handling technique: when the PT/CG changes the position of the child by using a specific handling technique ('Handling' has to be scored at the same time for 'Neuromotor action')
- Without a handling technique: when the PT/CG changes the position without using a specific technique ('Not specified neuromotor action' has to be scored at the same time for 'Neuromotor action'.)

A.5 SITUATION OF TREATMENT SESSION

The situation of the treatment is always scored except for situations in which the child is not visible.

5.1 Behaviors

5.1.1. Motor activity/play
5.1.2. Feeding
5.1.3. Bathing
5.1.4. Dressing/Undressing
5.1.5. Changing Diapers
5.1.6. Carrying
5.1.7. Not specified situation

A.6 ADDITIONAL CATEGORIES

A. Comforting

Comforting of the infant is scored when the therapeutic actions stop in order to comfort the child. When applicable the variables 'Situation of the treatment session', 'Position' and 'Neuromotor action' are scored / continue to be scored during comforting. When the child is held and cuddled to be comforted, the 'Neuromotor action' in general will be 'Sensory state event – Affective'. When the 'Neuromotor action' is not clear, 'not specified neuromotor action' is scored.

A.1 BEHAVIORS

a.1.1 No comforting
a.1.2 Comforting of the infant when infant is upset/crying/tired.

B. Interruption by operator

B.1 Behaviors

b.1.1 No interruption
b.1.2 Interruption

C. LOCOMOTION

C.1 BEHAVIORS

c.1.1. Crawling
c.1.2. Creeping
c.1.3. Bottom shuffling
c.1.4. Walking
c.1.5. Other
c.1.6. No locomotion

B. INDEPENDENT VARIABLES

Independent variables: the value of this variable is supposed not to change during the course of an observation. It gives the observer the opportunity to summarize briefly the important characteristics of the observation. Independent variables are to be scored after finishing the Observer XT in a dropdown menu.

B.1 TYPE OF SESSION (CLINICAL IMPRESSION)

Categories:

1. COPCA
2. TIP (based on NDT)
3. VOJTA
4. TIP (based on NDT) in combination with VOJTA
5. Cranio-sacral therapy
6. TIP (based on NDT) in combination with Cranio-sacral therapy
7. Constraint Induced Movement Therapy (CIMT)
8. COPCA in combination with CIMT

B.2 DRESSING

The way in which the infant is dressed during the treatment session. If the dressing situation changes during the session, score the predominant dressing situation.

Categories:
1. Dressed
2. Infant is partially dressed, wears more clothes than underwear only
3. Infant is wearing underwear only
4. Infant is undressed

B.3. FAMILY MEMBERS INVOLVED IN THE TREATMENT SESSION

The description of the family members that have an active role in the treatment session are included in scoring. This also implies that e.g. the presence of an infant twin sister of brother who does not play an active role in the session, is not scored as 'other family member present'.

Categories:
1. Mother present only
2. Father present only
3. Other adult relatives only, e.g. grandparents, aunt
4. Both caregivers but no other family members present
5. In addition to parent(s) also other family members present
6. Caregiver or caregivers present but no active role in the treatment session

B.4 ROLE OF THE CAREGIVER

The way in which the caregiver of family members are involved in the treatment session.

Categories:
1. Physical therapist performs treatment by means of handling techniques
2. PT performs treatment by means of specific Vojta techniques (holding the infant in specific 'Vojta positions' provoking reflex locomotion by pressure stimulation on specific defined points on the head, trunk or limbs).
3. PT performs treatment by means of handling in combination with Vojta techniques
4. Caregiver and physical therapist act together in handling techniques, physical therapist performs the treatment (hands on) while the caregiver guides the attention of the infant
5. Caregiver performs handling techniques. The PT instructs the caregiver how to handle.
6. PT and caregiver act together; PT trains caregiver how to perform the Vojta techniques
7. Caregiver performs the treatment by means of specific Vojta techniques
8. Caregiver performs the treatment by means of handling in combination with Vojta techniques
9. Caregiver and PT act together (hands off), caregiver is playing with the child and may provide the infant with minimal support but leaves the infant always with ample

opportunities for exploration. PT observes the caregiver-infant relationship and may give hints.
10. Caregiver is playing with the infant (hands off) and leaves the infant with ample opportunities for exploration.
11. PT is playing with infant (hands off) and leaves the infant with ample opportunities for exploration – caregiver observes
12. PT is playing with infant (hands off) and leaves the infant with ample opportunities for exploration – no specific role of caregiver

B.5. PRESENCE OF TWINS

Categories:
1. no = singleton infant
2. yes = twins

EARLY INTERVENTION IN INFANTS AT VERY HIGH RISK OF CEREBRAL PALSY

PART II

DOES PHYSIOTHERAPEUTIC INTERVENTION AFFECT MOTOR OUTCOME IN HIGH-RISK INFANTS? AN APPROACH COMBINING A RANDOMIZED CONTROLLED TRIAL AND PROCESS EVALUATION

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ABSTRACT

Aim: The aim of this study was to examine the effects of intervention in infants at risk of developmental disorders on motor outcome, as measured by the Infant Motor Profile (IMP) and using the combined approach of a randomized controlled trial and process evaluation.

Method: At a corrected age of 3 months, 46 infants (20 males, 26 females) recruited from the neonatal intensive care unit at the University Medical Centre Groningen (median birthweight 1210g, range 585–4750g; median gestational age 30wks, range 25–40wks) were included on the basis of definitely abnormal general movements. Exclusion criteria were severe congenital disorders and insufficient understanding of the Dutch language. The infants were assigned to either the family centred COPing with and CAring for Infants with Special Needs (COPCA) intervention group (n=21; 9 males, 12 females) or the traditional infant physiotherapy (TIP) intervention group (n=25; 11 males, 14 females) for a period of 3 months. Three infants assigned to the TIP group (one male, two females) did not receive physiotherapy. IMP scores were measured by blinded assessors at 3, 4, 5, 6, and 18 months. At each age, the infants were neurologically examined. Physiotherapeutic sessions at 4 and 6 months were videotaped. Quantified physiotherapeutic actions were correlated with IMP scores at 6 and 18 months.

Results: The IMP scores of both the COPCA and TIP groups before, during, and after the intervention did not differ. Some physiotherapeutic actions were associated with IMP outcomes; the associations differed for infants who developed cerebral palsy (n=10) and those who did not (n=33).

Interpretation: At randomized controlled trial level, the scores of both the TIP and COPCA groups did not differ in effect on motor outcome, as measured with the IMP. The analysis of physiotherapeutic actions revealed associations between these actions and IMP outcomes. However, the small sample size of this study precludes pertinent conclusions.

What this paper adds

- This paper shows that the family-centred COPCA programme and TIP applied for 3 months in high-risk infants had a similar effect on motor outcome, as measured with the IMP.
- This study indicates that video analyses of physiotherapeutic sessions may assist in the understanding of working mechanisms of physiotherapy.

Infants at high risk for neurodevelopmental disorders are in need of early intervention, yet at the moment it is unknown which intervention is the most successful.[1–4] In addition, current interventions primarily promote cognitive development and have little[1,2] or no[3,4] effect on motor development. Therefore, a new family-centred intervention programme, COPing with and CAring for Infants with Special Needs (COPCA) was developed with the aim of promoting family function and motor and cognitive development (Dirks T and Hadders-Algra M, personal communication 2003). COPCA is a family relationship-orientated programme that is based on (1) a focus on the family including an educational component[5,6] and (2) a motor component, based on neuronal group selection theory (NGST).[7]

The keywords in NGST are primary and secondary variability, denoting two consecutive developmental phases. Typically, both phases are characterized by the presence of a variable motor repertoire. During the phase of secondary variability the child learns by means of trial and error to adapt the various motor strategies to the specifics of the situation. During primary variability movement adaptation is not possible – motor behaviour consists of exploration of the possibilities available.[8] An early lesion of the brain may result in a reduction of the motor repertoire and in deficits in the processing of sensory information.[9] Both factors may interfere with the selection of adaptive strategies for specific tasks. The reduction of the repertoire may be associated with the absence of the best strategy typically available for a situation; hence the child has to choose between alternative non-optimal strategies. Deficits in the processing of sensory information will interfere with the learning process of adaptation, which is based on the processing of feedback of self-produced trial-and-error achievements.

Recently, an early intervention project (the Dutch Vroegtijdig Interventie Project (VIP)) was carried out to evaluate the effects of COPCA in infants at risk for developmental disorders in comparison with traditional infant physiotherapy (TIP). In the Netherlands, TIP is mostly based on the principles of neurodevelopmental treatment.[10] The VIP project has been designed with a dual approach: a randomized controlled trial (RCT) and process evaluation. The latter approach was added as it was anticipated that heterogeneity in the application of physiotherapy[11] could result in a reduction of contrast between the two interventions. For the process evaluation, two intervention sessions per infant were video recorded. Next, the physiotherapeutic actions during the interventions were quantified with the help of a standardized protocol.[11]

The major goals of the COPCA programme are strengthening family participation and strengthening functional mobility. Functional mobility may be improved by influencing motor function at the impairment level, as defined by the International Classification of Functioning, Disability and Health for Children and Youth. As the motor domain of COPCA is based on the principles of NGST, the primary measure of the VIP project was motor outcome measured with the Infant Motor Profile (IMP), a recently developed instrument based on NGST.[12,13]

The present study aimed to unravel whether COPCA intervention and COPCA-related goals influence motor function at impairment level. To this end, we used the IMP to evaluate motor development of the 46 infants included in the VIP project. We were interested particularly in whether COPCA intervention resulted in an increased motor repertoire and a better capacity for adaptive selection. In line with the design of the study, first we evaluated the effects of the two interventions on IMP scores at RCT level and then we assessed the associations between physiotherapeutic actions and IMP scores.

METHOD

Participants

Of the participants of the VIP study admitted to the neonatal intensive care unit of the University Medical Centre Groningen between March 2003 and May 2005, 46 were included in the project at a corrected age of 3 months (20 males, 26 females; median gestational age 30wks, range 25–40wks; median birthweight 1210g, range 585–4750g) on the basis of presenting with definitely abnormal general movements at a corrected age of 10 weeks, indicating a high risk of developmental disorders.[14,15] Exclusion criteria were severe congenital disorders and caregivers' insufficient understanding of the Dutch language. The infants were randomly assigned into two groups, the COPCA group (n=21; 9 males, 12 females) and the TIP group (n=25; 11 males, 14 females). On paediatrician's advice, three infants in the TIP-group (one male, two females) did not receive physiotherapy. The flow chart of selection of infants included in the study is presented in Figure 1. The groups did not differ for most characteristics, except for maternal education, which was significantly higher in the TIP group (Table 1). The trial was approved by the medical ethics committee of the University Medical Centre Groningen.

Intervention

The intervention period was between 3 and 6 months corrected age. COPCA was provided twice a week in the home situation. The frequency and location of TIP intervention depended on the paediatrician's advice. Three comparison infants did not receive physiotherapy. After this intervention period, the paediatrician decided whether to continue intervention and which type of intervention to use for the infants in both groups. As a result, 36 infants received physiotherapy between the ages of 6 and 18 months. In the COPCA group, 15 infants continued with physiotherapy (12 with COPCA (mean number of sessions 6) and three with TIP as no COPCA coach was available (mean number of sessions 33)), four infants stopped receiving physiotherapy, and data were missing for two infants.

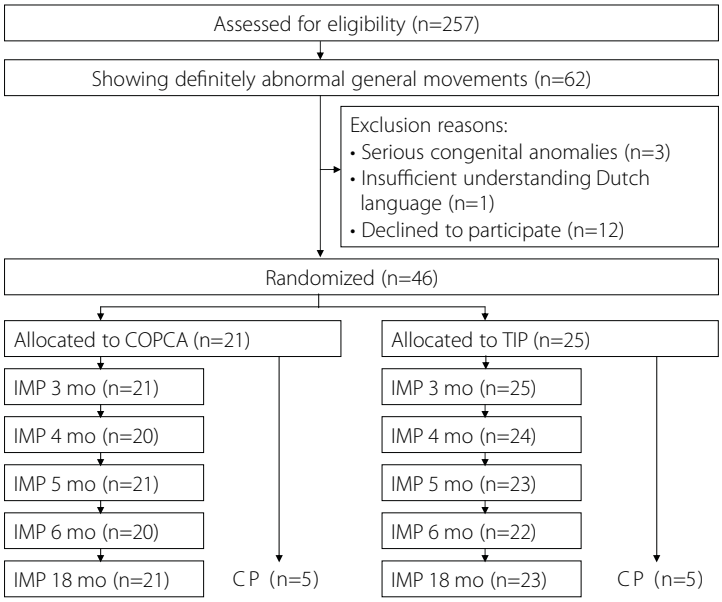

Figure 1: Flow diagram of participants of the Vroegtijdig Interventie Project (VIP). COPCA, COPing with and CAring for infants with special needs; TIP, traditional infant physiotherapy; IMP, Infant Motor Profile.

Table 1: Group characteristics for both the COPing with and CAring for infants with Special Needs (COPCA) and traditional infant physiotherapy (TIP)

	COPCA (n=21)	TIP (n=25)
Sex (n)		
- Male	9 (43%)	11 (44%)
- Female	12 (57%)	14 (56%)
Gestational age (n)		
- Preterm	19 (91%)	23 (92%)
- Term	2 (10%)	2 (8%)
Birthweight (grams)		
- Median	1210	1143
- Range	585-4750	635-3460
Brain lesion[a]		
- No severe brain lesion	18	22
- IVH grade 4 or PVL grade 3-4	3	3
Maternal education[b]		
- Low or middle	19 (90%)	14 (56%)
- High	2 (10%)	11 (44%)

Levels of education: low, primary education/junior vocational training; middle, secondary education/senior vocational training; high, university education/vocational colleges.

[a] IVH (Intraventricular haemorrhage), according to Volpe[17]; PVL (Periventricular leukomalacia), grading according to De Vries et al[18].

[b]Mann-Whitney U-test: p=0.013

In the TIP group, 21 infants continued with physiotherapy (all TIP; mean number of sessions 14), two infants did not receive physiotherapy between the ages of 6 and 18 months, and data were missing for two infants.

Measurements

The IMP assessment was carried out by one of the authors (CB-H) and Dr Victorine de Graaf-Peters, who were blinded to group status as part of an extensive assessment battery at 3, 4, 5, 6, and 18 months corrected age. The IMP is based on NGST. It is a video-based instrument used to evaluate spontaneous motor behaviour, applicable for infants from the age of 3 months until they have some months of walking experience. The IMP consists of 80 items organized into five domains: variation (i.e. the size of movement repertoire), variability (i.e. the ability to select motor strategies), symmetry, fluency, and performance. Items are scored in different positions, such as supine, prone, and sitting, and during reaching and grasping. The IMP results in five domain scores and a total score consisting of the mean of the domain scores. The reliability of the IMP is good.[12,13] The scoring of each IMP video was performed by two pairs of assessors blind to group allocation and previous IMP scores, either MD-M and MH-A, or TH and MH-A. Each person in the couple independently scored IMP items. In case of disagreement, scores were discussed until a consensus was reached. Interscorer agreement, assessed for TH and MH-A, was satisfactory for total IMP scores and domain scores, with intraclass correlation coefficients varying from 0.541 (domain symmetry) through 0.784 (domain variability), 0.799 (domain variation), 0.921 (domain fluency), and 0.944 (total IMP-score) to 0.995 (performance).

At 3 months, IMP data were available for all 46 infants. At 4, 5, and 18 months, the IMP data for two infants were missing, and at 6 months the IMP data for four infants were missing. Missing data were due to parental holidays or technical problems with the video.

All infants were neurologically examined with age-specific assessment techniques by one of the authors (CB-H) and Dr Victorine de Graaf-Peters, who were blinded to group allocation. Thus, the Touwen Infant Neurological Examination was applied at 3, 4, 5, and 6 months and the Hempel assessment at 18 months. At 18 months of age, the infants were classified as having either a normal neurological condition, simple minor neurological dysfunction, complex minor neurological dysfunction, or neurologically abnormal (development) – that is, the presence of a clear neurological syndrome such as cerebral palsy (CP). The reliability of the Hempel examination is satisfactory, but information on predictive validity is lacking.[16] For the two infants with missing IMP data at 18 months, the neurological examination was also missing. Therefore, it is unknown whether these two infants developed CP or not. One of them had no IMP assessment at 5 months. However, the other infants with missing IMP data did not develop CP.

Table 2: Total relative time spent on physiotherapeutic actions for infants with and without cerebral palsy (CP) for the family-centred COPing with and Caring for infants with Special Needs (COPCA) programme and traditional infant physiotherapy (TIP) interventions.

	COPCA, median (range)		TIP, median (range)	
	CP (n=5)	No CP (n=16)	CP (n=5)	No CP (n=16)
Facilitation	4,9 (0-9)	3,0 (0-43)	29 (14-55)	31 (12-64)
o Handling	1,8 (0-3)	0,9 (0-32)	14 (8-23)	17 (5-48)
o Pressure	0,0 (0-0)	0,0 (0-8)	4,3 (1-17)	7,7 (1-18)
o Transition	2,0 (0-3)	1,7 (0-5)	2,2 (2-11)	3,3 (1-16)
o Support device	0,0 (0-5)	0,0 (0-1)	0,0 (0-2)	0 (0-1)
Sensory experience	3,2 (1-11)	1,8 (0-5)	5,2 (3-7)	5,9 (0-23)
Passive experience	0,0 (0-2)	0,0 (0-1)	5,1 (0-11)	1,9 (0-13)
Spontaneous motor behaviour – no interference	32 (2-55)	45 (13-70)	25 (9-43)	17 (1-62)
Challenged to self produced motor behaviour – overflow into handling	0,3 (0-4)	0,0 (0-6)	4,4 (2-10)	7,4 (2-30)
o Little variation	0,2 (0-4)	0,0 (0-6)	3,5 (2-8)	5,2 (2-30)
o Large variation	0,1 (0-1)	0,0 (0-4)	0,0 (0-2)	0,2 (0-13)
Challenged to self produced motor behaviour – action continued by the infant	37 (18-61)	35 (19-61)	14 (4-30)	13 (2-35)
o Little variation	14 (3-25)	6,7 (0-34)	13 (4-24)	10 (2-21)
o Large variation	30 (5-36)	25 (3-42)	0,6 (0-7)	1,8 (0-22)
Family education	17 (8-32)	18 (0-37)	3,0 (2-15)	5,4 (1-30)
o Caregiver coaching	14 (7-31)	14 (0-36)	0,0 (0-1)	0,0 (0-0)
o Caregiver interferes with infant's actions	1,2 (0-3)	0,5 (0-3)	1,5 (0-1)	0,0 (0-1)
o PT guides infant	0,0 (0-0)	0,0 (0-7)	1,3 (0-2)	0,0 (0-7)
o PT interferes with infant's actions	0,3 (0-1)	0,3 (0-8)	1,8 (1-4)	2,2 (0-21)
o PT gives caregiver training	0,5 (0-2)	0,1 (0-1)	0,9 (0-8)	0,1 (0-5)
Communication	21 (8-29)	15 (0-43)	14 (9-48)	14 (1-40)
Contents of information				
o Handling	0,0 (0-0)	0,0 (0-0)	1,9 (0-7)	0,8 (0-10)
o Variation	2,0 (0-4)	1,0 (0-7)	0,0 (0-0)	0 (0-1)
o ADL handling	0,0 (0-0)	0,0 (0-0)	0,0 (0-5)	0 (0-5)
o ADL variation	0,0 (0-0)	0,7 (0-4)	0,0 (0-0)	0,0 (0-0)
Provide feedback	7,6 (1-11)	3,8 (0-13)	5,3 (3-6)	3,1 (0-17)
Information exchange	1,0 (0-6)	2,0 (0-26)	9,5 (1-19)	2 (0-22)
Instruct				
o Assign	0,1 (0-9)	1,2 (0-9)	0,1 (0-3)	0,2 (0-2)
o Give Hints	4,9 (3-6)	1,5 (0-7)	0,0 (0-1)	0,0 (0-3)
Impart knowledge	1,5 (0-4)	2,4 (0-11)	2,3 (1-12)	2,4 (0-8)
Not specified actions	4,6 (2-6)	2,9 (1-7)	5,1 (3-8)	3,0 (0-11)

Table 2: Total relative time spent on physiotherapeutic actions for infants with and without cerebral palsy (CP) for the family-centred COPing with and Caring for infants with Special Needs (COPCA) programme and traditional infant physiotherapy (TIP) interventions. (Continued)

	COPCA, median (range)		TIP, median (range)	
	CP (n=5)	No CP (n=16)	CP (n=5)	No CP (n=16)
Amount of support				
o No support	2,4 (0-22)	16 (7-28)	15 (5-23)	17 (2-40)
o Minimal support	9,2 (3-41)	21 (3-41)	4,5 (1-8)	4,3 (1-18)
o Clear support	18 (5-37)	17 (1-23)	12 (7-22)	21 (2-37)
o Full support	23 (3-42)	3,8 (0-24)	16 (4-47)	5,6 (0-30)
Imposed anteflexion of the pelvis				
o With anteflexion	0,0 (0-3)	0,0 (0-21)	13 (3-40)	15 (0-30)
o No anteflexion	39 (12-46)	41 (16-63)	32 (13-43)	35 (12-56)

Physiotherapeutic sessions were video recorded at 4 and 6 months corrected age. Video recordings were missing for three infants at 4 months (one from the TIP group; two from the COPCA group; none developed CP) and three infants at 6 months (one from the TIP group; two from the COPCA group; one developed CP) owing to logistical reasons (Dirks T, Blauw-Hospers CH, Hulshof LJ, Hadders-Algra M, personal communication 2010). Physiotherapeutic actions were classified by Lily Hulshof, a medical student undertaking a masters project and one of the authors (CB-H) according to the protocol developed by Blauw-Hospers et al.[11] using the computer programme Observer (Noldus, Wageningen, the Netherlands). In the protocol, all physiotherapeutic actions are defined. We recently reported that the inter- and intra-assessor agreement on assessment with the protocol are satisfactory: the intraclass coefficient of the relative duration of actions ranged from 0.76 to 1.00 for interassessor agreement and from 0.69 to 0.99 for intra-assessor agreement.[11] The assessors were blinded to the infants' group allocation, but it was inevitable that they got an impression of the type of intervention during classification. Examples of the physiotherapeutic actions described in the protocol are physiotherapeutic facilitation techniques (such as handling), spontaneous motor behaviour, communication actions, family involvement, and educational actions (see also Table 2). Observed physiotherapeutic actions were scored with a start and stop button, allowing for the calculation of total relative time spent on these actions. The actions for the two interventions differed substantially and, at 4 months, were largely comparable to those at 6 months (Dirks T, Blauw-Hospers CH, Hulshof LJ, Hadders-Algra M, personal communication 2010; Table 2). This was true also for the subgroup of children with CP (data not presented). Assuming that the two measurements at 4 and 6 months represented the actions during the intervention period better than a single measurement, we used the average of the 4- and 6-month values of the physiotherapeutic actions in the correlations with the IMP scores.

Statistical analyses

The power calculation was based on the total IMP score.[12] It indicated that two groups of 19 infants resulted in a power of 80% (a=0.05) to detect a clinically relevant change of 7.5 points (SD 8.2). Therefore, we aimed at recruiting at least 40 infants in order to be able to cope with attrition and loss of data. Statistical analyses were performed using the computer package SPSS (version 15.0; SPSS Inc., Chicago, IL, USA). Owing to the abnormal distribution of the data, non-parametric tests (Mann–Whitney U test) were used for intergroup comparisons. Differences with a p value of <0.05 were considered statistically significant.

Physiotherapeutic actions were correlated with the IMP scores at 6 months corrected age (i.e. at the end of the intervention period) and IMP scores at 18 months' corrected age (i.e. 1y after the end of the intervention) using bivariate correlations. Partial correlations were carried out using the control variables baseline IMP score, severe brain lesion (intraventricular haemorrhage grade 4[17] or periventricular leukomalacia grade 3 or 4[18]) and maternal education. Because of the probability of chance capitalization, correlations with a p value <0.01 were considered statistically significant.

In order to assess the effect of intervention between 6 and 18 months, we calculated relative IMP changes by dividing the differences in IMP scores between 6 and 18 months by the IMP scores at 6 months. The relative IMP changes were correlated with the number of physiotherapeutic sessions that the children received between 6 and 18 months.

RESULTS

IMP scores in the two intervention groups

Preliminary data analysis indicated that at 3 to 6 months infants with significant developmental problems scored too high on the domain variability. The overestimation was caused by inherent features of this IMP domain. First, items can only be assessed when a function is present. At an early age, the variability score is based on the performance of the head. The large majority of infants, including infants with neurological dysfunction, are able to make adaptive head movements. The items on adaptive selection of head movements are affected only in children with very severe disorders, resulting in lower scores in the domain variability. If other functions show a delayed development due to nervous dysfunction, the variability score is based only on head movement, which often results in an inappropriately high domain score. We therefore excluded the domain variability from the data analysis at 3 to 6 months. This implies that total IMP scores at 3 to 6 months were based on four instead of five domains.

The IMP domain scores and the total IMP score of the two intervention groups were similar at baseline at 3 months (Figure 2). Likewise, IMP domain scores and total IMP scores of the two groups did not differ during the intervention, immediately after the intervention

(at 6 mo corrected age), and 1 year after the intervention (18 mo corrected age; Figure 2). The similarity of IMP scores in the two intervention groups was also found in the subgroups of children with and without CP. The relative IMP changes between 6 and 18 months were not associated with the number of physiotherapeutic intervention sessions between 6 and 18 months.

Neurological outcome

At 18 months, 10 infants were diagnosed with CP; five in the COPCA group and five in the TIP group. All had a spastic form of CP: two unilateral and eight bilateral. The Gross Motor Function Classification System levels[19] ranged from levels I to V: one infant was classified as level I (COPCA group), five as level II (two from the COPCA group; three from the TIP group), three as level III (one from the COPCA group; two from the TIP group), and one as level V (COPCA group). The last child also had significant additional impairments (visual impairment and epilepsy). Twenty-nine infants developed complex minor neurological dysfunction (13 from the COPCA group; 16 from the TIP group) and five developed simple minor neurological dysfunction (three from the COPCA group; two from the TIP group). Two infants had not been reassessed at 18 months (two from the TIP group).

Physiotherapeutic actions and IMP scores

Preliminary analyses indicated that correlations between physiotherapeutic actions and IMP scores differed for infants who developed CP (n=10) and those who did not (n=34; Table 2). The differences suggested that specific analyses for the two subgroups were required.

In infants with CP, physiotherapeutic actions were not related to IMP scores at 6 months. However, some physiotherapeutic actions were related to IMP scores at 18 months. Two COPCA-related actions were associated with positive outcome. First, the time spent during physiotherapy with caregiver coaching showed a positive correlation with the IMP domain variability (r=0.920; p=0.009). Coaching was defined as 'aiming to empower caregivers so that they can make their own decisions during daily-care activities in the home environment. The coach listens, informs, and observes (hands off), while the caregiver is involved in daily routines with the child, including play, thereby creating a situation in which the caregivers feel free to explore and discuss alternative strategies.' Second, time spent with challenging the infant to self-produced motor behaviour, continued by the infant with little variation, showed a positive correlation with the total IMP score (r=0.924; p=0.008). The total time spent with challenging the infant to self-produced motor behaviour (with little and large variation) just failed to show a significant association with the total IMP score (r=0.914; p=0.011). Finally, time spent with the TIP-related action sensory experience showed a negative correlation with the total IMP score (r=-0.969; p=0.001).

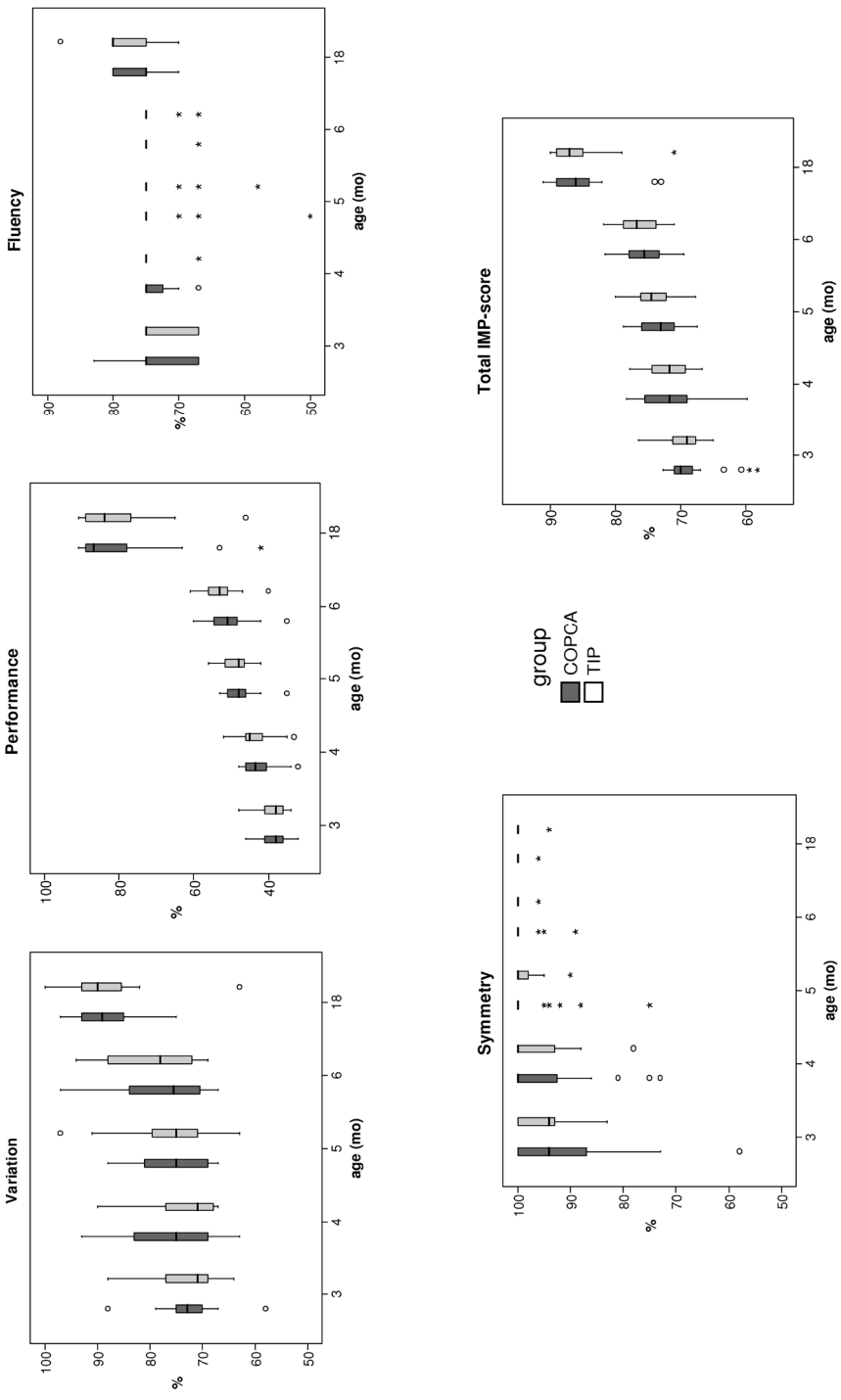

Figure 2: Infant Motor Profile scores for COPing with and CAring for Infants with Special Needs (COPCA) programme and Traditional Infant Physiotherapy (TIP) at the ages of 3, 4, 5, 6 and 18 months. Figures are boxplots. Straight lines mean that interquartiles and mean are the same.

In the children without CP, only a significantly negative correlation between the action 'instruct by means of assigning' (i.e. the physiotherapist advises the caregivers what to do) and the domain fluency (r=-0.601; p=0.003) at 6 months was found.

DISCUSSION

At the level of the RCT, we found no difference in motor outcome between the two intervention groups. But the a priori scheduled analysis of the contents of physiotherapeutic sessions indicated that some COPCA-based physiotherapeutic actions in children with CP were related to better IMP scores. In contrast, some TIP actions were associated with worse IMP scores.

It may be considered a limitation of the study that only about a quarter of the infants developed CP, and the small size of the subsample makes it hard to draw conclusions regarding the effect of intervention in children with CP. Nevertheless, it is interesting that most significant associations between physiotherapeutic actions and outcome were found in this small subsample. The children who did not develop CP also showed neurological dysfunction in early infancy and, in general, also at the age of 18 months. Children with minor forms of neurological dysfunction may also profit from early intervention (Blauw-Hospers CH, Dirks T, Hulshof LJ, Bos AF, Hadders-AlgraM, personal communication 2010).

The fact that the IMP is a recently developed instrument is also a possible limitation. The present study indicated that the IMP domain variability cannot be used in infants at high risk for developmental disorders below and including 6 months' corrected age. On the other hand, the application of the IMP, which addresses the profile of infant motor functions, may also be regarded as a strength of the study. The IMP does not only provide information on more traditional aspects of motor behaviour, such as performance, symmetry, and movement fluency, but also on variation and variability. The last two domains are based on NGST,[8,9] the theoretical basis of the motor goals of the COPCA programme. It may, of course, be argued that we had a bias favouring the effect of COPCA and that this may have affected IMP scores. However, we tried to avoid this as much as possible by having different teams of assessors for the analyses of the physiotherapeutic actions and the IMP scores. In addition, all assessors were blinded to group allocation. The uniform neuromotor condition at the onset of intervention, that is, the presence of definitely abnormal general movements, enabled us to compare groups with similar clinical presentations at the onset of the intervention.

Systematic reviews and meta-analyses indicate that early intervention in high-risk infants has little or no effect on motor development. Some studies have indicated an effect on cognitive development, for instance the Infant Health and Developmental Program[20] has been associated with better outcomes at 24 and 36 months. Indeed, we found no effect on

motor outcome at the level of the RCT in the VIP project, nor on secondary outcomes such as the Alberta Infant Motor Scales and the Paediatric Evaluation of Disability Inventory, but a minimal cognitive advantage was found for the COPCA group (Blauw-Hospers CH, Dirks T, Hulshof LJ, Bos AF, Hadders-Algra M, personal communication 2010). The limited effect on motor development may be based on neurobiological constraints, as animal studies have indicated that intervention after a lesion of the brain at an early age has considerably less effect on motor development than on cognitive outcome.[21] This implies that there are limitations to finding interventions that promote measurable functional changes in young children with evolving motor and developmental disabilities.

Another explanation for the absence of differences in outcome between the COPCA and the TIP group may be the heterogeneity in interventions, which makes it difficult to compare interventions at RCT level.[11,22] The detailed analyses of physiotherapeutic sessions enabled us to cope with the heterogeneity in paediatric physiotherapy[11] (Dirks T, Blauw-Hospers CH, Hulshof LJ, Hadders-Algra M, personal communication 2010). It revealed that time spent on physiotherapeutic actions was associated with motor outcome. We would like to stress that the relations found are associations and not causations. We controlled for factors that may have affected the associations, such as baseline IMP scores, severity of brain lesion, and maternal education, but it is conceivable that other aspects of infant–therapist interaction may also play a role. An ideal study design to evaluate the effects of COPCA would consist of an RCT in which COPCA would be compared with no intervention, but such a design is ethically unjustified.

The process analysis indicated that communication items were associated with motor outcome, that is, COPCA-related coaching was associated with better outcome and TIP-related instructing, by means of advising the caregivers, with worse outcome. Coaching aims to empower caregivers so that they can make their own decisions on what to do during daily care activities in the home (Dirks T, Blauw-Hospers CH, Hulshof LJ, Hadders-Algra M, personal communication 2010). In medical professions, the role of patients and professionals is shifting from a more paternalistic approach to a more 'shared decision-making' approach and a full family-orientated approach (Dirks T, Blauw-Hospers CH, Hulshof LJ, Hadders-Algra M, personal communication 2010). When clients are more involved in treatment and are in charge of decisionmaking, this could influence their sense of personal control, satisfaction with treatment, compliance, transfer into the daily routine of disease management, and, consequently, better outcomes.[23,24] The approach of coaching reflects an attitude of 'shared decision' or, even more so, 'parent-made decision', whereas the approach 'instructing by means of assigning' could be regarded as a sign of paternalism. In COPCA, coaching creates a process in which the family's needs and wants are translated into regular solutions on how to cope with the problems related to the infant's development from the family's own perspective, thereby creating a situation in which caregivers feel free to explore

and discuss alternative strategies (Dirks T, Blauw-Hospers CH, Hulshof LJ, Hadders-Algra M, personal communication 2010). Coaching in COPCA also includes the provision of hints on how infant motor development may be promoted during family routines. Hints deal with how parents may challenge children's motor actions at the limit of their abilities and how to vary their motor activities. Interestingly, COPCA-related actions, with which the families became acquainted between 3 and 6 months corrected age, were not related to outcome at 6 months, but first with outcome at 18 months corrected age. This suggests indeed that the families had integrated into daily life certain strategies that fitted their own routines, thereby ensuring the provision of daily opportunities for the child to practise motor skills.

TIP includes optimization and normalization of functional activities. Interestingly, we found no positive associations between actions aiming at optimizing movement quality, such as handling techniques, and motor outcome. In contrast, the TIP action sensory experience was associated with worse outcome at 18 months. Sensory experience, such as massage, may be associated with accelerated development.[25] In our study,sensory experience was defined as tactile and vestibular stimulation of the infant with the aim of promotion of body awareness,[11] which means that it involved passive experience. Passive experience is known to be associated with considerably less cortical activity than active motor experience.[26]

Our findings are in line with those of Palmer et al.,[27] who reported that developmental outcome was better in children who received an infant stimulation programme than in children who had received intervention according to neurodevelopmental treatment. Also, the analysis of the associations between physiotherapeutic actions and secondary motor outcomes revealed that actions that were characteristic for COPCA were associated with better outcome at 18 months, and those that were characteristic for TIP, such as handling, were associated with worse outcome (Blauw-Hospers CH, Dirks T, Hulshof LJ, Bos AF, Hadders-Algra M, personal communication 2010).

In COPCA, motor goals are based on the NGST. They aim at enhancing the infant's motor repertoire (variation) and at the promotion of the selection of adaptive strategies (variability). We found associations between COPCA-based physiotherapeutic actions and variability in IMP scores (and also the total IMP score), but none between physiotherapeutic actions and variation. This suggests that it is harder to influence the size of the motor repertoire than the ability to select from the repertoire.

CONCLUSION

The present study suggests that elements characteristic of the COPCA approach, such as caregiver coaching and challenging the infant to self-produced motor activity, are associated with improved motor development and, in particular, with an improved ability

to select the most adaptive strategy in a specific situation. The limited size of the present study stresses the need for more studies that evaluate the effectiveness of COPCA and other intervention programmes involving larger samples of children with CP. Sample sizes of such studies depend on the type of measure used to evaluate outcome.

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LEARN 2 MOVE 0-2 YEARS: EFFECTS OF A NEW INTERVENTION PROGRAM IN INFANTS AT VERY HIGH RISK FOR CEREBRAL PALSY; A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background: It is widely accepted that infants at risk for cerebral palsy need paediatric physiotherapy. However, there is little evidence for the efficacy of physiotherapeutic intervention. Recently, a new intervention program, COPCA (Coping with and Caring for infants with special needs - a family centered program), was developed. COPCA has educational and motor goals. A previous study indicated that the COPCA-approach is associated with better developmental outcomes for infants at high risk for developmental disorders. LEARN 2 MOVE 0-2 years evaluates the efficacy and the working mechanisms of the COPCA program in infants at very high risk for cerebral palsy in comparison to the efficacy of traditional infant physiotherapy in a randomized controlled trial. The objective is to evaluate the effects of both intervention programs on motor, cognitive and daily functioning of the child and the family and to get insight in the working elements of early intervention methods.

Methods/design: Infants are included at the corrected age of 1 to 9 months and randomized into a group receiving COPCA and a group receiving traditional infant physiotherapy. Both interventions are given once a week during one year. Measurements are performed at baseline, during and after the intervention period and at the corrected age of 21 months. Primary outcome of the study is the Infant Motor Profile, a qualitative evaluation instrument of motor behaviour in infancy. Secondary measurements focus on activities and participation, body functions and structures, family functioning, quality of life and working mechanisms. To cope with the heterogeneity in physiotherapy, physiotherapeutic sessions are video-recorded three times (baseline, after 6 months and at the end of the intervention period). Physiotherapeutic actions will be quantified and related to outcome.

Discussion: LEARN 2 MOVE 0-2 years evaluates and explores the effects of COPCA and TIP. Whatever the outcome of the project, it will improve our understanding of early intervention in children with cerebral palsy. Such knowledge is a prerequisite for tailor-made guidance of children with CP and their families.

Trial registration: The trial is registered under NTR1428.

BACKGROUND

Cerebral Palsy (CP) is the most common cause of physical disability in pediatric rehabilitation.[1] Little evidence exists that current interventions are effective in optimizing daily life functioning.[2] LEARN 2 MOVE 0-2 (L2M 0-2) is part of the Dutch national LEARN 2 MOVE research program[3-5], which evaluates new interventions in rehabilitation for children and adolescents with CP in different age cohorts.

Because the diagnosis CP requires an age of at least 18 months[6,7], L2M 0-2 focuses on infants at high risk for CP. Neurological findings, the presence of a lesion of the brain or other factors may indicate that infants are at risk for CP. It is generally assumed that infants at risk for CP need physiotherapy. Theoretically, intervention at early age when the brain is very plastic, should be more effective than intervention which starts beyond infancy.[8] However, knowledge on the efficacy of early intervention is limited. Systematic reviews indicated that early intervention programs may have a positive effect on cognitive development of young children, but no or minimal effect on motor development.[2,9,10] Interestingly, it is unknown which elements of intervention lead to improvement in function. The limited evidence for efficacy of current interventions led to the development of a new intervention program, COPCA (Coping with and Caring for Infants with special needs - a family centered program[11], unpublished data Dirks et al.). COPCA is based on new insights in the field of education and family care[12,13] and the motor developmental principles of the Neuronal Group Selection Theory (NGST).[14,15] The COPCA intervention has been evaluated in the Groningen VIP (Vroege Interventie Project) study. At RCT-level, COPCA was associated with a minimally better cognitive development than traditional infant physiotherapy (TIP), but the two interventions groups did not differ in traditional measures of motor development until 18 months. After process analyses of physiotherapeutic sessions, COPCA-based physiotherapeutic actions were associated with improved functional ability and better motor outcome. This was true in particular for infants who developed CP[16] (unpublished data Blauw-Hospers et al.). These first findings on a possibly beneficial effect of the COPCAprogram encouraged us to further investigate the effects of COPCA in a population at very high risk for CP. The framework of LEARN 2 MOVE 0-2 offered this possibility.

METHODS/DESIGN

The objective of L2M 0-2 is to evaluate the efficacy and working mechanisms of the new intervention program COPCA in infants at very high risk for developing CP. To evaluate the efficacy, the COPCA approach will be compared with regular care, traditional infant physiotherapy (TIP), in a randomized controlled trial (RCT).

We will recruit 40 infants at very high risk for cerebral palsy. The study is coordinated by the research team ofthe University Medical Center Groningen (UMCG). The Medical

Ethics Committee of the UMCG granted approval for the study. The trial is registered under NTR1428. Participation is voluntary and participants can withdraw at any time without affecting regular treatment. The intervention period is 12 months in duration and has no known risks for participants.

Study sample

Forty infants will be recruited via their treating physician or physiotherapist. The infants will be recruited in the provinces of Groningen, Friesland, Drenthe, Overijssel and in and around the city of Amsterdam. In these regions 24 hospitals are located.

Inclusion criteria

Infants aged 1 to 9 months corrected age (CA) at high risk for developing CP, based on the presence of one of the following:

a) Cystic periventricular leukomalacia, diagnosed on serial ultrasound assessments of the brain.[17]
b) Unilateral or bilateral parenchymal lesion of the brain.[18]
c) Term/near-term asphyxia resulting in Sarnat 2 or 3[19] with brain lesions on MRI and/or with neurological dysfunction during infancy suggesting the development of CP.
d) Neurological dysfunction suggestive of development of CP.

Exclusion criteria

Infants are excluded on the basis of one of the following criteria:

a) An additional severe congenital disorder, such as serious congenital heart disorder.
b) Caregivers have an insufficient understanding of the Dutch language.

Power calculation

Power calculation based on the primary outcome measure, the Infant Motor Profile (IMP[20]; see measurements) indicates that two groups of 19 infants result in a power of 80% (a = 0.05) to detect a clinically relevant change of 7.5 points in the total IMP score (SD = 8.2).

Recruitment procedure

Paediatricians, physiatrists and physiotherapists are informed about the study by both written and oral information. Information is published in various local and national journals directed at professionals and caregivers. The treating physician or physiotherapist informs eligible families about the study and informs the research-team in the UMCG about them. If caregivers are interested in the study, an information letter is sent and they are free to ask more information. If caregivers decide to participate, an assignment form is sent back.

Randomisation will take place in blocks stratified according to the type of brain lesion or neurological dysfunction. Infants are assigned to one of the two interventions and baseline measurements will start. Parents, caregivers and therapists can not be blinded with respect to type of intervention. Assessors will be blinded with respect to group allocation.

Intervention

Infants participating in the study will receive either COPCA or TIP. Intervention is carried out in the infant's home and coordinated by the UMCG-team; evaluation is carried out by the UMCG-team. COPCA will be provided by therapists with a specific training in COPCA, TIP by paediatric physiotherapists selected by the paediatrician in charge of the child's care. Intervention will be provided once a week during a year.

COPCA

COPCA is a family relationship oriented program. COPCA aims to promote activities and participation of the infant with special needs and its family, taking into account the limitations imposed by bodily impairments. COPCA consists of two components:

a) A family involvement and educational component, based on recent insights in the family and educational field.[12,13] Important aspects are family autonomy and rearing the child from the family's own educational perspective.[21,22]
b) A neurodevelopmental component based on the principles of the Neuronal Group Selection Theory.[14,15] Important aspects are variation and variability, aiming to increase the infant's motor repertoire and improved ability to select a specific strategy fit for function in a specific daily life situation.

In COPCA principles of coaching are used to promote creative exploration of the competencies of the family members including the infant with special needs in order to stimulate self-made decisions and improve the quality of life. The physiotherapist, called coach, listens, informs and observes while the caregiver is involved in daily routines with the child, including play, thereby creating a situation in which caregivers feel free to explore and discuss alternative strategies. Key words of COPCA intervention are variation, exploration, trial and error, self produced motor behaviour (no 'hands on'), coaching (no training), family autonomy and family rituals (unpublished data Dirks et al).

TIP

Control therapy is TIP, which - in the Netherlands – is based to a large extent on the 'living concept' of Neuro-Developmental Treatment (NDT).[23] TIP based on NDT focuses primarily on limitations imposed by bodily impairments and functional activities of the infant with special needs. The two major components are:

a) Neurodevelopmental principles, consisting of a mix of neuromaturational assumptions, sensorimotor problem solving strategies and the principles of the dynamic systems theory. The therapist plays a key role in teaching and instructing these principles. By providing sensorimotor experiences, the therapist learns the infant to engage in developmental activities.
b) Family members are seen as 'the most important people on the baby's team' in the planning of treatment goals, according to Bly.[24]

Typical development is the framework for treatment in NDT. Problem solving is used to identify missing or atypical elements of functional movements and posture. The therapist treats the infant and selects during the treatment handling (hands on) strategies to facilitate and prepare the infant for age specific function. The caregivers are instructed how to continue and integrate these treatment strategies, which often involve hands-on techniques, into daily life. For the implementation of NDT in daily practice this means that a large repertoire of facilitation techniques like handling are used to reduce atypical functional activities and to prepare the infant for optimally independent function (unpublished data Dirks et al.). Due to the different influences which are incorporated in TIP a large heterogeneity in treatment application exists.[25]

Measurements (table 1)

Primary outcome focuses on the performance of mobility-related activities measured by the Infant Motor Profile (IMP)[20,26], secondary measures on participation and quality of life of participants and parents and on body functions and structures. Secondary outcomes assess child-related as well as caregiver-related variables. Possible effect modifiers such as medical history, demographic variables and compliance of therapists and caregivers will be taken into account.

The infants will be assessed at inclusion (T0), and at 3, 6 and 12 months after the onset of the intervention (T1, T2, T3). In infants included prior to the age of 8 months, an additional assessment is scheduled at the corrected age of 21 months (T4). Assessments will take place at infants' home and/or at the UMCG.

Primary outcome is motor performance as measured by the IMP, a video-based assessment which provides information on a child's motor repertoire and its ability to adapt motor behaviour to the specifics of the situation.[20]

Table 1: Measurements LEARN 2 MOVE 0-2

Instrument	Baseline (T0)	After 3 mo (T1)	After 6 mo (T2)	After 12 mo (T3)	At 21 mo CA*
Primary Outcome					
IMP	+	+	+	+	+
Secondary Outcome, child					
Neurological assessment	+	+	+	+	+
AIMS	+	+	+	+	+
GMFM	+	+	+	+	+
Bayley PDI	+	+	+	+	+
Bayley MDI	+	+	+	+	+
VABS (P)	+		+	+	
PEDI (P)	+			+	
ITQOL (P)	+			+	
Secondary Outcome, family					
Video parent child interaction	+		+	+	
Utrechtse Coping List (P)	+			+	
NOSI-K (P)	+			+	
RDI	+	+	+	+	+
MPOC (P), MPOC-SP (T)	+			+	
FES (P)	+		+	+	
CBS list QoL (P)	+		+	+	
Working mechanisms					
Assessment postural control	+		+	+	+
Video therapeutic session	+ #		+	+	
DAIS	+		+	+	
Weekly diaries, parents	+	+	+	+	
Weekly diaries, therapists	+	+	+	+	+

* CA = corrected age, the additional assessment at 21 months corrected age is scheduled for infants who enter the study before the corrected age of 8 months. The assessment is required to determine in all infants the diagnosis of CP as good as possible. # The first video of a therapeutic session is made 1 month after the onset of intervention. P = parental questionnaire or interview, this means that for the three child outcome measures it are assessments by means of proxy, T = assessment of therapist, i.e. service provider

Secondary child related outcomes

1. Neurological condition, according to the Touwen Infant Neurological Examination[27,28], in order to specify the neurological condition of the child, for instance the absence or presence of CP.
2. Measurements of infant motor skills:
   a. AIMS (Alberta Infant Motor Scales). The AIMS is an instrument designed to assess gross motor development during infancy in infants with typical and atypical

development. It has a good reliability and validity[29], but in older infants the AIMS suffers from ceiling effects.

b. GMFM (Gross Motor Function Measure).[30] The GMFM is designed to assess gross motor development in children with CP. It has good reliability and validity but in infants it suffers from bottom effects. The latter also implies that at early age or in children with severe motor dysfunction only a few items can be performed.

c. Bayley Scales of Infant Development (BSID-II), Psychomotor Development Index (PDI) which measures general motor performance.[31,32] The Bayley Scales are frequently applied clinical measures of infant development with a good reliability and validity (assessment: about 20 min).

The three measurements partially overlap, but each of the assessments provides its own type of information: AIMS and GMFM on gross motor development (AIMS appropriate for the youngest ages, GMFM for the older infants), Bayley's PDI on general motor development and IMP on the quality of motor performance. The IMP, AIMS, GMFM and neurological examination will be integrated into one assessment which lasts about 30 min.

3. Bayley Scales of Infant Development, Mental Development Index (MDI)[31,32] to measure cognitive development (assessment about 20 min)
4. Vineland Adaptive Behavior Scales (VABS). The VABS is a scoringlist which assesses by means of structured interview of caregivers functional status in communication, daily living skills, socialization and motor skills in children with or without disabilities of less than 18 years. The VABS has a good reliability and validity in children with CP.[33,34]
5. Pediatric Evaluation of Disability Inventory (PEDI)[35,36] to assess adaptation to and participation in activities of daily life. The PEDI is also an assessment based on a structured interview of caregivers. It provides information on functional abilities and caregiver assistance in the domains of mobility, self care and social functioning for children with CP aged 6 months to 7 years. The PEDI has a moderate to good reliability and validity.[36,37] VABS and PEDI will be integrated into one interview which lasts about 45-60 min.
6. Infant and Toddler Quality of Life Questionnaire (ITQOL)[38,39] to assess quality of life. This is a reliable and validated questionnaire to assess health related quality of life in young children. Time to complete questionnaire about 20 min.

Secondary family related outcomes

1. Video-analysis of caregiver's behaviour during two daily life activities (bathing, playing) according to Mahoney et al. (Maternal Behavior Rating Scale)[40] to document caregiver's ability to tune behaviour to the child (information on parenting capacities[41]). Bathing lasts in general 15 to 30 minutes, playing will be video-taped for 10-15 minutes.
2. Utrechtse Coping Lijst to document coping (UCL).[42] This inventory evaluates whether parents are able to deal in a competent way with the situation of having a child with CP.

Sanderman and Ormel (1992) demonstrated that the UCL has a satisfactory reliability and validity.[43] It takes about 10 minutes to complete the UCL.

3. De Nijmeegse Ouderlijke Stress Index, short version (NOSI-K) to document stress of the caregivers.[44] The NOSI-K is a concise questionnaire based on the Parent Stress Index.[45] It is a parental questionnaire for children aged at least 2 years. Data of the PERRIN project indicated that also in children < 2 years the NOSI-K can be used as a measure of parental stress (Ketelaar, personal observation). It takes about 5 minutes to complete the NOSI-K.
4. Reaction to Diagnosis Interview (RDI).[46] The RDI is a semistructured interview to document beliefs, memories and emotional reactions to a diagnosis, such as cerebral palsy. The interview lasts about 15 minutes, has a good reliability and promising validity.[47,48] Various studies used the RDI to investigate how parents react to the diagnosis of cerebral palsy.[47,49] In L2M 0-2 the RDI will primarily be used in an explorative way: no data are available on the process of reaction to the chain of diagnoses resulting in the final diagnosis of CP. Parents of children who participate in L2M 0-2 in general will be faced with the diagnosis of the adversities around the child's birth (e.g., preterm birth, asphyxia), with the diagnosis 'at high risk for developmental problems' and finally with the diagnosis CP. Secondary, we will explore whether parents in the COPCA-group achieve a better resolution than the parents in the control group. The RDI interview will be audio-recorded and be analyzed afterwards.
5. The Measure of Processes of Care, parental and professional forms (MPOC and MPOC-SP).[50] The MPOC is a parental questionnaire to quantify the extent to which they experience family-centeredness in the care for their child. The MPOC-SP is an equivalent questionnaire to measure the perception of service providers of the family-centeredness of care. The MPOC and MPOC-SP have sufficient reliability and validity.[51,52] It takes about 10-15 minutes to complete the MPOC-questionnaires.
6. The Family Empowerment Scale (FES). The FES is a questionnaire providing information on systems advocacy, knowledge, competence and self-efficacy. It has sufficient reliability and validity.[53] It takes less than 10 minutes to complete the FES.
7. CBS-list to document caregiver's quality of life http://statline.cbs.nl/StatWeb. It will take each parent less than 5 minutes to complete this small questionnaire.

Working mechanisms

In order to get a better understanding of the working mechanisms of early intervention also the following measurements are included:

1. Assessment of postural control during reaching by means of multiple surface EMG recordings and kinematics[54,55]. This assessment allows a precise determination of the size of the infants' repertoire of postural adjustments, the infant's ability to select a specific adjustment for a situation and his/her capacity to adapt motor output. The assessment takes about half an hour.

2. Assessment of caregiver's behaviour during two daily life activities (see above). This video-based assessment will provide information on quality and quantity of the implementation of treatment principles into daily life.[40]
3. Assessment of the actual contents of COPCA and TIP sessions by means of video recordings of therapeutic sessions and activities of daily life. Videos will be analysed with the Observer program according to Blauw-Hospers et al. 2010.[25]
4. Weekly diaries: parents fill in weekly diaries on program contents and therapists will provide structured information on goals and activities of treatment sessions. The diaries take 10-15 minutes to complete.
5. Daily Activities of Infants Scale (DAIS)[56]: parents classify in a 24-hour picture-logbook the activities of their children during one 24-hour period. The DAIS supplies especially information on play position and equipment use.

Data-analysis

The analysis of the effect of COPCA-intervention will be performed according to techniques used in previous studies, which implies amongst others the inclusion of multivariate statistics (in order to take into account effect modifiers such as preterm versus full term birth, type of brain lesion, social class, family well being), preference patterns of postural activity, developmental trajectories and variation indices[57,58,55] (unpublished data Blauw-Hospers et al).

DISCUSSION

In this paper we have presented the background and design for a randomized controlled trial comparing a new intervention, COPCA, with regular physiotherapeutic intervention for infants at very high risk for cerebral palsy. We aim to assess whether the COPCA approach is more beneficial for infants at risk for cerebral palsy and their families than current interventions and to get insight in the working mechanisms and effective components of early intervention.

As mentioned above, some studies show a positive effect of early intervention on cognitive development[59,10], but it is unknown which elements of the intervention lead to cognitive improvement. Regarding motor development, there is even less evidence for efficacy and effective elements of intervention.[59,2,9] One of the explanations could be the heterogeneity in interventions, which is associated with overlap in intervention strategies between study and control groups. The overlap hampers the comparison of interventions at RCT-level. Therefore, we expect at RCT-level only minor differences in this study to the advantage of COPCA. To cope with the heterogeneity in physiotherapy, the study includes detailed process evaluation on the basis of quantification of videorecordings of

physiotherapeutic sessions. This allows for the assessment of the effectiveness of specific components of physiotherapeutic sessions in order to assess the effectiveness of specific components of the intervention. Recent studies using this approach showed positive associations between COPCA-related physiotherapeutical actions and developmental outcome at the age of 18 months, especially in infants who developed CP[16] (unpublished data Blauw-Hospers et al.).

We hypothesize that in our study in infants at very high risk for CP, physiotherapeutic actions based on the COPCA approach, are related to better outcomes, both in terms of child-related items and family related items. It is already known that interventions in preterm infants directed at parent child interaction have a positive effect on motor, cognitive and neurobehavioural outcome.[60,61] By focusing on family related items, caregiver child interaction may be improved and this may influence cognitive and motor development. The focus on family autonomy is supposed to support families in their own decision making processes and may improve educational skills and coping strategies to deal with the situation. In our study, we combine a family centered approach with a motor approach. Based on previous studies and theoretical frameworks, we expect COPCA or COPCA-based actions for the child to have a positive effect on cognitive, motor and daily functioning. The evaluation of working mechanisms, e.g. changes in postural control and presence of specific daily life activities, will provide further clues on the understanding of physiotherapy. This means that no matter what the outcome of the project on the level of the RCT will be, it will improve our understanding of early intervention in children with cerebral palsy. Such knowledge is a prerequisite for tailor-made guidance for children with CP and their families.

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LEARN2MOVE 0-2 YEARS: A RANDOMIZED CONTROLLED TRIAL ON EARLY INTERVENTION IN INFANTS AT VERY HIGH RISK OF CEREBRAL PALSY

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ABSTRACT

Aim: Evidence for early intervention in infants at very high risk (VHR) of cerebral palsy is limited. Therefore, we performed a randomized controlled trial in VHR-infants, comparing effects of COPCA (COPing with and CAring for infants with special needs) and Typical Infant Physiotherapy (TIP).

Method: Forty-three VHR-infants (median gestational age 32 weeks, 26 boys) were included before 9 months corrected age, based on a severe brain lesion or clear neurological dysfunction. They were randomly assigned to one year of COPCA (n=23) or TIP (n=20). Infants were assessed during and after the intervention with a battery of neuromotor, cognitive, functional and family tests, with the Infant Motor Profile (IMP) as primary outcome. Physiotherapeutic intervention sessions were video-taped, quantitatively analyzed and used for process analyses. Outcome was evaluated with non-parametric tests and linear mixed effect models.

Results: Infant outcome was comparable after receiving COPCA or TIP and not associated with specific physiotherapeutic actions. Age and brain lesion influenced infant outcome most. However, concerning the family, COPCA-related intervention elements were associated with better family empowerment.

Interpretation: One year of COPCA and one year of TIP in VHR-infants have similar effects on child and family outcome. Yet, specific COPCA-elements are associated with better family outcome.

What this paper adds

- One year of COPCA- or TIP-intervention resulted in similar VHR-infant outcome
- Age and type of brain lesion influenced infant's developmental outcome mostly
- COPCA-related intervention elements were positively associated with family empowerment
- Knowledge about contents of intervention assists in understanding active ingredients

Worldwide, infants at risk for neurodevelopmental disorders such as cerebral palsy receive early intervention. Many different intervention programs exist. Gradually our knowledge on the effect of early intervention increases. Reviewed post-discharge intervention programs for premature infants affect cognition until preschool, but effects on motor development are less and limited to infancy.[1] However, most preterm infants do not develop cerebral palsy (CP), as they do not have a serious brain lesion, such as periventricular leukomalacia (PVL) or cerebral infarctions.[2] Currently, little is known about the effects of early intervention in such very high risk (VHR) infants.

Recently, two systematic reviews[3,4] addressed the effect of early intervention in VHR-infants. They concluded that limited evidence for the effect of early intervention in VHR-infants is available, as only a few studies have been performed that applied various interventions and usually suffered from a lack of power and other methodological shortcomings. Both reviews suggested that a combination of interventional ingredients might be most promising for a beneficial effect, but opinions on the nature of the ingredients varied. This means that additional information on the effect of early intervention in VHR-infants is urgently needed.

In a previous study on the effect of three months of intervention in young VHR-infants, the VIP-project,[5,6] we combined the standard design of a randomized controlled trial (RCT) with a detailed process analysis of the interventions: COPing with and CAring for infants with special needs – a family centred program (COPCA) and the control intervention Typical Infant Physiotherapy (TIP). At RCT-level, both intervention groups developed similarly. Process analysis revealed that contents of intervention was associated with outcome, especially in the subgroup of infants diagnosed with CP. Challenging the infant and coaching the family were positively associated with motor outcome, whereas sensory experience was negatively associated with motor outcome. However, only about a quarter of the groups was diagnosed with CP. Therefore, we embarked on another intervention study in infants at even higher risk for CP, the LEARN2MOVE 0-2 years (L2M0-2) study,[7] using a similar double approach of RCT design and process analysis of the COPCA- and TIP-interventions. COPCA and TIP were now applied for a longer period: one year. Outcome was evaluated in a broad way, including child (neuromotor and cognitive), functional (daily life) and family outcome. We focused on the following questions: 1) do VHR-infants receiving COPCA or TIP differ in neuromotor, cognitive or functional outcome 2) do families receiving COPCA or TIP differ in outcome; 3) are specific physiotherapeutic actions related to child and family outcome; 4) is dosage of intervention expressed in daily activity of infant bathing as a measure of the implementation of intervention in daily life[8] associated with outcome; and 5) does the nature of the brain lesion, and especially the most severe brain lesion cystic periventricular leukomalacia (cPVL), affect the effect of intervention? We hypothesized that no or minor differences between COCPA and TIP are present at RCT-level on infant outcome measures, due to heterogeneity in interventions and knowledge from other intervention trials. We expected a more positive family outcome for COPCA, as COPCA is a family centred

approach. We hypothesized on the basis of our previous trial[5,6] that specific PT-actions - such as coaching and challenging - will be positively related to motor and functional outcome. Moreover, we hypothesized a better functional outcome in infants in whom the intervention was best implemented, measured by bathing activities. This hypothesis was based on the assumption that a higher exposure to intervention elements is associated with a better outcome. Finally, we expected that early intervention has least effect in infants with more severe brain lesions, as we assumed that a more affected brain will have less capability to reorganize or compensate.

METHOD

Participants

Infants were eligible for the study when they presented between 0 and 9 months corrected age (CA) with a VHR for CP. The latter[2] meant the fulfilment of one of the following criteria: 1) cystic PVL; 2) severe asphyxia with brain lesions on magnetic resonance imaging (MRI); 3) parenchymal lesions as result of infarction or haemorrhage; or 4) clinical dysfunction suspect for development of CP. Infants were recruited between November 2008 and November 2013 by paediatricians, child neurologists and physiotherapists from 12 hospitals in the northern half of the Netherlands. Seventy-seven infants fulfilled the inclusion criteria and caregivers of 43 infants gave informed consent to participate (Figure 1). The 43 infants in the study were randomly assigned to receive one year COPCA (n=23) or TIP (n=20). Randomization was stratified according to the four above mentioned inclusion criteria, with random sequence generating and concealment of groups by one of the authors (TD). After inclusion, imaging data were reclassified in order to obtain a uniform classification of brain lesions. Reclassification was performed by an experienced child neurologist (RJV) into the following categories: a) PVL, divided into non-cystic and cystic; b) cortical infarction; c) posthaemorrhagic porencephaly; d) basal ganglia or thalamic lesions; e) no or non-specific brain lesions. The study was approved by the Medical Ethical Committee of the University Medical Center of Groningen and registered in the Dutch trial register under NTR1428.

Interventions

COPCA consists of two main components: 1) a family and educational component and 2) a neurodevelopmental component. The first stresses family autonomy and coaches families to cope with their situation and make their own decisions. The neurodevelopmental component is based on the Neuronal Group Selection Theory. It aims to increase the size of the motor repertoire (variation) and to enhance adaptability in an active learning process with trial and error experiences.[9] TIP in the Netherlands is an eclectic mix of different approaches and theories, traditionally based on NeuroDevelopmental Treatment (NDT).

However, over time, a more functional approach with more family involvement, has been integrated resulting in a heterogeneous mix of physiotherapeutic ingredients.[9]

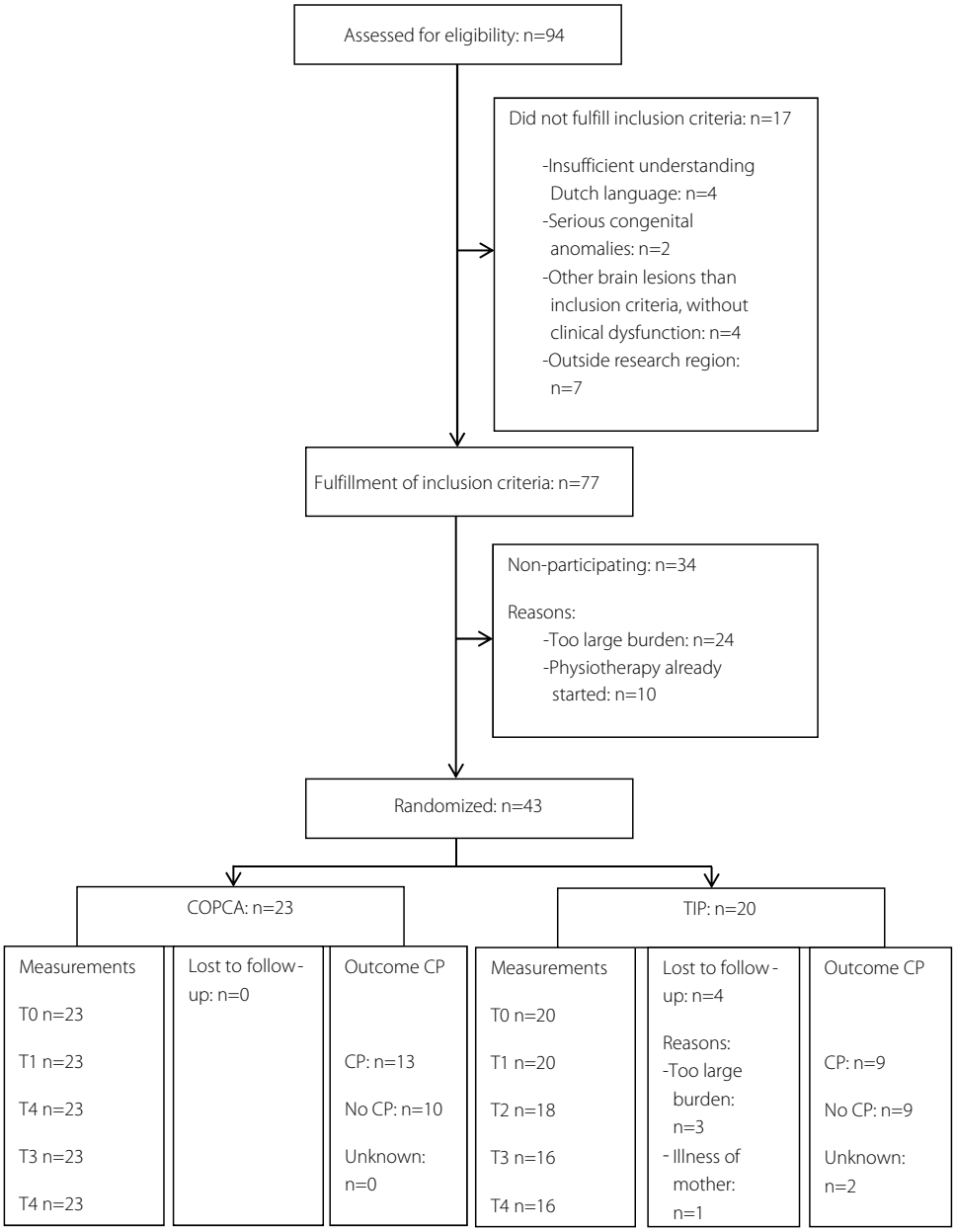

Figure 1: Flow diagram participants

The randomized parallel intervention started after inclusion and lasted one year. COPCA was provided at home once a week; TIP was in general also provided once a week at home, but occasionally it was delivered in an outpatient setting or in another frequency.

Supplementary Table 1: Neuromotor, cognitive, functional and family outcome measures at the different measurements during and after the intervention period

Measures	T0	T1	T1	T3	T4
IMP	+	+	+	+	+
TINE	+	+	+	+	+
GMFCS					+
AIMS	+	+	+	+	+
BSID-II PDI	+	+	+	+	+
BSID-II MDI	+	+	+	+	+
GMFM-88	+	+	+	+	+
GMFM-66	+	+	+	+	+
GMFM-adapted	+	+	+	+	+
PEDI	+		+	+	
FES	+		+	+	

Measurement: T0 = baseline (before the intervention period); T1 = after 3 months of intervention; T2 = after 6 months of intervention; T3 = after 12 months of intervention; T4 = at 21 months corrected age (after the intervention period). IMP = Infant Motor Profile; TINE = Touwen's Infant Neurological Examination; GMFCS = Gross Motor Function Classification system; AIMS = Alberta Infant Motor Profile; BSID-II – Bayley Scales of Infant Development, PDI = Psychomotor Developmental Index, MDI = Mental Developmental Index; GMFM = Gross Motor Function Measure; CA = corrected age, the additional assessment at 21 months corrected age is scheduled for infants who enter the study before the corrected age of 8 months; PEDI = Pediatric Evaluation of Disability Index; FES = Family Empowerment Scale. The GMFM is developed for children with CP, but infrequently used below age 2, because infants are usually not yet diagnosed with CP at that age. We used total scores of the original GMFM-88 and the shortened version GMFM-66. In addition, we applied the infant adaptation of the GMFM (Hielkema et al. 2013), which we called 'GMFM-adapted'.

Infant and family measurements

In the time period between November 2008 and September 2015, in each infant an extensive battery of tests was performed at baseline (T0, i.e., immediately after inclusion, before start of the intervention), after 3 months (T1), after 6 months (T2) and after 12 months of intervention (T3, i.e., at the end of the study's intervention period) and at 21 months CA (T4; only if the infant had an age below 8 months CA at inclusion, as in the other infants T3 and T4 coincided; n=3). Supplementary table 1 shows which measurements were used at the various measurement moments (see also Hielkema et al 2010).[7] Assessors were blinded for type of intervention, caregivers were asked not to inform them.

Our primary outcome was the Infant Motor Profile (IMP),[10] a video-based measurement to assess motor behaviour. The IMP does not only assess motor performance, but also the

quality of motor behaviour in the domains of variation (i.e., the size of the motor repertoire), adaptability (i.e., the ability to select adaptive motor strategies), fluency and symmetry. IMP-scores are expressed in percentages of the maximum score and are based only on the abilities of the infant at the time of the assessment.

Secondary neuromotor outcome measures consisted of the Touwen Infant Neurological Examination (TINE),[11] Gross Motor Function Classification System (GMFCS),[12] the Albert Infant Motor Scale (AIMS),[13] the Gross Motor Function Measure (GMFM)[14] and the Bayley Scales of Infants Development - Psychomotor Developmental Index, second edition (BSID-II PDI).[15] The TINE was used to document neurological condition and provided information on the absence or presence of CP at the last measurement (21 months CA). In case of CP, severity was classified according to the GMFCS. Realizing that our primary outcome measure was relatively new and that evaluation of motor development of VHR infants is difficult we also documented motor development with other instruments. The AIMS and GMFM were used to document gross motor function, the BSID-II PDI to assess gross and fine motor capacity. Of the AIMS and BSID-II PDI raw scores were used as percentiles and developmental indices of many infants were below the 5th percentile or at the lowest level (below 55) and therefore lacked discriminatory sensitivity in our groups. Cognitive development was assessed with BSID-II's Mental Developmental Index (BSID-II MDI);[15] again total raw scores were used in the analyses.

For functional outcome, i.e. functioning in daily life, we interviewed parents with the Dutch version of the Pediatric Evaluation of Disability Index (PEDI).[16] The PEDI results in a total score and three subscores: self-care, mobility and social function.

Family functioning was measured with the Family Empowerment Scale (FES),[17] an instrument that measures empowerment in families with children with developmental problems. The original questionnaire consists of three subscales: 1) empowerment in the family system, 2) empowerment in the service system and 3) parents' involvement in the community. The first two subscales were translated into Dutch for the L2M-study.[18] Both the two subscales and their total score were used as measures of family empowerment.

All above described measurements have shown to be sufficiently valid and reliable,[7] except the Dutch version of the FES, as the psychometric properties of the Dutch version had not been evaluated. The psychometric properties of the original FES are adequate.[17]

Quantification of intervention sessions

We aimed to video-record physiotherapy sessions three times: 1 month, 6 months and 12 months after the onset of intervention. As video-recording after 12 months was only moderately successful (31 videos (72% of participants) obtained), we only used video-recordings obtained after 1 month (n=41) and after 6 months (n=37). Comparable with the VIP-study, contents of the 1 and 6 months videos was largely similar (cf. Dirks et al. 2011[9]).

Supplementary Table 2: Percentages of time spent on physiotherapy actions for COPCA and TIP

Physiotherapy actions	**COPCA** (n=23) Median % (range)	**TIP** (n=20) Median % (range)	**ICC's** (n=10)
Neuromotor actions			
Facilitation techniques**	0 (0-6)	10 (1-29)	0.788
Sensory experience*	1 (0-17)	5 (0-15)	0.928
Passive motor experience**	0 (0-3)	1 (0-11)	0.782
SPMB, no interference	43 (19-74)	33 (21-54)	0.786
CSPMB, infant continues activity*	38 (0-68)	27 (6-56)	0.947
CSPMB, activity flow over into hands-on techniques**	0 (0-6)	10 (0-28)	0.983
Not specified neuromotor actions	6 (1-75)	6 (1-11)	0.702
Educational actions			
Caregiver training**	0 (0-11)	13 (0-65)	0.921
Caregiver coaching**	82 (4-98)	0 (0-40)	0.945
Not specified educational actions**	6 (1-75)	83 (13-100)	0.933
Communication			
Information exchange	5 (0-23)	7 (1-17)	0.819
- About COPCA	0 (0-1)	0 (0-3)	-
- About NDT**	0 (0-1)	1 (0-6)	-
- About family issues	5 (0-21)	5 (0-11)	0.696
Instruction	7 (1-20)	5 (1-17)	0.942
- Giving hints	2 (0-8)	1 (0-15)	-
- Multiple options	0 (0-8)	1 (0-8)	-
- Strict instruction	3 (0-7)	1 (0-16)	0.551
Provide feedback	15 (2-37)	22 (5-31)	0.908
- Ask & listen	1 (0-13)	0 (0-5)	0.620
- Share information	4 (0-12)	6 (1-22)	0.837
- Evaluate procedure	10 (0-26)	8 (2-25)	0.683
- What went right/wrong	0 (0-0)	0 (0-1)	-
Not specified communication	57 (24-89)	60 (44-78)	0.866
Position			
Supine	29 (0-58)	29 (1-55)	0.998
Prone	17 (5-52)	19 (4-41)	0.984
Side	2 (0-15)	2 (0-9)	0.976
Sitting	30 (0-70)	26 (10-60)	0.977
Standing	0 (0-14)	1 (0-32)	0.998
Walking	0 (0-4)	0 (0-4)	0.984
Transition**	2 (1-7)	5 (1-15)	0.920
Not specified position	2 (0-67)	2 (0-13)	0.831

Supplementary Table 2: Percentages of time spent on physiotherapy actions for COPCA and TIP (Continued)

Physiotherapy actions	**COPCA** (n=23) Median % (range)	**TIP** (n=20) Median % (range)	**ICC's** (n=10)
Situation			
Motor activity and play	96 (46-100)	95 (66-100)	0.969
Feeding	0 (0-42)	0 (0-32)	0.998
Dressing	0 (0-14)	0 (0-17)	0.965
Carrying	1 (0-15)	1 (0-10)	0.953

% = median percentage of time spent on physiotherapy actions during physiotherapy sessions 1 and 6 months after the start of intervention; differences between groups tested with Mann Whitney U-tests, *p<0.05; **p<0.01; ICC = Intraclass Correlation Coefficient. ICC's were calculated on the basis of 10 videos by two independent observers. ICC's were calculated if more than 2% of time was spent on a PT-action

Therefore, we decided to use the mean scores of these two intervention sessions for further analyses. This implies that in infants in whom only one of these intervention videos was available, single video information was used (filmed after 1 or 6 months of intervention).

Video-recordings were analysed with the Groningen Observer Protocol 2.0 (GOP 2.0)[19] with the computer program The Observer (version 11.5, Noldus, Wageningen). Total percentage of time spent on specific physiotherapeutic actions was scored within five main categories: neuromotor actions, educational actions, communication, position, and situation. Within each category, specific behaviours could be specified in subcategories (so-called modifiers). Two persons from the L2M0-2 study group, (RT and SJH), scored the videos independently and had overall a good to excellent interobserver reliability (details in supplementary table 2).

Quantification of infant positioning during bathing

We had scheduled to videotape bathing sessions at T0, T2 and T3. We aimed to analyse the bathing sessions to measure implementation of intervention into daily life activities (cf. Dirks et al. 2016[8]). Unfortunately, we were not very successful in collecting these video-data (missing videos: T0: n=2, T2: n=17, T3: n=14). Major reasons for missing videos were; 1) infants were showered with their parent (n=13 videos), 2) parents did not allow videotaping of bathing (n=8 videos), infants who were lost to follow-up before completion of the trial (n=6 videos) and logistical problems (n=6 videos). Due to the large proportion of missing data we decided not to use the bathing videos as a measure of implementation of the interventions in the analyses.

Data analyses

Power calculation was based on the IMP, our primary outcome measure. A sample size of 19 infants in both intervention groups, resulted in a power of 80% (α=0.05) to detect a clinically relevant change of 7.5 points in the total IMP score (SD = 8.2).

To achieve data reduction in the process analysis on the role of specific physiotherapeutic actions, we used factor analysis by applying principal axis factoring with an Oblimin rotation (as we dealt with interrelated physiotherapeutic actions; SPSS version 21). The factor analysis resulted in three components: 1) NDT versus COPCA factor, a dimension reflecting the diametrically opposed core elements of NDT (hands-on techniques and training) and COPCA (coaching and challenging self- generated motor activities), with a high score reflecting NDT-like actions and a low score COPCA-like actions; 2) non-directive communication and self-produced motor behaviour (SPMB), i.e., physiotherapeutic actions incorporated in the COPCA-approach ; and 3) directive communication and training, i.e., physiotherapeutic actions that are discouraged in COPCA (Table 1). Total variance explained with these three factors was 45% (factor 1: 21%; factor 2: 15%; factor 3: 9%), with a Kaiser-Mayer-Olkin Measure of 0.681. Factor loadings per infant were used as indicators of contents of intervention and we considered a minimal factor loading's value of 0.45 as significantly contributing to the factor.

Our study design was based on the RCT, comparing the infant and family outcomes at different measurement times. At the RCT-level we used univariate statistics only to compare baseline characteristics and outcome at 21 months CA. For this purpose, we used SPSS version 21. As the data were not normally distributed, we used non-parametrical statistics. Differences in baseline characteristics and outcome between the two intervention groups were tested with Mann Whitney U and Chi-square tests. Estimates of differences of the median outcome values at 21 months CA were expressed by Hodges Lehmann.

Multilevel analyses were performed with nlme (linear and non-linear mixed effect models) library in R version 3.3.1[20] to study longitudinal potential differential effects of COPCA and TIP on the main motor (IMP), cognitive (BSID-II MDI), functional (PEDI) and family (FES) outcome parameters, taking into account the age in corrected months and possibly confounding factors. We used linear mixed effects models to describe the subject-specific time profiles per infant, as this type of analysis takes into account correlation between observations from the same infant. We first tested possible effects over time of intervention (COPCA versus TIP), taking into account possible interaction effects of intervention with age. In these analyses we did not use measurement moment as indicator of time but corrected age in months (and its square), to get the best model fit and avoid introducing error by neglecting the unstructured nature of the data. In the analyses, we adjusted a priori for the following background variables: gestational age, level of parental education, and presence of cystic PVL (a major predictor of CP[21]), as these factors are known to influence motor and

cognitive outcome.[1,2,21] We repeated these analyses for each of the outcome variables in a similar way for the three factors describing physiotherapy (1= NDT versus COPCA; 2=non-directive communication; 3=directive communication), using similar models for each outcome and again, a priori adjusted for the selected covariates. We considered p-values below 0.01 as statistically significant.

Table 1: Factor analysis physiotherapeutic actions

	Factors		
PT-actions	1: NDT versus COPCA	2: Non-directive communication	3: Directive communication
Facilitation techniques	0.796		
Passive motor experience	0.763		
Challenged to SPMB, activity flows over into hands-on techniques	0.738		
Feedback: share information	0.609		
Caregiver training	0.519		-0.604
Information about NDT	0.467		
Caregiver coaching	-0.785		
Challenged to SPMB, infant is allowed to continue activity	-0.534		
Feedback: ask & listen to caregivers		0.778	
Self Produced Motor Behaviour (SPMB), no interference		0.615	
Information about family issues		0.610	
Information about COPCA		0.461	
Instruct: giving hints		0.459	
Instruct: strict instruction			-0.600
Feedback: evaluate procedure			-0.660
Feedback: what went right & wrong			-0.456

The table shows results of factor-analysis, applying principal axis factoring with Oblimin rotation. Numbers shown in the table are factor loadings, i.e. to which extent the different physiotherapeutic actions (PT-actions) contribute to the different factors. Factor loadings above 0.45 were regarded as contributing sufficiently to the factor. Only factor loadings above 0.45 are shown in the table. Positive factor loadings contribute positively to the factor, negative factor loadings contribute negative to the factor (i.e. are oppositely related to the concerning factor. For example: In case of factor 1, NDT versus COPCA, it means: facilitation techniques (positive loading) contribute to the factor's NDT-component whereas caregiver coaching (negative loading) contributes to factor's COPCA-component).

RESULTS

Participation

Of the 43 included infants (n=23 COPCA, n=20 TIP), four infants were lost to follow-up, all from the TIP-group (Figure 1). Reasons for withdrawal from the study were maternal illness (n=1), and study burden (n=3). Of two 'lost' infants we did obtain information on outcome in terms of CP and GMFCS-level around 21 months CA, based on information from medical records, obtained with caregivers' permission.

Baseline characteristics of caregivers and infants, of both intervention groups were comparable (Table 2). In both groups frequency of intervention was somewhat lower than the intended once a week, amongst others due to holidays and logistic factors. At 21 months CA 22 out of 41 infants (54%) were diagnosed with CP, without significant differences between COPCA and TIP. Also, no significant differences in severity of CP expressed by GMFCS-levels were present (Table 2).

Neuromotor, functional and family outcome

At RCT-level neuromotor, functional and family outcome of the two intervention groups at the various measurement moments was similar (supplementary table 3).

Also the multilevel analyses showed that the effect of COPCA and TIP intervention on the various outcome measures was comparable (Table 3a). Outcome was especially affected by age (IMP, BSID-MDI and PEDI) and the presence of cystic PVL (BSID-MDI). No interaction effects of intervention with age and cystic PVL were found. The FES was independent of infant's age and brain lesion.

We repeated the multilevel analyses with the three factors describing interventional elements with physiotherapeutic actions (Table 3b). None of the factors were significantly associated with infant outcome, although the association between factor 2 and IMP approached significance; it suggested that more time spent with non-directive communication might have been associated with worse IMP-scores. Also in these analyses infant outcomes were mainly associated with age and cystic PVL. Family outcome was associated with one of the physiotherapeutic factors: factor 1 was associated with total FES score, indicating that less time spent with the NDT-approach and more time spent with the COPCA-approach was associated with better FES scores.

Table 3 shows the results of the linear mixed effects models with random intercept (all models) and random slope (random linear time effect, IMP models only). In table 3a, effects of intervention on outcome are shown. In table 3b, effects of interventional elements, measured by factors 1, 2 and 3, are shown. Besides the effects of intervention (3a) and interventional elements (3b) on outcome, covariates statistically significant contributing to

outcome are shown. No significant effects of caregivers' educational level, gestational age or interaction effects for intervention with both age and cystic periventricular leukomalacia were found (data not shown in the table).

Table 2: Baseline characteristics and outcome CP

	COPCA (n=23)	TIP (n=20)	p-value
Gestational age (weeks): median (range)	32 (26-41)	29 (26-41)	0.10
Preterm/term# (n)	15/8	13/7	0.99
Birth weight (grams): median (range)	1915 (770-4410)	1375 (720-5400)	0.07
Gender# (n): female/male	8/15	9/11	0.50
Twins# (n)	6	4	0.64
Maternal age at infant's birth (years): median (range)	29 (19-45)	31 (17-41)	0.34
Educational level mother (n)			
Low/medium/high	5/13/5	6/6/8	0.64
Unknown	0	0	
Educational level father (n)			
Low/medium/high	8/10/5	5/5/9	0.17
Unknown	0	1	
Age at baseline (months): median (range)	1.4 (0.1-8.6)	2.5 (0.9-9.0)	0.07
Brain lesions# (n)			
- PVL	7 (cystic: 5)	6 (cystic: 5)	
- Cortical infarction	2	1	0.93
- Posthaemorrhagic porencephaly	5	7	
- Basal ganglia/thalamus	5	3	
- No/non-specific lesion	4	3	
Frequency of interventions per month: median (range)	3.0 (1.8-4.0)	2.5 (1.3-4.3)	0.09
Diagnosis at 21 months CA#			
- CP	13 (57%)	9 (45%)	0.17
- No CP	10 (43%)	9 (45%)	
- Unknown	0 (0%)	2 (10%)	
GMFCS of infants with CP			
- Level 1	3 (23%)	0 (0%)	
- Level 2	4 (31%)	3 (33%)	0.25
- Level 3	1 (8%)	4 (44%)	
- Level 4	2 (15%)	1 (11%)	
- Level 5	3 (23%)	1 (11%)	
Type of CP#			
- Unilateral spastic	4 (31%)	1 (11%)	0.18
- Bilateral spastic	9 (69%)	8 (89%)	

CP = cerebral palsy; COPCA = COPing with and CAring for infants with special needs – a family centered programme); TIP = typical infant physiotherapy; CA= corrected age; PVL = periventricular leukomalacia; GMFCS = Gross Motor Classification System; # = nominal variable

p-values based on non-parametric tests; for ordinal, interval and ratio variables tested with Mann Whitney U; for nominal variables# tested with chi square, linear by linear association.

Supplementary table 3: Outcome in both intervention groups at the various measurement moments

	T0 median age 2m (0.1-9)		T1 median age 5m (3-12)		T2 median age 8m (6-15)		T3 median age 14m (12-21)		T4 median age 21 m (20-22)		
	COPCA (n=23) median (range)	TIP (n=20) median (range)	COPCA (n=23) median (range)	TIP (n=20) median (range)	COPCA (n=23) median (range)	TIP (n=18) median (range)	COPCA (n=23) median (range)	TIP (n=16) median (range)	COPCA (n=23) median (range)	TIP (n=16) median (range)	HL estim (95% CI)
IMP Total score	66 (58-75)	70 (56-75)	72 (60-77)	73 (62-83)	73 (58-84)	76 (62-84)	76 (59-88)	79 (67-89)	82 (69-94)	81 (69-89)	0 (-5;4)
• **Variation**	71 (65-79)	69 (61-81)	69 (60-83)	72 (54-88)	72 (59-89)	73 (59-95)	71 (59-91)	71 (62-90)	72 (60-96)	72 (60-90)	0 (-6;5)
• **Adaptability**	76 (71-86)	67 (64-69)	86 (83-92)	85 (71-93)	75 (50-100)	80 (50-90)	80 (50-100)	85 (63-100)	92 (75-100)	87 (67-96)	4 (-2;9)
• **Performance**	36 (30-61)	39 (29-63)	50 (32-68)	55 (37-74)	58 (32-84)	60 (39-81)	75 (33-88)	75 (57-89)	83 (33-92)	84 (49-90)	-1 (-7;5)
• **Fluency**	67 (50-75)	70 (50-100)	75 (67-75)	75 (67-75)	75 (67-75)	75 (63-75)	75 (70-88)	75 (70-80)	75 (67-90)	73 (60-80)	0 (0;5)
• **Symmetry**	87 (67-100)	89 (50-100)	90 (67-100)	94 (63-100)	92 (50-100)	95 (75-100)	89 (56-100)	93 (61-100)	89 (61-100)	88 (67-100)	0 (-11;6)
AIMS	5 (2-21)	7 (2-19)	11 (2-22)	12 (4-46)	20 (3-39)	16 (6-45)	37 (6-57)	32 (12-57)	50 (5-56)	45 (10-56)	3 (-6;1)
BSID-MDI	11 (6-67)	18 (4-67)	41 (11-75)	49 (7-74)	63 (20-91)	62 (10-89)	84 (51-105)	85 (66-110)	104 (55-125)	104 (13-126)	0 (-13;12)
BSID-PDI	12 (5-36)	13 (7-36)	25 (8-46)	28 (7-54)	35 (6-59)	35 (4-61)	56 (19-70)	47 (32-70)	67 (10-90)	64 (22-76)	1 (-8;13)
GMFM-88	6 (2-19)	6 (3-21)	10 (3-20)	13 (4-24)	16 (4-31)	17 (5-29)	23 (7-39)	19 (8-42)	28 (4-48)	36 (15-66)	-4 (-14;5)
GMFM-66	16 (8-27)	17 (8-24)	23 (10-29)	23 (17-43)	27 (14-44)	25 (10-47)	43 (16-63)	37 (18-56)	49 (10-67)	53 (27-62)	-2 (-11;8)
GMFM-adapted	6 (2-21)	7 (3-22)	12 (3-24)	14 (5-44)	19 (3-44)	19 (5-50)	37 (7-64)	32 (7-65)	51 (5-71)	58 (19-70)	-7 (-18;6)

Supplementary table 3: Outcome in both intervention groups at the various measurement moments (Continued)

	T0 median age 2m (0.1-9)		T1 median age 5m (3-12)		T2 median age 8m (6-15)		T3 median age 14m (12-21)		T4 median age 21 m (20-22)		
	COPCA (n=23) median (range)	TIP (n=20) median (range)	COPCA (n=23) median (range)	TIP (n=20) median (range)	COPCA (n=23) median (range)	TIP (n=18) median (range)	COPCA (n=23) median (range)	TIP (n=16) median (range)	COPCA (n=23) median (range)	TIP (n=16) median (range)	HL estim (95% CI)
FES Total score	94 (73-120)	94 (80-104)	NT	NT	98 (82-120)	92 (70-108)	99 (80-120)	96 (75-107)	NT	NT	NT
• **Family**	50 (33-60)	47 (38-55)	NT	NT	51 (41-60)	51 (41-60)	50 (39-60)	48 (40-59)	NT	NT	NT
• **Service system**	45 (33-60)	45 (35-53)	NT	NT	48 (41-60)	46 (28-52)	48 (31-60)	46 (27-53)	NT	NT	NT
PEDI Total score	1 (0-23)	2 (0-24)	NT	NT	17 (3-52)	19 (3-56)	45 (5-81)	38 (25-98)	NT	NT	NT
• **Self care**	0 (0-10)	0 (0-11)	NT	NT	7 (1-17)	9 (1-17)	13 (4-25)	15 (9-25)	NT	NT	NT
• **Social functioning**	1 (0-11)	2 (0-11)	NT	NT	7 (1-52)	7 (2-12)	17 (1-28)	15 (9-28)	NT	NT	NT
• **Ambulation**	0 (0-3)	0 (0-2)	NT	NT	3 (0-13)	3 (0-28)	14 (0-39)	11 (2-45)	NT	NT	NT

Note: Because we continued with the statistically more appropriate longitudinal multilevel analyses, we only show median data during the intervention period and statistical analyses only at 21 months corrected age. AIMS=Alberta Infant Motor Scale; COPCA = COPing with and CAring for infants with special needs; FES=Family Empowerment Scale; GMFM=Gross Motor Function Measure; HL estim = Hodges Lehmann estimate of the median difference; IMP=Infant Motor Profile; m=months; MWU = Mann Whitney U; PEDI=Pediatric Evaluation of Disability Index; TIP=typical infant physiotherapy; T0=baseline; T1=after 3 months, T2=after 6 month, T3=after 12 months intervention; T4=around 21 months corrected age; 95%CI = 95% Confidence Interval; NT=not tested

Table 3: Longitudinal analyses, using linear mixed effect models.

3a: Model with interventions COPCA (=0) and TIP (=1)

	IMP – total score		BSID II MDI – raw score		PEDI – total score		FES – total score	
	regression coefficient	p-value	regression coefficient	p-value	regression coefficient	p-value	regression coefficient	p-value
Intervention	0.69	0.632	-4.1	0.322	-3.7	0.368	-4.8	0.356
Age	1.39	**0.001**	7.6	**<0.001**	1.1	0.090	0.31	0.156
Quadratic age	-0.031	**0.001**	-0.15	**<0.001**	0.13	**0.001**	NA	NA
Cystic PVL	-2.8	0.144	-15.8	**0.004**	-9.7	0.015	6.6	0.243

3b: Model with factors 1) NDT versus COPCA; 2) non-directive communication; 3) directive communication

	IMP – total score		BSID II MDI – raw score		PEDI – total score		FES – total score	
	regression coefficient	p-value	regression coefficient	p-value	regression coefficient	p-value	regression coefficient	p-value
Factor 1	0.13	0.823	-1.8	0.285	0.24	0.845	-5.5	**0.009**
Factor 2	-1.4	0.018	-2.3	0.165	-1.6	0.181	-0.47	0.644
Factor 3	-0.77	0.240	1.5	0.402	2.5	0.057	0.76	0.456
Age	1.4	**<0.001**	7.7	**<0.001**	1.1	0.060	1.2	0.22
Quadratic age	-0.03	**<0.001**	-0.15	**<0.001**	0.13	**<0.001**	NA	NA
Cystic PVL	-2.8	0.031	-10.5	**0.005**	-8.8	**0.002**	0.22	0.83

p-value <0.01 considered as statistically significant, bold numbers show statistically significant p-values; PVL = periventricular leukomalacia; NA = no added value

Table 3 shows the results of the linear mixed effects models with random intercept (all models) and random slope (random linear time effect, IMP models only). In table 3a, effects of intervention on outcome are shown. In table 3b, effects of interventional elements, measured by factors 1, 2 and 3, are shown. Besides the effects of intervention (3a) and interventional elements (3b) on outcome, covariates statistically significant contributing to outcome are shown. No significant effects of caregivers' educational level, gestational age or interaction effects for intervention with both age and cystic periventricular leukomalacia were found (data not shown in the table).

DISCUSSION

In our study, infant outcome was not influenced by type of intervention or associated with interventional elements. Age and type of brain lesion, in the form of cPVL, determined infant's developmental outcome most; they did not interact with type of intervention. At RCT-level COPCA was not associated with better family outcome, but COPCA-related actions were associated with better family empowerment.

Being aware of overlap between interventions and having knowledge of previous studies, the similar outcome in the randomized intervention groups was not unexpected. It raises the question whether the RCT is always the gold standard for measuring

effectiveness of interventions, especially if heterogeneity within interventions is present.[5,22] Knowing about RCT's pitfalls, we did a detailed process analysis of physiotherapy contents, independent from group randomization, to retrieve distinguishing interventional elements. After analysing contents of intervention, a clear contrast was found between NDT-related actions (hands-on techniques, caregiver training) and COPCA-related actions (challenging the infants to self- produced motor behaviour, caregiver coaching). Despite the clearly discriminating interventional elements, we did not find any significant association between the elements and infant outcome. This finding differs from our previous study,[5,6] in which multiple associations between contents of intervention and infant outcome were present. The current absence of associations may be related to differences in study design. First, in the L2M-study, most infants had severe brain lesions; in the VIP-study, most infants had no or non-significant brain lesions. It could be surmised that the presence of serious brain lesions alters the effect of early physiotherapy. Recent reviews and intervention studies suggest that multifaceted interventions may be most effective for VHR-infants.[3,4] Where we did find comparable infant outcome in our study, the GAME-study (Goals-Activity-Motor-Enrichment)[23] noted an advantage for the GAME-intervention on infant's motor and cognitive outcome. The difference in outcome may be related to differences in neuromotor approach: COPCA uses a 'hands-off' strategy to stimulate infants to develop own strategies, whereas the GAME-study uses combined principles of motor learning and dynamic systems theory, in which manual guidance is provided when needed and withdrawn when the infant shows the ability to begin to demonstrate the motor action. Differences in outcome for infants with severe brain lesions (L2M0-2 and GAME-study) compared with infants with no or non-significant brain lesions (VIP-project), may suggest that severely affected infants may benefit from some hands-on assistance, whereas infants with less severely affected neuromotor development may profit more from trial and error to develop their own motor strategies. Also, the intervention's duration and dosage may have affected outcome. The VIP-project provided a three months intervention twice a week, the L2M-study a one year intervention once a week. Literature suggests positive effects of short and intensive interventions.[24] Unfortunately, we did not succeed in gathering sufficient data about implementation of the intervention, i.e. dosage of interventional elements in daily life activities. Our findings emphasize the need for good measurement tools for implementation of interventions into daily life.

We did find an association between interventional elements and family outcome: family empowerment was negatively associated with NDT-related actions and positively with COPCA-related actions. One of COPCA's key components is coaching, aiming to empower caregivers in making their own decisions, both within their own family system and in the health care system.[9] The positive relation between COCPA-related actions and family empowerment may be the result of an effect of coaching over time. Empowering

caregivers aims to promote a sense of mastery over situations, which is positively related to psychological health of caregivers[25] and may influence caregivers' health and well-being on the longer term.

Strengths of our study are the longitudinal evaluation of VHR-infants from early age onwards, knowledge about infants' brain lesions, the detailed process analysis of intervention contents and the broad evaluation of child and family with a range of different outcome measurements. The longitudinal design allowed for a mixed-effect model analysis, allowing for the adjustment for potential confounders, taking into account the correlation structure in the data. Our study is one of the few early intervention studies that had brain imaging data for all infants[1], and therefore, we were able to study relations between severe brain lesions and outcome and possible interaction effects. The detailed process analysis made it possible to study real contents of the intervention programs, and allowed to uncover potential working elements within the intervention programs. It is a strategy to cope with the large heterogeneity within interventions. Knowledge about contents of intervention is needed, because information of active ingredients is the basis for establishing evidence-based interventions. Development is known to be influenced by many factors that are interrelated[25], and therefore we used a broad spectrum of outcome measurements, both for infant's and family outcome, to gain insight in the complex infant and family system.

A limitation of our study is the small sample size, which resulted in underpowering after drop outs. This may have occluded possible effects of intervention at RCT-level. Another limitation is the selective attrition in the TIP group, which may be explained by caregivers' perceptions that the study offered no gains, as the infant would anyway receive TIP. Caregivers in the COPCA-group were aware that they received a novel intervention and this may have contributed to the absence of drop outs in the COPCA-group. The inclusion of a few infants who presented with clinical signs suggestive of CP but without a severe lesion of the brain is another limitation, as none of them was diagnosed with CP. Looking back, it would have been better to include only infants with severe brain lesions. The absence of information on dosages of intervention in daily life certainly is also a limitation.

In conclusion, our study shows that COPCA and TIP as performed in the Netherlands have a similar effect on child and family outcome. In addition, the study demonstrated positive associations between COPCA-elements and family outcome, but not between interventional elements and infant outcome. Based on our findings and previous studies, we suggest to combine different ingredients as possibly effective elements in early intervention for VHR-infants: aiming to empower families by coaching and providing them with sufficient information, stimulating infant's neuromotor development by trying to elicit self-produced motor behaviour, with some assistance if the infant is not able to perform by him- or herself, in a challenging environment with adaptations when needed, and sufficient dosing and implementation of the interventional elements into daily life.[3,4] We

recommend for future studies collaboration of networks nationally and internationally, to have a longitudinal follow-up of VHR-infants in larger study groups, in which contents and implementation of intervention is further investigated.

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MEASURING GROSS MOTOR FUNCTION IN YOUNG INFANTS WITH OR AT VERY HIGH RISK OF CEREBRAL PALSY

PART III

GMFM IN INFANCY: AGE-SPECIFIC LIMITATIONS AND ADAPTATIONS

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ABSTRACT

Purpose: To evaluate longitudinal applicability of the Gross Motor Function Measure (GMFM) in infants younger than 2 years.

Methods: Twelve infants at very high risk for cerebral palsy were enrolled between 1 and 9 months corrected age. The children were assessed 4 times during 1 year with the GMFM-66, GMFM-88, and other neuromotor tests.

Results: Longitudinal use of the GMFM in infancy was hampered by age and function-specific limitations. The GMFM-66 differentiated less at lower-ability levels than at higher-ability levels. The GMFM-88 demonstrated flattening of the developmental curve when infants had developed more motor abilities. We formulated adaptations for the longitudinal use of GMFM in infancy.

Conclusions: To facilitate use of the GMFM in infancy, an adapted version may be an option. Further research is required to assess reliability and validity, and in particular, the sensitivity to change of the suggested adaptations.

INTRODUCTION AND PURPOSE

The Gross Motor Function Measure (GMFM) is a reliable and valid instrument to measure gross motor functioning in children with cerebral palsy (CP).[1-4] It is widely used for both clinical and research purposes. The GMFM was developed in the 1980s, as a measurement tool to de tect changes in gross motor development in children with CP. The originally published GMFM had 88 items, subdivided into 5 dimensions: A, lying and rolling; B, sitting; C, crawling and kneeling; D, standing; and E, walking, running, and jumping. A child developing typically will perform all items around the age of 5 years. The more recent version of the GMFM-88, the GMFM-66[1], adapted the original instrument to be an interval measure. It takes "not observed" behavior into account by estimating scores for items not shown on the basis of shown items. The resulting total score has limited the contribution of prior dimensions A and B and, to a lesser extent, of the prior dimension C. The GMFM-66 can be used to calculate only total scores and not dimension scores.[1] It is conceivable that the limited contribution of dimensions A and B makes the GMFM-66 less suitable for young infants, as they will score only or primarily in the first dimensions. To improve use of the GMFM in busy clinical practices, subsets of items based on a child's ability are used in the GMFM-66 item sets and the GMFM basal and ceiling approach. Both versions have a good reliability and validity in children aged 2 to 6 years.[5,6]

The achievement level of children with CP depends on the severity of impairment. Severity of gross motor impairment is currently expressed in terms of the Gross Motor Function Classification System (GMFCS).[7] For children with CP at GMFCS levels I and II, gross motor development as measured by the GMFM-66 reaches a plateau around 6 to 7 years.[8] Children at GMFCS levels III, IV, and V will reach their plateau at an earlier age.[9] This means that the upper age limit of the GMFM depends on the child's GMFCS level. Lower age limits for the application of the GMFM have not been indicated.[1] However, it could be argued that a lower age limit exists, as CP is often not reliably diagnosed before the age of 18 months.[10] Limited information is available on the use of the GMFM in infants younger than 18 months who are at risk for or suspected of developing CP.

The original validation sample of the GMFM of 111 children with CP, aged 5 months to 15.4 years, included assessments of 21 children aged between 5 months and 2 years. It was reported that younger children showed more change in GMFM scores with increasing age. The youngest children showed most changes in dimensions A, B, and C. Interrater reliability and agreement between the professionals' and the parents' prior judgments were lowest on these 3 dimensions.[1,11] Three other groups of authors addressed characteristics of GMFM scores in infancy.[12-14] They did not agree on the applicability of the GMFM to monitor gross motor development at an early age. Jelsma et al[12] described the development of GMFM scores over a period of 8 months in 12 infants who showed clear neurologicaldysfunction at the age of 4 months. They reported that GMFM scores do not increase in a linear fashion

and may vary to a great extent.[12] Difficulties in assessing GMFM in very young children may have contributed to the variation. Kolobe et al[13] described changes in GMFM scores over a 6-month period in 42 infants with CP or motor delay, indicating that application of the GMFM for children younger than 2 years is hampered by age and developmental characteristics of infancy. Wei et al[14] studied the use of the GMFM-88 in children aged 3 to 36 months. On the basis of Rasch analysis, they excluded some items of dimensions B, C, and E and constructed a version with 73 items. This GMFM-73 was no more reliable than the GMFM-66. They therefore concluded that the prior GMFM-66 is a reliable and valid instrument for children younger than 3 years.[14]

The aim of this study was to describe developmental changes seen in infants at high risk for CP by using the GMFM-88 and GMFM-66 over a 1-year period. We planned to describe problems encountered in (a) the application of items, (b) scoring of items, and (c) developmental changes over time and to compare the infants' developmental trajectories on the GMFM-88 and GMFM-66, that is, the changes over the 1-year period, with the developmental trajectories measured with 3 other scales of infant motor development (the Alberta Infant Motor Scale (AIMS)[15], the Bayley Scales of Infant Development–II Psychomotor Development Index (BSID-II PDI, Dutch version)[16], and the Infant Motor Profile (IMP).[17] Our aim was also to present suggestions for adaptation of the GMFM for use in infancy.

METHODS

Subjects

Twelve infants (7 boys and 5 girls) from the LEARN2MOVE 0-2 years study[18] participated. The medical ethics committee of the University of Groningen granted approval for the study. The trial is registered with the Dutch Trail Registry as NTR1428. Infants were included after their parents gave informed consent. Inclusion criteria were a corrected age between 1 and 9 months and a very high risk for CP. The latter was based on the presence of 1 of the following criteria: (a) cystic periventricular leukomalacia, diagnosed on serial ultrasound assessments of the brain[19] (n=2), (b) unilateral or bilateral parenchymal lesion of the brain[20] (n=4), (c) term/nearterm asphyxia resulting in Sarnat[21] score 2 or 3 (n=4) with brain lesions on magnetic resonance imaging, and/or (d) neurological dysfunction during infancy, suggesting the development of CP (n=2). Exclusion criteria were an additional severe congenital disorder, such as serious congenital heart disorder, or caregivers with insufficient understanding of the Dutch language. The median gestational age was 39 weeks (range, 27-41 weeks); median birth weight was 3140 g (range, 720-5400 g).

Study Design

The GMFM-88 and GMFM-66 were used as part of an extensive assessment battery that occurred over a 2- to 3-day period.[18] The GMFM was examined at baseline (T0) and after 3 months (T1), 6 months (T2), and 12 months (T3). Most examinations were carried out at the children's homes with one or both parents present. Assessments were performed by 2 trained GMFM examiners, with the assistance of an assessor with a master's degree in human movement sciences. All assessments were video recorded. Total GMFM-88 scores and dimensions scores were determined. In addition, GMFM-66 scores were determined with the Gross Motor Ability Estimator.

Other neuromotor tests used were the AIMS[15], the BSID-II PDI, Dutch version[16], and the IMP.[17] The AIMS is a reliable and valid[15] instrument to assess gross motor development in infants from birth through 18 months or when a child is independently walking. The BSID-II PDI is a reliable and valid tool frequently used to measure fine and gross motor skills.[16] Both the AIMS and the BSID-II PDI are discriminative, norm-referenced measures standardized on a population-based sample.[15,16] Clinically, the AIMS and BSID-II PDI are not only used to detect children at risk for developmental disorders but they are also often applied as tools to describe developmental change.[22,23] The IMP is a recently developed video-based assessment that provides information on a child's motor repertoire and his or her ability to adapt motor behavior to the specifics of the situation. It is suitable for the evaluation of motor development in infants developing typically or atypically. The IMP consists of 5 subscales: variation, variability, performance,symmetry, and fluency. The initial studies of the psychometric properties of the IMP indicate satisfactory to good reliability and validity.[17,24] In this study, we used the IMP's performance scale to measure motor abilities in a way comparable to that of the other neuromotor tests.

Neurological condition was assessedwith the Touwen Infant Neurological Examination.[25] The Touwen Infant Neurological Examination assessment at T3 was used to describe the infant's neurological outcome at the end of the study period. The Touwen Infant Neurological Examination is a reliable neurological examination that includes traditional neurological signs and also quality of motor behavior.[25] Children were classified as neurologically normal, minor neurological dysfunction, or neurologically abnormal. The latter implies the presence of a clear neurological syndrome, such as a hemisyndrome. The GMFCS levels were determined to give an impression of the level of functioning, keeping in mind that GMFCS levels are less precise at young ages and should be redetermined after the age of 2 years.[26]

Data Analyses

We first plotted developmental trajectories of the GMFM-88 and GMFM-66 scores and the other neuromotor tests (AIMS, BSID-II PDI, IMP performance scale) and assessed changes over time with non–parametric-related sample tests (Friedman and Wilcoxon sign rank tests). An α level of less than .05 was considered statistically significant. For the AIMS and the BSID-II PDI, raw scores were used because most infants scored below the minimum score for their age. The use of raw scores has been described for the BSID-II PDI, with the argument that using raw scores may have advantages in comparison with using developmental indexes for certain infants, for example, infants born preterm.[27] Similar arguments may be applicable for the AIMS.

Next, we summarized the problems encountered in the application of GMFM-88 and GMFM-66 and formulated suggestions for adaptations to improve application of the GMFM in infancy. Finally, we applied the suggestions in our study sample and calculated adapted GMFM scores. We visualized and compared the developmental trajectories of the original and adapted GMFM scores and compared them with those of the other neuromotor tests.

RESULTS

Neuromotor Development

At the final examination, 6 children were classified as neurologically abnormal, the other 6 showedminor neurological dysfunction. Details of neuromotor condition measured with the various tests are provided in Table 1.

Developmental Trajectories of GMFM Scores and Other Neuromotor Tests

Both GMFM-88 and GMFM-66 scores and the scores on the other neuromotor tests (AIMS, BSID-II PDI, IMP performance scale) changed significantly over time (Friedman P=.0001; Figure 1A).During the first 6 months of observation, the infants showed a substantial increase in scores of all neuromotor tests (Wilcoxon P: AIMS, .002; BSID-II PDI, .003; IMP performance, .002; GMFM-88 total score, .002; GMFM-66, .002). In the second half year of observation, the scores of the AIMS (P = .007), BSIDII PDI (P = .007), IMP (P = .010), and GMFM-66 (P =.003) continued to show statistically significant increases, whereas the increase in GMFM-88 total score failed to reach statistical significance.

Inspection of the individual GMFM-88 data revealed that most infants clearly changed over time. Some children, however, showed only minor changes in GMFM-88 scores, that is, only minor improvement or deterioration in GMFM-88 scores. This phenomenon was observed especially between T2 and T3 (Figure 2A), where the curve of the GMFM-88 in

comparison with the other neuromotor tests flattened (Figure 1A). The relative flattening of the GMFM-88 curve was brought about especially by dimension A, where scores dropped with increasing age (Figure 1B).

The GMFM-66 scores improved between T2 and T3 in 11 of 12 infants (Figure 2B). However, we also noted that application of the GMFM-66 resulted in identical scores in 8 of 24 assessments at T0 and T1 (score 22.66; Figure 2B), whereas the GMFM-88 (and the other measures of motor development) suggested more heterogeneity. The GMFM-88 scores at T0 and T1 were identical only on 2 occasions (Figure 2B). The findings suggest that the GMFM-88 is the better tool to differentiate gross motor function in infants with relatively low motor abilities, whereas the GMFM-66 differentiates better when infants have developed more motor skills.

The advantages and limitations of the GMFM-88 and GMFM-66 in infancy may hamper, however, their longitudinal use in infancy. We therefore embarked on the development of adaptations of the GMFM, which may result in scores that reflect developmental change and within-group variation throughout infancy.

In the next paragraphs, we first describe the problems that we encountered when applying the GMFM-88. We continue with suggestions for solutions to improve the use of the GMFM in infancy to monitor development at young age. Finally, the resulting adaptation of the GMFM was applied to describe developmental change in the 12 infants included in the study.

Table 1: Developmental outcome on the various neuromotor tests.

	T0 (baseline)	T1 (3 months)	T2 (6 months)	T3 (12 months)
Age				
- Median	3.5	7	10	15.5
- Range	1.5-7	4.5-10	7.5-14	14-20
AIMS				
- Median	6	12	22	43
- Range	2-19	4-46	7-45	5-57
BSID-II PDI				
- Median	14	31	37	56
- Range	8-36	7-54	4-61	4-107
IMP performance				
- Median	67	74	76	80
- Range	56-75	62-83	62-84	64-87
TINE				
- N/MND/A*	0/3/9	0/4/8	0/4/8	0/6/6
GMFCS				
- I/II/III/IV/V	Not applied	Not applied	Not applied	1/2/1/0/2

AIMS: Alberta Infant Motor Scale; BSID-II PDI: Bayley Scales of Infants Development Scales – Psychomotor Development Index; GMFCS: Gross Motor Function Classification System; IMP: Infant Motor Profile; TINE: Touwen Infant Neurological Examination; * N: neurologically normal; MND: Minor Neurological Dysfunction; A: neurologically abnormal.

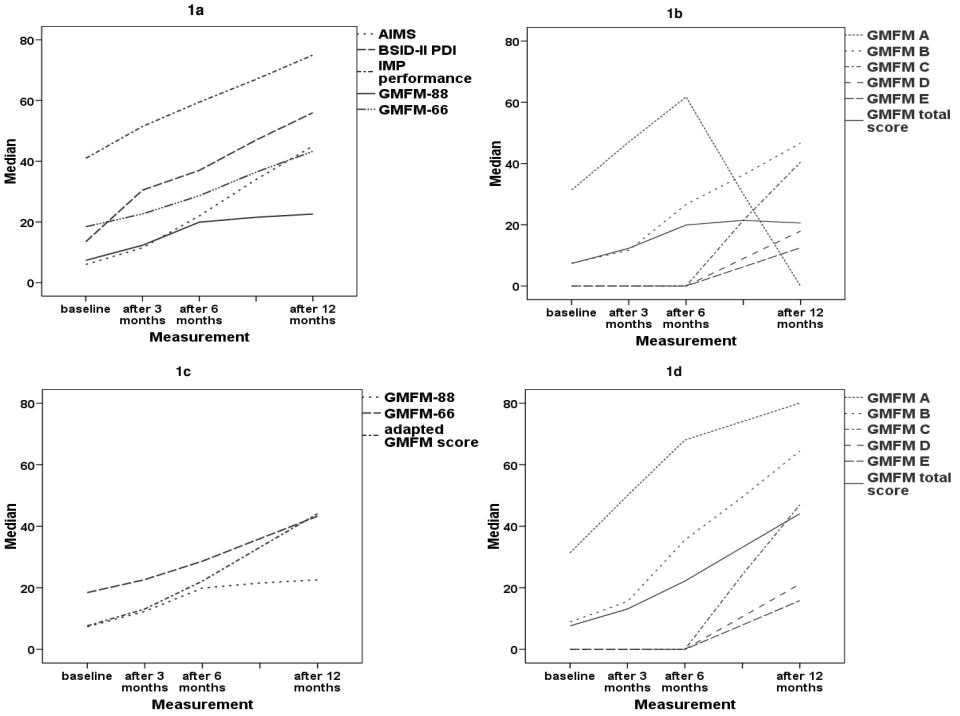

Figure 1. Developmental curves of group values of the GMFM and other neuromotor tests. a, Total GMFM-88 scores, GMFM-66, and other neuromotor tests. b, GMFM-88 total scores and dimension scores. c, Total GMFM-88, GFMF-66, and adapted GMFM scores. d, Adapted total GMFM-88 scores and adapted dimension scores. AIMS indicates Alberta Infant Motor Scale; BSID, Bayley Scales of Infant Development Psychomotor Development Index; GMFM, Gross Motor Function Measure; IMP, Infant Motor Profile.

GMFM: Practical Problems and Their Solutions

The practical problems and suggestions for solutions are summarized in Table 2. The nature of the practical problems during GMFM assessments was related to the infants' abilities, in particular, their ability to crawl. In the 48 measurements that were performed, we assessed 31 times (of the 48 measurements) an infant who did not show progression in the prone position; 6 times an infant who crept (abdominal crawling), and 11 times an infant who crawled (move on all fours, without abdominal support). During 5 assessments, the infant walked independently.

Infants Who Are Not Yet Able to Crawl on All Fours.

Few problems were encountered for the infants who were not yet able to crawl. Infants who were not crawling demonstrated items in dimensions A and B, with an occasional

addition of the "creeping" item of dimension C (C38). The difficulties met were related to the specifics of infant behavior. The items and the difficulties encountered are listed in Table 2. This table also includes suggestions for adaptation. The ability to creep is not included in the GMFM-66. In our opinion, creeping is an important motor ability, as it is the earliest form of locomotion[30-32], and being able to locomote and thereby to explore the environment is associated with improved cognition.[33] Therefore, we suggest including the "creeping" item in the evaluation of infant performance. We suggest giving credit for the creeping item if infants are able to crawl, because the presence of the ability to crawl usually puts an end to creeping behavior.

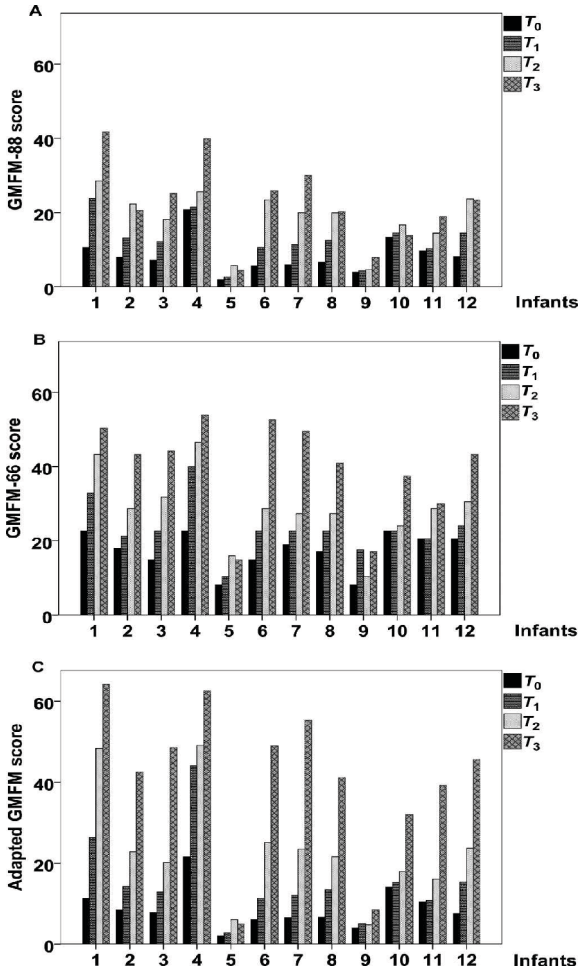

Figure 2. GMFM scores of individual infants. A, Total GMFM-88 scores. B, GMFM-66 scores. C, Total adapted GMFM scores. GMFM indicates Gross Motor Function Measure.

Infants Younger Than 2 Years Who Prefer the Prone Position (With or Without Progression in Prone Position).

When infants are able to roll, some will immediately turn to the prone position when placed in the supine position. This means that they are awarded no points for the supine position, although for most children, it is obvious that they are able to perform supine position items. Our suggestion for adaptation of GMFM scoring in infants who immediately turn into the prone position when placed in the supine position is the following: the score of dimension A would be equal to the score of all prone position items divided by the maximum prone position score of dimension A (including rolling into prone position; maximum 30 points).

Infants Younger Than 2 Years Who Are Able to Crawl on All Fours.

By the time infants develop more motor abilities, they usually will not show the previously acquired easier ones. For example, when an infant is able to crawl, he/she usually does not show prone position behavior, as the infant has a strong urge to crawl. The easier items cannot be elicited either, as verbal instruction does not work very well in infancy. The inability to follow verbal instructions makes the situation in infants different from that in older children. As the GMFM is based on behavior that is observed, this may result in relatively low scores and no or rather small improvements in the total GMFM score despite favorable progression of motor development. Especially dimension A is difficult to elicit when an infant is able to crawl. This may induce a sudden drop in the score of dimension A with increasing age (Figure 1B), and interfere with an increase in total GMFM-88 score matching advanced development (Figure 2A).

Our suggestions for adaptation of GMFM scoring in infants who are able to crawl on all fours include the following (for details, see Table 2). First, if the infant does not show the items of dimension A, award an 80% score for dimension A. This is an arbitrary choice based on the dual notion of advanced development and the observation that most children do not reach a maximum GMFM score. Second, remove items A3, B19, B20, B34, C49, C50, D60, D61, E70, E73, and E74. Removal of the items results in lower maximum scores for the GMFM dimensions. Adapted maximum scores for the various dimensions are A, 48 (originally 51); B, 51 (originally 60); C, 36 (originally 42); D, 33 (originally 39); and E, 63 (originally 72). An alternative approach would be to use clinical judgment to infer what the infant would be able to achieve. However, we refrained from this solution to keep as closely as possible to one of the basic principles of GMFM assessment: scores are based on observed behavior.

Table 2: GMFM-88 items that were problematic in infants, with suggestions for adaptations

Item	Encountered problems	Suggested solution
a) GMFM - Dimension A: Lying and rolling		
A1: Supine, head in midline: Turns head with extremities symmetrical 0. does not maintain head in midline 1. maintains head in midline 1-3 seconds 2. maintains head in midline, turns head with extremities asymmetrical 3. turns head with extremities symmetrical	Difficult to interpret or score as two phenomena are assessed, i.e., ability to maintain the head in midline position and dependency of arm movements on head position.	Adapted scoring: 0. does not maintain head in midline 1. maintains head in midline 1-3 seconds 2. maintains head in midline > 3 seconds, arm motility depends on head position 3. maintains head in midline > 3 seconds, arm motility independent of head position
A3: Supine: lifts head 45˚ 0. does not initiate neck flexion 1. initiates neck flexion 2. lifts head <45˚ 3. lifts head >45˚	Difficult to interpret as most typically developing infants do not lift their head > 45^0 in supine position.	Remove the item.
A11: Prone on forearms: lifts head upright, elbows extended, chest raised 0. does not initiate head lifting 1. initiates head lifting, chin does not clear mat 2. lifts head, does not attain upright, weight on forearms 3. lifts head upright, elbows extended, chest raised	A11 overlaps with A10 (score 0 and 1 are the same), which makes dimension A less sensitive to changes. We suggest to change A11 to prevent this overlap.	Adaptation of item A11: Prone on forearms: 0. does not use forearms to lift chest 1. initiates use of forearms to lift chest, but does not succeed 2. weight on forearms, without elbow extension 3. weight on forearms, with elbow extension
A14/15: Prone: rolls to supine over right/left side 0. does not initiate rolling 1. initiates rolling 2. rolls part way to supine 3. rolls to supine over right/ left side	Difficult to interpret or score as the word initiates suggests a voluntary action of the infant. It is however in infancy not always clear whether the rolling action of an infant is voluntary or involuntary.	Add to the instruction that any rolling action, voluntary or involuntary, allows for a positive score.
b) GMFM – Dimension B: Sitting		
B18: Supine, hands grasped by examiner: pulls self to sitting with head control.	Infants with better motor abilities refuse to lie in supine or will make a game of pull to sit and will deliberately 'hang' in the examiner's hands.	Infants who are able to sit up independently are awarded 3 points.

Table 2: GMFM-88 items that were problematic in infants, with suggestions for adaptations (Continued)

Item	Encountered problems	Suggested solution
B19/20: Supine: rolls to right/left side, attains sitting 0. does not initiate sitting from right/left side lying 1. rolls to right/left side, initiates sitting 2. rolls to right/left side, partially attains sitting 3. rolls to right/left side, attains sitting	Difficult to elicit in infancy.	Remove the item.
B30: Sitting on mat: Lowers to prone with control 0. does not initiate lowering to prone 1. initiates lowering to prone 2. lowers to prone, but 'crashes' 3. lowers to prone with control	Infants with better motor abilities will not lower to prone but will move for example to crawling position.	Adaptation of item B30: Sitting on mat: Lowers with control to any prone position, including crawling position. 0. does not initiate lowering to prone 1. initiates lowering to prone 2. lowers to prone, but 'crashes' 3. lowers to prone with control
B34: Sit on bench: Maintains, arms and feet free, 10 seconds 0. does not maintain sitting on bench 1. maintains, arms propped and feet supported, 10 seconds 2. maintains, arms free and feet supported, 10 seconds 3. maintains, arms and feet free, 10 seconds	Limited attention span interferes with the maintenance of this position.	Remove the item.
c) GMFM – Dimension C: Crawling and kneeling		
C38: Prone: Creeps forward 1.8 m 0. does not initiate creeping forward 1. creeps forward <60 cm (2ft) 2. creeps forward 60 cm-1.5 m (2-5 ft) 3. creeps forward 1.8 m (6 ft)	Infants with better motor abilities will not show creeping anymore.	If an infant is able to crawl, award 3 points.
C39: 4 Point kneeling: maintains, weight on hands and knees, 10 seconds (with or without progression) 0. does not maintain weight on hands and knees 1. maintains weight on hands and knees, <3 seconds 2. maintains weight on hands and knees, 3-9 seconds 3. maintains weight on hands and knees, 10 seconds	Limited attention span interferes with the maintenance of this position; this interferes in infants who are well able to crawl on all fours.	If an infant is able to crawl on all fours, it may be inferred that he/she is able to maintain weight on hands and knees for at least 10 seconds. In other words, infants able to crawl on all fours are awarded 3 points.

Table 2: GMFM-88 items that were problematic in infants, with suggestions for adaptations (Continued)

Item	Encountered problems	Suggested solution
C49&C50: High kneeling: attains half kneeling on right/left knee using arms, maintains, arms free, 10 seconds. 0. when placed, does not maintain holding 1. when placed, maintains holding on, 10 seconds 2. attains, half kneeling holding on, maintains 10 seconds 3. attains, half kneeling using arms, maintains arms free, 10 seconds	Difficult to elicit.	Remove the item.
d) GMFM – Dimension D: Standing and GMFM – dimension E: Walking, Running and Jumping		
D60&D61: High kneeling: attains standing through half kneeling on right/left knee, without using arms. 0. does not initiate standing 1. initiates standing 2. attains standing using arm(s) 3. attains standing through	Difficult to elicit.	Remove the item.
E70: Standing: walks forward 10 steps, stops, turns 180º, returns. 0. walks forward 10 steps, does not stop without falling 1. walks forward 10 steps, stops, does not initiate turn 2. walks forward 10 step, stops, turns <180º 3. walks forward 10 steps, turns 180º, returns	Difficult to elicit, especially the 'stopping' and returning part.	Remove the item.
E73&E74: Standing, walks forward 10 consecutive steps between parallel lines 20 cm apart/on a straight line. 0. does not initiate walking forward 1. walks forward <3 consecutive steps 2. walks forward 3-9 consecutive steps 3. walks forward 10 consecutive steps	Difficult to elicit.	Remove the item.

Table 2: GMFM-88 items that were problematic in infants, with suggestions for adaptations (Continued)

Item	Encountered problems	Suggested solution
E75&E76: Standing: steps over a stick at knee level, right/left foot leading. 0. does not initiate stepping over stick 1. steps over stick 5-7.5 cm 2. steps over stick at mid-calf level 3. steps over stick at knee level	Some infants perform this item with help.	Give a partial score (i.e. score 1) if an infant performs this item with help.
E88: Standing on 15 cm step: jumps off, both feet simultaneously. 0. does not initiate jumping off step, both feet simultaneously 1. jumps off, both feet simultaneously, but falls 2. jumps off, both feet simultaneously, but uses hands on floor to avoid falling 3. jumps off, both feet simultaneously	Some infants perform this item with help.	Give a partial score (i.e. score 1) if an infant performs this item with help.

Developmental Trajectories of the Adapted GMFM Scores

Application of the adapted GMFM scores resulted in GMFM trajectories that like the GMFM-66 trajectories did not flatten (Figure 2C). The adapted GMFM total score improved significantly over time (Friedman P = .0001), not only during the first 6 months of observation (Wilcoxon P= .002) but also during the second 6 months (Wilcoxon P=.003). Inspection of the individual data showed improvement over time in virtually all instances and substantial heterogeneity in scores (only 2 instances of identical scores at T0 and T1). Application of the adapted GMFM abolished the decrease of dimension A of the GMFM-88 with increasing age and changed it into an increase (Figure 1D). Visual inspection of the developmental curves of the various versions of the GMFM (eye balling) of the children who were diagnosed with CP (n = 6) and those not diagnosed with CP (n = 6) suggested that the curves of the 2 groups were largely similar, however, with lower scores in children with probable CP than in children without probable CP (Figure 3).

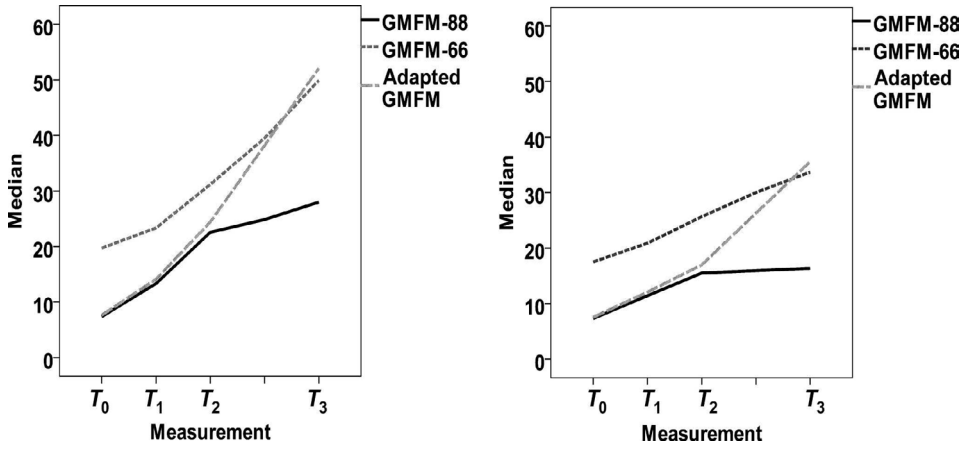

Figure 3. GMFM scores over time for infants with and without probable CP. Left, Infants who will probably not develop CP. Right, Infants who will probably develop CP. CP indicates cerebral palsy; GMFM, Gross Motor Function Measure.

DISCUSSION

This study indicated that the application of the GMFM in infancy is associated with practical problems. This held true for the GMFM-88 and GMFM-66, but for each version in a different way, which hampers the longitudinal use of the GMFM during infancy. We therefore made some suggestions for an adapted GMFM for infants younger than 2 years.

The finding that GMFM-88 scores improved less when infants grew older could be largely attributed to behaviors specific to young children: infants, in general, do not show previously acquired motor abilities when they are able to perform more difficult ones. This means that infants who show progress in motor behavior "fail" to show "easier" behavior with negative consequences for the GMFM-88 score. This was also described by Kolobe et al.[13] They suggested awarding points for some items when other items are already passed[13], similar to some of our adaptations. Jelsma et al[12], who applied the GMFM-88 in infancy, reported nonlinear development. We found similar non-linearity that disappeared with the use of the adapted GMFM. Wei et al[14], however, did not describe practical problems when using the GMFM to assess children from 0 to 3 years and concluded that the GMFM-66 is a reliable and valid instrument at young ages. A possible explanation for the different appreciation of the applicability of the GMFM in the Wei et al study could be related to the group studied. While in the current study and the studies of Kolobe et al[13] and Jelsma et al[12], infants at a very high risk for CP with and without an established diagnosis were assessed. On the contrary, Wei et al assessed children who all had the diagnosis CP at the ages of 3 to 36 months. In general, it is difficult to diagnose CP during the first postnatal year. In children with the more severe forms of CP, however, the probable diagnosis of CP can be made

earlier.[10] This might imply that the youngest infants studied by Wei et al had a severe type of CP and relatively low motor abilities. Such children usually are not able to crawl, which makes the GMFM easier to apply. In addition, a substantial part of the Wei et al sample was older than 2 years, which increases the possibility for instruction of the child. Moreover, in contrast to our study, the focus of the Wei et al study was not on developmental change, as only 40% of the children had more than 1 assessment.

We choose the GMFM-88 as a starting point for our suggestions for an adapted GMFM version to prevent loss of important information, especially in the lower-ability dimensions and to be able to profit from the fact that the GMFM-88 also furnishes dimension scores in addition to the total score. The presence of dimension scores is an advantage because, in infancy, dimension scores reflect functional level in more detail than the total score. The GMFM-66 contains few items from the lower-ability dimensions, thereby possibly limiting its sensitivity to change in the youngest infants. The GMFM-66 and adapted GMFM version reached about the same point after 12 months (Figure 1C). However, in the beginning, the GMFM-66 did not differentiate as well as the adapted version, because the GMFM-66 uses only a few lower-ability items. The adapted GMFM version is designed for clinical use, that is, the documentation of individual trajectories reflecting developmental change from an early age onwards by means of measurable and interpretable items. To this end, we combined the clinical usefulness of the GMFM-88,maintaining the dimension scores, with the longitudinal advantages of the GMFM-66. Inclusion of the lower-ability dimension items has the advantage of applicability in young infants and severely affected infants.

The strengths of our study are the exploratory character to discover and solve practical problems and the longitudinal design with 4 data points at early ages, which made it possible to analyze 48 assessments of 12 children. Infants were at risk of CP, according to well-defined strict inclusion criteria.[18] At the data collection points, GMFM scores were compared with those of 3 other neuromotor tests, which allowed for a comprehensive comparison.

In contrast, the small sample size is a major limitation. We based our suggestions for adaptations on critically judging whether items would work in infancy taking into account the age-specific characteristics of the developing infant. It is good to note that some of our decisions have a clinically based character. We tested the adaptations of the GMFM in our small study population. This means that our study certainly precludes firm conclusions. More research in larger groups of infants is needed to study the applicability, reliability, and validity of the adapted GMFM version for infants, and in particular its sensitivity to change. Another limitation is the varying age at which the infants were included and examined. Infants were included between 1 and 9 months corrected age and were examined 3, 6, and 12 months after inclusion. We do not consider this a major limitation, because developmental change is more important in children with or at high risk of CP than age-

related performance. In this study, half of the children were diagnosed with CP at 18 months. The age of 18 months is relatively early to diagnose CP. It is conceivable that some of the children grow out of their diagnosis, while others will grow into it.[10] Interestingly, visual comparison of the developmental trajectories of GMFM scores of the infants with CP at 18 months with those of children without CP suggested that the GMFM curves in both groups were similar. In addition, it may be regarded as a limitation that we used the raw scores of the AIMS and BSID-II PDI. We used raw scores as they showed changes over time while percentile scores (AIMS) or developmental scores (PDI) were insensitive to change as the children consistently scored below the minimal required level to calculate these scores (see also Janssen et al[27]). In our comparison between GMFM scores and development measured with other neurodevelopmental tools, we were hampered by the fact that no reference standard exists for testing change in and evaluation of motor function in infancy.[34]

Finally, it is good to realize that at the end of the study, the infants' ages were 14 to 20 months. All had neurological dysfunction. But it was not clear whether all infants would develop CP, because especially the milder types of CP are difficult to diagnose at early ages.[10,11]

CONCLUSIONS

Application of the GMFM before the age of 2 years is hampered by age-specific limitations. We therefore suggest age and function-specific adaptations to facilitate the use of the valuable GMFM in infancy. Our preliminary data suggest that the sensitivity to change of the adapted GMFM version is promising. Further research is, however, required to assess the reliability and validity of the adapted version of the GMFM in infancy.

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LETTER TO THE EDITOR

TIME TO UPDATE THE GROSS MOTOR FUNCTION CLASSIFICATION SYSTEM (GMFCS) FOR EARLY AGE BANDS BY INCORPORATION OF ASSISTED MOBILITY?

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We recently questioned how to classify young children with severe forms of cerebral palsy (CP) according to the Gross Motor Function Classification System (GMFCS).[1,2] The issue arose from the introduction of assisted mobility at an early age. The following case serves as an example.

A 22-month-old girl had a history of prematurity and cystic periventricular leukomalacia. The girl fulfilled the clinical criteria for bilateral spastic CP, including a stereotyped posture and motility, hypertonia, more pronounced in the legs than in the arms, and exaggerated reflexes. She was not able to roll from the supine to prone positions or reverse. In the prone position, she did not bear weight on her arms, but she was able to lift her head from the surface for a very short period, although she did not succeed to maintain her head lifted. The girl was not able to sit independently, but with trunk support, she was able to look around and move her head in different directions. She was able to balance her head in supported sitting position, but she was not able to maintain her head against gravity in the prone position, and not able to roll. She fulfilled the criteria of GMFCS level V ("physical impairments limit voluntary control of movement. Infants are unable to maintain antigravity head and trunk postures in prone and sitting. Infants require adult assistance to roll"), than those of GMFCS level IV ("infants have head control but trunk support is required for floor sitting. Infants can roll to supine and may roll to prone"), according to the classification before the second birthday.

However, the girl had used a manual wheelchair for a month. In the wheelchair, the girl was able to move around by herself, at home and in the clinic, and showed goal directed, voluntary locomotion. In terms of functional mobility, this means that she was able to move independently indoors. Using the general age-independent rules to determine the GMFCS level, this would mean that the girl fulfilled the criteria for GMFCS level IV: "Self-Mobility with Limitations; may use Powered Mobility." The GMFCS also states that the distinction between levels IV and V is based on rules for independent mobility: "Children and youth in Level V have severe limitations in head and trunk control and require extensive assisted technology and physical assistance. Self-mobility is achieved only if the child/youth can learn how to operate a powered wheelchair." According to this decision rule, the girl's gross motor function also would be better classified as a GMFCS level IV.

Our case illustrates that the introduction of assisted mobility in children with CP before the age of 2 years may result in difficulties in determining the appropriate GMFCS level, as the general criteria for the distinction between levels IV and V do not match the criteria of the GMFCS before the second birthday. The beneficial effect of wheeled mobility at an early age is increasingly acknowledged. Being able tomove around and explore the environment is associated with a positive effect on development.[3,4]

We therefore propose to adapt the criteria for GMFCS level IV for children younger than 2 years in the following way: "Infants have head control but trunk support is required

for floor sitting. Infants may roll to supine and prone. Children may achieve self-mobility using amanual or powered wheelchair." For level V below age 2 years, we recommend the following adaptation: "Physical impairments limit voluntary control of movement. Infants are unable to maintain antigravity head and trunk postures in prone and sitting. Infants require adult assistance to roll. Some children achieve self-mobility using a powered wheelchair with extensive adaptations." It is known that the accuracy of the GMFCS classification is lower before the second birthday.[5] Conceivably, the suggested adaptations may result in a higher stability of the higher GMFCS levels from early age onwards.

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GENERAL DISCUSSION

9

This thesis started with the description of the intriguing, complex process of early brain development, the multiple factors that may affect it, and questions whether it is possible to positively contribute to this process.

The introduction covered principles of brain development on the basis of the 'modified Kennard principle': *'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'*. In the following discussion, those principles are presented again, but now discussed in the light of the findings of this thesis, i.e., are the results of the studies in line with the expectations and – last but not least – does this have consequences for early intervention?

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

'…have as little of it as possible'

The statement that less severe brain damage results in better outcome than more severe brain damage, was confirmed in this thesis. Both the review (chapter 2) and the intervention studies (chapter 4 and 6) showed that infants with severe brain lesions are more at risk of developing neurodevelopmental disabilities than infants without or with less severe brain lesions. Especially, infants with cystic periventricular leukomalacia (cPVL) with diffuse damage of the white matter, are at very high risk. Percentages of the infants who developed Cerebral Palsy (CP) were 86% in the review, and both in the Vroegtijdig Interventie Project (VIP) and LEARN2MOVE0-2 (L2M0-2) study 100%.

Severity of brain lesion is one of the major predictors for outcome, but not the only factor, nicely illustrated with the findings in the VIP- and L2M0-2-study. Infants in the VIP-study were included on the basis of clinical observation, presenting with definitely abnormal general movements, and only a minority (13% (6/46)) of them had a severe brain lesion. In the L2M0-2 study, inclusion criteria were largely based on severe brain lesions, resulting in 77% (33/43) of the infants presenting with a severe brain lesion. Indeed, better neurodevelopmental outcome was found for infants who participated in the VIP-study than in the L2M0-2-study, in line with the hypothesis 'have as little brain damage as possible'. In the VIP-study, less than a quarter of the infants developed CP, in the L2M0-2-study about half of the infants. However, mentioned numbers also show that severity of brain lesion is not the only predicting factor for outcome: in the VIP-study, the percentage of infants who developed CP was higher (23% (10/44 (2 unknown))) than the percentage of infants with severe brain lesions (13%), i.e., about half of the infants who developed CP did not have a severe brain lesion. In the L2M0-2-study, it was the other way around: most infants had severe brain lesions (77%), but the percentage of infants who developed CP was lower (54% (22/41 (2 unknown))), i.e. part of the infants with a severe brain lesion did not develop CP. The results emphasise that extent and severity of brain lesions are important , but definitely not the only predicting factor for

outcome. Clinical observation, such as use of general movements as shown in the VIP-study, is also an important predictive tool for neurodevelopmental outcome. This is in line with literature findings, which show that combining instruments, such as brain imaging, clinical observation and examination, predict outcome best.[1,2,3]

Concerning possibilities for intervention in relation to severity of brain lesions, the intervention studies showed also interesting findings. In both intervention studies, outcome at RCT-level was comparable for COPCA (COPing with and CAring for infants with special needs) and TIP (Typical Infant Physiotherapy), and no interactions between brain lesion and intervention on outcome were found in the L2M0-2-study. After analysing contents of intervention, specific interventional elements were related to infant outcome in the VIP-study, but not in the L2M0-2-study. These findings may be related to the differences in infant characteristics: as described above, majority of infants in the L2M0-2-study had severe brain lesions and were generally more severely affected than infants in the VIP-study, in which most infants did not have severe brain lesions. Differences in findings may imply that a less severely affected brain may be more susceptible for interventional elements than a more affected brain, which may have less abilities to reorganize and compensate. It raises questions about whether interventions should be specifically tailored to the type and extent of the brain lesion or the infant's clinical presentation. It is conceivable that an infant has to show a certain degree of motor abilities, to be able to intervene on, or to be responsive to motor challenges by the caregiver or physiotherapist. In case motor abilities are very limited due to extended brain damage, challenging is difficult and assistance may be an alternative.

With increasing possibilities of imaging techniques, localizing brain injury becomes more and more accurate, which improves understanding relations between localization, extent of brain damage and outcome.[4,5] It may assist in studying effects of intervention in infants with specific brain lesions. However, literature and this thesis show that clinical observation and examination should not be forgotten.

'…have it early'

The statement '…have it early' is based on principles of brain plasticity, in which effects of brain damage were measured in a young, immature brain, compared with a more mature brain. In this thesis, predominantly very early brain damage was studied, i.e. in the preterm or term neonatal period. Therefore, I will discuss this statement a little bit different than it is meant by the original principle, and will focus on differences in brain lesions and outcome for infants born preterm in comparison with those born near or around term age.

According to the WHO definition[6], a preterm infant is born below a gestational age (GA) of 37 weeks, with specification of time frames: moderate to late preterm between 32 and 37 weeks GA; very preterm between 28 and 32 weeks GA; extremely preterm below

28 weeks GA. In the VIP-study, inclusion took place on the Neonatal Intensive Care Unit (NICU), and majority of the included infants was born preterm (91% (42/46)), often very or extremely preterm (78% (36/46)). It reflects a selected NICU-population with a relatively high proportion of preterms.[7] In the L2M0-2-study, numbers are a bit different: 67% (29/43) of the infants was born preterm, 51% (22/43) very or extremely preterm. The differences in GA's, were also represented in type of brain injury: in the VIP-study, infants who had brain lesions most often presented with lesions related to prematurity: periventricular brain lesions or intraventricular haemorrhages. In the L2M-0-2-study type of injury was strongly related to GA: moderately to late preterm and term infants had most often cortical infarctions, basal ganglia or thalamic lesions. Extremely and very preterm infants presented usually with periventricular leukomalacia. Posthaemorrhagic porencephaly was present both in preterm and term infants, but more in preterm infants. What should be noted is, that being born at term, does not mean that timing of brain injury was also near or at term age. For example, posthaemorrhagic porencephaly could be the result of preterm brain injury, but consequences may present after term birth.

It is difficult to compare outcome of the VIP- and L2M0-2-study based on GA's, because more infants with severe brain injury participated in the L2M0-2-study. In the VIP-study, 19% (7/36) of the very to extremely born infants developed CP, in the L2M0-2-study 64% (14/22). However, from the very to extremely preterm infants, only 11% (4/36) in the VIP-study had a severe brain lesion, whereas 82% (18/22) of the infants in the L2M0-2-study had. In both intervention studies, severe brain injury in the form of cPVL, was only present in preterm infants. It resulted in all cases in CP, usually a more severe type. It may reflect the sensitivity of the preterm infant and its brain, in the period in which the subplate is active and in which damage to the subcortical white matter is often diffuse, affecting the important process of neural migration.[8] It may be concluded that the combination of prematurity with severe brain lesions makes infants more vulnerable for severe neurodevelopmental disorders than infants with severe brain lesions at near term or term age. Those findings are comparable with literature.[9,10,11] In this sense, the statement 'have brain damage early' holds not true. But as mentioned before, the original statement does not focus on the period which we investigated now and therefore, we could not extend our findings to later periods of brain development. Another point that should be mentioned is that studies in this thesis and in cited literature have been performed in Western countries, having in general quickly applied and good organized medical neonatal care. Accessibility to standard high care and newly developed interventions for term newborns, such as hypothermia, diminish mortality and morbidity.[12,13] Therefore, concluding that preterm brain injury causes more severe neurodisability than term injury, cannot automatically be extended to countries where access to and timing of providing optimal health care is not as common as in our countries.[14]

Next to the 'best' timing of brain injury, the optimal timing of intervention is an important question. General principles of 'the early the better', based on the principles of brain plasticity, are usually applied, also in our intervention studies. Clear evidence however, that early intervention is better than later or no intervention, is lacking, especially for the very high risk infants.[15,16,17] This thesis does not help answering the question about optimal timing of intervention, because we did not include a control group without or with a later start of intervention, which is in general regarded unethical.

'…have it just on one side'

Findings in this thesis endorse the theorem that unilateral brain damage results in general in better outcome than bilateral brain damage. In the VIP-study, the number of infants with severe brain lesions was low (n=6) and lateralization was not specified. In the L2M0-2-study, more than half of the brain lesions were bilateral. Seventy-four percent (14/19) of the infant with bilateral lesions developed CP, all of them bilateral CP. Sixty-two percent (8/13) of the infants with unilateral lesions developed CP, of them 63% (5/8) unilateral and 37% (3/8) bilateral CP. Unilateral lesions resulted more often in less severe CP with lower Gross Motor Function Classification System (GMFCS)-levels,[18] bilateral lesions resulted in higher GMFCS-levels. Results of the L2M0-2-study are comparable with results from the systematic review (chapter 2): unilateral lesions often result in better motor and cognitive outcome than bilateral lesions.

However, it is intriguing that literature and the L2M0-2-study also showed that unilateral brain lesion may result in bilateral CP and vice versa. One of the explanations may be that infants with diagnosed unilateral brain lesions, may also have had some contralateral injury, perhaps too small to identify with used imaging. On the other hand, it may also tell something about the bilateral connections needed for certain motor function, and regenerating or compensating mechanisms within a brain which may compensate for bilateral damage.[19,20] Knowledge and assumptions about underlying working mechanisms of the bilateral working brain, have been implemented in interventions. Examples are the Constraint Induced Movement Therapy (CIMT) and Bimanual Training, specifically targeted at children with a unilateral type of CP.[20] This type of intervention is also under investigation in infancy, with youngest infants of 7 months old, and preliminary results are promising.[21] Prerequisite for starting such an intervention however, is that there should be an asymmetry and generally, at very young age asymmetries are not yet present.

To conclude, I can agree with the statement 'have brain damage just on one side', as unilateral brain lesions result less often in neurodevelopmental disability than bilateral ones. However, as shown in this thesis, individual exceptions are not unusual and may tell us something about the complex wiring of the brain. Interventions targeting asymmetries can just be started when asymmetries become present. Therefore, they seem not to play a

specific role in very early intervention, but studies show promising results after asymmetries have become present, even at young ages.

'…be a girl'

Boys are known to be at higher risk of brain lesions and neurodevelopmental disorders.[22,23] The systematic review (chapter 2) showed that sparse information is available on the effects of sex on outcome for infants with severe brain lesions. The studies which did report about sex differences, suggested more boys presenting with brain lesions, but no clear sex differences in motor and cognitive outcome. Findings of the review are in line with findings in the intervention studies. In the VIP- and L2M0-2-study, the number of included boys and girls differed a bit: in the VIP-study participated 20 boys and 26 girls, in the L2M0-2-study 26 boys and 17 girls. Whereas in the L2M0-2-study inclusion was mainly based on brain lesions, the difference may be a representation of the higher vulnerability for brain lesions in boys.[23,24] In both intervention studies, no effect of sex on outcome was found.

The question whether intervention should be sex specific is an interesting one. The first idea that comes to my mind is not to specify when outcome is not known to be different with a clearly known reason. However, you may wonder if intervention already differs for boys and girls, as interaction of caregivers or physiotherapists with boys and girls may differ. This may be related to personal and cultural gender specific views, but also to sex specific infant behaviour.[25]

'…come from a supportive family'

As mentioned in the introduction, enrichment of the environment is supposed to have positive effects on infant development. In better socio-economic circumstances, it is usually easier to enrich an environment than in circumstances in which the availability of resources is low. In the systematic review (chapter 2), information about socio-economic status was very limited, and therefore, no conclusions could be drawn from it. In the VIP- and L2M0-2-study, caregivers educational level was used as an indicator for socio-economic status. Socio-economic status is not always related to educational level, and therefore it is only used as a proxy measure. In the VIP-study, regarding cognitive outcome, infants with mothers with lower educational levels seemed to benefit more from the COPCA-intervention than from the TIP-intervention.[26] A hypothesis for this finding may be that one of the core components of COPCA, i.e., challenging infants to discover their abilities, may be more incorporated in daily activities in families with higher educational levels, and less in families with a lower educational level. Therefore, stimulating caregivers to challenge their infant may have more effect in lower educated families, and may enrich the infant's environment and stimulate infants to explore, which may positively influence cognitive development.[27] In the L2M0-2-study however, no effects of educational level on outcome were observed. Again, this

may be related to the studied group: a more injured brain, may be less sensitive for (subtle) intervention effects.

Knowledge about the importance of the family and considering caregivers as the experts concerning their child, resulted in the last decades in development of family centred care principles. Family centred care is based on partnerships between families and professionals, in which information is shared, with mutual and equal respect, and decisions in health care are made within the context of the family, aiming to empower families to make their own decisions in health care.[28,29,30] In chapter 3, developments within regular physiotherapy over the years as applied in the Netherlands were studied, aiming to objectify whether theoretical developments have been implemented in practice. Fitting into developments about family centred care, results showed indeed that family involvement increased over the years. Despite larger family involvement, results also suggested that largest part of involvement was still in a relation in which the therapist informed or showed caregivers how they should perform actions. Therefore the goal to form equal partnerships between professionals and caregivers has not been achieved yet. Results are in line with literature: principles of family centred care are widely accepted, but implementation into clinical practice is not always evident.[29] In COPCA, education to the caregivers was most often provided by means of coaching, indicating more partnership than in the control intervention TIP, where training was more common (chapter 6).

Concerning intervention effects on family outcome, I can only discuss the findings from the L2M0-2- study, as family outcome was not measured in the VIP-study. Interestingly, the only effect of intervention on outcome in the L2M0-2-study was found for family outcome and not for infant outcome: COPCA-related intervention elements were positively associated with family empowerment. With the assumption that intervention may only have limited effects on outcome of very high risk infants, as it may not overrule detrimental effects of brain damage, it is not surprising that in the L2M0-2-study only an association of interventional elements with family outcome was observed. However, if family outcome can be influenced positively, it may be conceivable to have a positive effect on infant outcome at the longer term. More family empowerment may reinforce feeling of control over situations, which may have a positive effect on caregivers well-being.[31,32] If caregivers feel better, it is easier to interact in a positive way with their infant. Positive caregiver-infant interactions may benefit child outcome, for example on child's behaviour or well-being.[33] Apart from a possible positive influence of family empowerment on long term infant outcome, the positive association of interventional elements with family outcome by itself may have attractive consequences for society. Caregivers who are better able to make decisions in the health care process, are more self-managing and less dependent from professionals, which may result in diminishing health care costs. Moreover, if well-being is positively influenced, caregivers utilizing mental health care services may also decrease.

'…and live near a good hospital'

Living in the neighbourhood of good hospitals, provides accessibility to the facilities the health care system offers. Whether it is better to live near a good hospital if you have brain damage, sounds logical, but this thesis cannot confirm the statement because all infants had access to neonatal and paediatric care in the Netherlands, which is regarded as high standard care in a Western developed country. Imaging was also available, by ultrasound or MRI. Early accessibility to imaging and high standards of care, makes early detection of infants at high risk possible. However, availability of good imaging techniques does not automatically mean that outcome will be better.[34]

Besides accessibility to good neonatal care, all studied infants had good opportunities for follow-up. All children were monitored by physiotherapists and had also follow-up assessments by paediatricians or child neurologists. Follow-up has several goals: signalling of atypical development, monitoring individual development and predicting future development. Ideally, a measure which has all properties should be used for follow-up. However, practice reveals that it is difficult to develop such a 'gold standard' instrument in infancy.[35] Frequently used measures for children with CP are the GMFCS[18] and the Gross Motor Function Measure (GMFM)[36], both with good psychometric properties in childhood, but less used below the age of two years. In Chapter 8, use of the GMFCS as a classification measure for the severity of CP in infancy is discussed. It advocates for the incorporation of assisted mobility at early age, as implementation of early powered mobility is more and more common.[37] It is known that motor and cognitive development are interrelated.[38,39] Being able to move and therefore explore the world around, may have positive influences on cognition.[40] Therefore, I not only advocate the implementation of assisted mobility in the GMFCS for classification, but also the use of assisted mobility at young age to broaden the infants world and create the opportunity to explore if motor abilities are not sufficient to do so. Unfortunately, creating such opportunities are in general more available in good health care circumstances than in countries in which health care is less developed. In Chapter 7, use of the GMFM in infancy has been described. The GMFM appeared to be difficult to use in infants. Therefore, some suggestions for adaptations in infancy were made. First results are promising, but should be investigated further. Disadvantage of use of an 'extra' infancy instrument is that later on the 'standard' GMFM-measurement is used, and comparison over time is then more difficult. Therefore, development of an instrument which can be used in infancy and later on, with the ability to detect infants at risk, representing actual functioning and the possibility to predict future outcome, would be desirable. The primary outcome used in the VIP- and the L2M0-2-study, the Infant Motor Profile, seems to have many of suggested properties, but norm data are not yet available. Moreover, it is also an instrument for a specific age range and can only be used until children have had some walking experience. Because infancy is a period in which many changes in development

take place with large variation, it is questionable whether the 'ideal' instrument to measure all properties could be developed. Therefore, the combination of use of instruments, together with clinical examination and use of other information such as imaging, remains important. Combining different sources of information, is most easy in good health care circumstances. However, it should be prevented that it results in 'overclassification'. Purpose of classification and measurement should always be kept in mind and not everything possible has to be done. Deciding about measuring, classification and predicting, should be consistent with interests of families and therefore, could differ per family. Some caregivers want to know exactly what they can expect, some do not. I think that both should be respected, under the condition that it does not harm the infant or the family.

Methodological considerations

Studying infants at high risk for cerebral palsy involves many methodological challenges. The first factor which influences most studies is that – fortunately – prevalence of very high risk infants is low. CP is known to have an incidence of about 2 per 1000 newborns. Not all infants are in the picture from birth onwards as being at risk of CP. In general, families of infants recognized as being high risk have already a large burden of care, and additional participation in research may be too much. Therefore, numbers of infants who are eligible for early intervention studies such as described in this thesis is low.

In the described intervention studies, all infants received intervention, either COPCA or TIP. No control group without intervention was included. Actually, knowledge about development in at risk infants without intervention would be very valuable, as it tells something about the 'natural course'. However, it is hardly possible to realize this, as withholding infants intervention is generally considered as unethical, even if no clear evidence exists that doing something is better than doing nothing. Another option to know more about natural course is to compare developmental outcome with that of infants in countries where early intervention is not as common as it is in the Netherlands. However, besides not receiving intervention, infants usually grow up under other circumstances, and therefore results cannot be compared fairly.

What is striking in many early intervention studies, also in this thesis, that effectiveness is limited. On the one hand, this could be related to the fact that natural developmental course can only be influenced to a limited extent, on the other hand, it can be questioned whether adequate study designs are used. What is known, is that contents of physiotherapy is in general heterogeneous. Physiotherapeutic theories develop over time, and application in practice may be a mix of different ingredients, as a result of individual preferences and experiences.[41,42] Therefore, to compare interventions in a two-arm randomized clinical trial (RCT), may be not the best form, as interventions are heterogeneous and partially overlapping.[43] In the first place, due to the existing heterogeneity, more insight is needed in

what really happens within interventions. Both in the VIP- and the L2M0-2-study, a detailed process analysis was performed, providing insight in real contents of applied interventions. Where no difference in outcome on RCT-level was found, associations between contents of intervention and outcome were present, revealing that it is of added value. Besides the added value, it should be noted that you must remain aware of what has been studied: contents of intervention may be related to infant's, caregivers' or physiotherapist's characteristics. Interrelations between characteristics and outcome may be confounding factors in studying relations between interventional elements and outcome. However, no differences in contents of intervention for infants who did and who did not develop CP were found, which suggests that the influence of confounding is limited. Other alternatives for RCT's which have been proposed in literature are for example practice-based evidence, cohort studies, single subject designs, or qualitative research.[43,44,45]

Another methodological shortcoming in early intervention research is that no 'gold standard' for measuring outcome exists, which makes it more difficult to compare outcome of different studies and for example to use them for meta-analysis. Not only being able to measure infant outcome is important, but also the needs and interests of caregivers.

What is also needed, is more information about dosing of interventions. In both the VIP- and the L2M-studies frequency of interventions sessions was reported, but what really matters is knowing about the transfer of interventional elements into daily life activities. If interventional elements are implemented in daily life, dosing is much higher than in some physiotherapy sessions of 30 to 60 minutes. Unfortunately, data from this thesis are not sufficient to answer the question about what dosage is effective. Therefore, it is recommended to develop adequate and realistic measures for dosing of interventional elements in daily life.

Clinical implications

Infants at very high risk of developing CP are a challenging population. It is not known whether applying intervention is better than withholding intervention, as we do insufficiently know about the natural course. Results of this thesis and findings from literature[15,16,17] suggest however, that contents of early intervention should be a mix of ingredients and may have to be individually tailored, adapting to characteristics and wishes of the infant and their families. Suggestions for most effective ingredients of early intervention are: challenging the infant, to elicit motor activities, and coaching the caregivers. Both are positively related to outcome, either infant or family outcome. Moreover, results suggest that effects of intervention on infant outcome may differ, depending on the extent of brain injury or clinical disabilities. If the infant is less severely affected, influencing infant outcome may be possible; if an infant is more severely affected, influencing infant outcome may be limited. Our findings may have the following clinical consequences: in less severely affected infants,

challenging motor activities without assistance and encouraging the infant to find his or her own motor strategy, should be encouraged. In more severely affected infants, motor capacities may be too limited for the infant to find a motor strategy on its own, and more assistance may be provided, either by the caregiver or therapist, or by adaptive aids.[17]

The role of the family is important in early intervention, perhaps even more important in higher risk infants than in relatively low risk infants. In general, burden on the family is high, especially if the infant is severely affected, and every developmental phase requires new adaptations. Therefore, not only infants, but also their families are at risk, for example for being overloaded or getting (mental) health problems. Especially in this high risk families, awareness of and taking into account their needs and wants is important. Being aware of these needs and share thoughts about decision making in the health care process, paves the way for family centred care, with partnerships between professionals and caregivers. Caregivers of children with CP indicate that creating partnerships is important, to promote the ability to find the way within the complex care system around them.[46] In the L2M0-2-study, interventional elements like coaching seem to create such partnerships, associated with better family empowerment. Although most professionals agree on the issue of the importance of family centred care, the actual implementation needs more change in current practice. Herewith it is important, that caregivers have still the role of caregivers, who are experts about their child, and that they do not feel being the therapist for their child. Role of professionals should be that they provide caregivers with enough information, with the result that caregivers feel competent and empowered to make their own decisions in the health care process, fitting to the needs and values of the family. It is of importance that caregivers who are less familiar and experienced with self-management, feel also sufficiently supported by professionals. This may mean that professionals coach some families more at a distance and other families sometimes more in a directive way, if this meets the needs of the family.

What has not been mentioned yet, but what is important in my opinion are two other factors, not directly measured in this thesis: 1) intervention should be fun to stay motivated and 2) there should be a good relationship between the physiotherapist and the family. If these conditions are not met, I suppose intervention will not work at the long term. If interventional elements are applied into daily life activities and if caregivers and infants enjoy them, it becomes a habit and not a need. Prerequisite for implementing interventional elements into daily life, is that caregivers have confidence that it is useful to apply. Trust in efficacy requires a good relationship between professional and caregiver. However, assessing the quality of the relationship between professional and caregiver is difficult, as it is not easy to quantify by observation and asking will often give socially desirable answers.

Future perspectives

This thesis contributes to solving the complex puzzle of effectiveness of early intervention in very high risk infants. Yet, I conclude that still many questions to be answered remain. Future research may help to unravel stepwise the best way to guide infants with special needs and their families.

One of the recommendations to gather more knowledge about developmental courses of high risk infants and efficacy of interventions, is to capture data of high risk infants in large databases and to collaborate nationally and internationally.

Improvement of techniques and measures to detect infants at risk and to predict outcome, may create opportunities to start intervention as early as desired, and to focus on specific characteristics, to be able to provide individually tailored intervention. However, first more knowledge is needed about which interventional elements work for which infants and which timing is best.

Focus until now in infants at risk is often on what factors induce atypical development. However, what is also shown in this thesis is that some infants with poor baseline characteristics, such as severe brain lesions, perform quite well. For future research, it would be interesting to provide more insight in the nature of protecting or favourable factors which result in better outcome, instead of focusing on unfavourable factors. Knowledge about protecting factors may assist in implementing such factors in early intervention.

To provide knowledge about working elements within early intervention, the role of the caregivers is essential. Caregivers are the persons who know eminently what they value and what they miss in interventions and are experts about their infant. Off course, theoretical knowledge and evidence are the basis for developing interventions, but if they do not join caregivers and infant needs, they have a great chance to fail. Therefore, I recommend to ask caregivers who participated in interventions about their opinions and recommendations and to involve caregivers from the beginning in future studies.

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SUMMARY

This thesis aims to unravel a part of the complex and intriguing puzzle of early brain development. Primary aim is to study effects of early intervention in infants at very high risk (VHR) of cerebral palsy (CP). CP is the most common cause of physical disability in pediatrics, originating from disturbances in early brain development. CP manifests with limited mobility due to difficulties with movement and postural control, often accompanied by other developmental disabilities, such as cognitive or behavioural problems. Secondary aims are a) increasing knowledge about VHR-infants' early development and factors influencing development, b) providing insight in contents of early intervention and associations between interventional elements and outcome, and c) evaluating use of motor function measures for VHR-infants.

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

Chapter 2 reviews the literature on motor and cognitive outcome of VHR-infants with severe brain lesions. The studies included showed that severe brain injury is strongly associated with development of CP, most often in infants with cystic periventricular leukomalacia (86%) and less often in infants with term stroke (30%). In case of development of CP, usually unilateral lesions result in unilateral CP and bilateral lesions in bilateral CP. However, unilateral lesions may result in bilateral CP and vice versa. Intellectual disability has been described in 27-50% of the infants with severe brain lesions. Information about other influencing factors was little; sex specific outcome was only provided in few studies and socioeconomic class influences have been provided only sporadic.

Chapter 3 investigates contents of conventional infant physiotherapy during the last decades, as provided in the Netherlands. Within infants physiotherapy, developments occurred over time: over the years families are more involved, both in communication and in being educated by the physiotherapist. Involvement is most often in the form of training, providing feedback, exchange of information, or instruction. Neuromotor actions, such as facilitation, sensory experience and challenging the infant to self produced motor behaviour, did not change significantly over time. The results indicated that theoretical concepts have been implemented partly in practice.

PART 2: Early intervention in very high risk infants

In Chapter 4, results of the Vroegtijdig Interventie (Early Intervention) Project (VIP) are presented. In the VIP-study, infants at very high risk of CP, based on presenting with definitely abnormal general movements, were included. Infant motor outcome, measured by the Infant Motor Profile, was compared for the newly developed COPCA-intervention (Coping with and Caring for infants with special needs – a family centred programme) with

the control group TIP (Typical Infant Physiotherapy). Infants were randomly allocated to receive either COPCA or TIP between 3 and 6 months corrected age. In the Randomized Controlled Trial (RCT), infants receiving COPCA or TIP had similar outcome. After analysing contents of intervention, associations were present between interventional elements and outcome: some COPCA-related items were positively associated with outcome and some TIP-elements were negatively associated with outcome, especially in those infants who developed CP. However, only about a quarter of the included infants developed CP and the intervention period was only three months.

Therefore, a design for a new intervention study was developed, the LEARN2MOVE0-2 years (L2M0-2) study (chapter 5). Main differences compared with the VIP-study are: infants at higher risk for CP were included, i.e., mainly included on the basis of severe brain lesions, and the intervention period was longer: one year instead of three months. Besides infant outcome, also family outcome was included.

Results of the L2M0-2-study are presented in Chapter 6. In the L2M0-2-study more than half of the included infants developed CP. Comparable with the VIP-study, no differences at RCT-level for COPCA and TIP were shown. In contrast to the VIP-study, no associations between interventional elements and infant outcome were found in the L2M0-2-study. However, family outcome did show an association with intervention: family empowerment was positively associated with COPCA-related interventional elements.

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

No 'gold standard' for measuring motor function in infancy is available. Often used measures in children with CP are the Gross Motor Function Measure (GMFM) and the Gross Motor Function Classification Measure (GMFCS). Both are known to be reliable and valid instruments, but generally applied in children who are already diagnosed with CP, i.e., usually after the age of 18-24 months. In Part 3 of this thesis, results and suggestions for use of the GMFM and GMFCS in infancy are provided.

Chapter 7 describes difficulties encountered with using the GMFM in infancy based on the first infants included in the L2M0-2-study. Suggestions for adaptations for use of the GMFM in infancy were provided, amongst others with eliminating or adapting items which are difficult to elicit in infancy and those items which require the ability to follow instructions. First results of the use of the adapted GMFM in the pilot study are promising and may better reflect the infant's actual motor function. However, further research is needed to define reliability, validity en responsivity of the suggested adaptations for the GMFM in infancy.

In Chapter 8, application of the GMFCS in infancy is discussed. Over the years, use of assisted or powered mobility is provided more and more at younger ages, also below the age of two years. The current GMFCS applies also to children below the age of two years,

but assisted mobility is not included in the description. Therefore, suggestions were made to implement assisted mobility also in the definition of the GMFCS for 0-2 years.

In conclusion, this thesis shows that infants with severe brain lesions are at high risk of developing neurodevelopmental disabilities, more than infants with only clinical signs of dysfunction. Contents of early intervention changed over the years. In the beginning of the 21st century, the family centred COPCA-intervention was developed, providing early intervention in infants with special needs. In the two studied intervention trials, infants who received COPCA or TIP have comparable outcome at RCT-level. However, specific elements of interventions were associated with outcome: in the VIP-project with infant outcome and in the L2M0-2-study with family outcome. Measuring outcome in high risk infants at young age is challenging, but a prerequisite for adequately measuring effects of early intervention. Therefore, some suggestions have been provided for adaptations in infancy for two often used measures: the GMFM and the GMFCS.

For future research, advancements in early detection and predicting outcome of infants at high risk may assist improved understanding of efficacy of provided interventions. Knowledge about contents of intervention is needed to study underlying working mechanisms. Being able to study outcome of early intervention and reflecting infants' actual functioning, measures in infancy need further investigation and optimization. Studies should not only focus on infant outcome, but also on family outcome, which may be more malleable than the infant brain when the infant has a severe brain injury.

Samenvatting

Veel factoren kunnen de vroege hersenontwikkeling beïnvloeden. Meestal verlopen zwangerschap, geboorte en de periode na de geboorte gelukkig zonder problemen. Een kind ontwikkelt zich, leert lopen, gaat naar school en groeit op tot een zelfstandige volwassene. Soms verloopt deze ontwikkeling echter niet zo vanzelfsprekend. Dit kan komen door problemen tijdens de zwangerschap, rond de geboorte of in de eerste levensmaanden. Hierbij kan worden gedacht aan vroeggeboorte, zuurstofgebrek rond de geboorte, infecties of andere problematiek. Door complicaties voor, tijdens of na de geboorte kan de hersenontwikkeling anders verlopen dan verwacht. Vroege problematiek in de ontwikkeling van de hersenen kan leiden tot cerebrale parese (CP), de meest voorkomende fysieke beperking bij kinderen. CP uit zich door problemen in houding en beweging, meestal in de vorm van spasticiteit. Het gaat vaak gepaard met andere problemen in de ontwikkeling, zoals cognitieve problemen, gedragsproblemen en/of epilepsie. CP kan zich aan een kant van het lichaam uiten (unilateraal), of aan twee kanten (bilateraal). De ernst van de CP en de mate waarin armen en benen zijn aangedaan kan verschillen. Alle kinderen hebben in meer of mindere mate problemen met zich voortbewegen. Doordat het jonge brein in ontwikkeling is, wordt vaak in de loop van de tijd pas duidelijk of een kind wel of niet CP zal ontwikkelen. De meeste kinderen met CP krijgen begeleiding vanuit de kinderrevalidatie. Omdat wordt verondersteld dat de hersenen vroeg in de ontwikkeling het meest vormbaar zijn, is de aanname dat het goed is om zo vroeg mogelijk te starten met interventie. Er is echter nog veel onduidelijkheid over de werkzaamheid en de beste vorm van interventie.

Het hoofddoel van dit proefschrift is het onderzoeken van de effecten van vroege interventie bij kinderen die een zeer hoog risico lopen op het ontwikkelen van CP (hierna 'zeer hoog risico kinderen' genoemd), ofwel door een hersenbeschadiging, ofwel door een klinische uiting van een anders verlopende hersenontwikkeling. Daarnaast beoogt het proefschrift meer zicht te krijgen in:

- Hoe de ontwikkeling van zeer hoog risico kinderen verloopt
- Welke factoren de vroege ontwikkeling van zeer hoog risico kinderen kunnen beïnvloeden
- Hoe de inhoud van kinderfysiotherapie samenhangt met de ontwikkeling van kind en gezin
- Welke ontwikkelingen binnen de kinderfysiotherapie over tijd hebben plaatsgevonden
- De toepassing van motorische testen voor zeer hoog risico kinderen

Deel 1: Factoren die de ontwikkeling van hoog risico kinderen kunnen beïnvloeden

Hoofdstuk 2 geeft een overzicht van de literatuur over motorische en cognitieve uitkomsten van kinderen met een vroege ernstige hersenbeschadiging. De onderzoeken laten zien dat een ernstige hersenbeschadiging duidelijk geassocieerd is met de ontwikkeling van CP. Het overgrote deel (86%) van kinderen met cystevorming in de diepgelegen witte stof van de hersenen (cystische periventriculaire leukomalacie) ontwikkelde CP. Van de kinderen die rond de uitgerekende datum van geboorte een hersenbloeding of –infarct hadden gehad ontwikkelde iets minder dan een derde (30%) CP. Als er sprake was van CP, resulteerde een eenzijdige hersenlaesie vaak in een unilaterale CP en bilaterale hersenlaesies vaak in bilaterale CP. Maar er werd ook gezien dat eenzijdige laesies zich uitten in bilaterale CP en andersom. Cognitieve problemen in de vorm van een duidelijke beperking in leren en toepassen van kennis werden gezien bij 27-50% van de kinderen met een vroege ernstige hersenbeschadiging. Over andere factoren die de ontwikkeling kunnen beïnvloeden werd weinig beschreven. Weinig onderzoeken beschreven specifieke uitkomsten apart voor jongens en meisjes en informatie over sociaaleconomische factoren werd bijna niet gegeven.

Hoofdstuk 3 beschrijft de inhoud en ontwikkelingen over de tijd binnen reguliere kinderfysiotherapie zoals die in Nederland gegeven wordt in twee tijdsperiodes (2003-2005 en 2008-2015). Er worden een aantal ontwikkelingen gezien: het betrekken van gezinnen bij de behandeling neem toe, zowel op het gebied van communicatie als educatief, in de vorm van overbrengen van fysiotherapeutische kennis en handelingen naar ouders. Het betrekken van het gezin is meestal in de vorm van training, feedback geven, informatie uitwisselen en instructies geven. De inhoud van neuromotorische handelingen, zoals faciliteren van bewegingen, sensorische ervaringen geven en het kind uitdagen tot eigen motorische acties, veranderde niet duidelijk in de loop van de jaren. De resultaten laten zien dat theoretische concepten binnen de kinderfysiotherapie gedeeltelijk geïmplementeerd zijn over de tijd.

Deel 2: Vroege interventie bij kinderen met een zeer hoog risico op cerebrale parese

In hoofdstuk 4 worden resultaten beschreven van het Vroegtijdig Interventie Project (VIP). In het VIP-onderzoek zijn kinderen geïncludeerd met een hoog risico op het ontwikkelen van CP. Een hoog risico op CP werd gebaseerd op de aanwezigheid van duidelijk afwijkende General Movements (GM's) rond de leeftijd van drie maanden. GM's zijn gegeneraliseerde bewegingen van de zuigeling, die leeftijdsspecifieke kenmerken hebben. Duidelijk afwijkende GM's rond de leeftijd van drie maanden betekenen een duidelijk verhoogd

risico op CP. De motorische uitkomsten van deze hoog risico kinderen werden gemeten met de Infant Motor Profile (IMP), waarmee wordt gekeken naar de kwaliteit van spontaan motorisch gedrag. IMP-uitkomsten van de recent ontwikkelde COPCA-interventie (COPing with and CAring for infants with special needs, a family centred programme (Omgaan met en zorgen voor jonge kinderen met specifieke behoeften – een gezinsgericht programma)) werden vergeleken met de controlegroep TIP (Typical Infant Physiotherapy (reguliere kinderfysiotherapie)). Kinderen die aan het onderzoek meededen werden door middel van loting toegewezen aan een van beide interventies (gerandomiseerd vergelijkend onderzoek, RCT). De interventieperiode was van drie tot zes maanden, gerekend vanaf de uitgerekende datum van geboorte van het kind. Uitkomsten voor de kinderen in de COPCA- en de TIP-groep van de RCT waren vergelijkbaar. De inhoud van interventies werd ook geanalyseerd, en na deze analyses bleken bepaalde elementen binnen de interventie gerelateerd aan uitkomsten: enkele COPCA-gerelateerde elementen waren positief geassocieerd met uitkomst en enkele TIP-gerelateerde uitkomsten waren negatief geassocieerd met uitkomst, vooral bij de kinderen die CP ontwikkelden. Hierbij moet gezegd worden dat maar een kwart van de kinderen CP ontwikkelde en de interventie periode van drie maanden kort was.

De bevindingen van het VIP-project leidden tot de opzet van een nieuw onderzoek: het LEARN2MOVE0-2 jaar onderzoek (hoofdstuk 5). De grootste verschillen met het VIP-onderzoek zijn a) kinderen met een nog hoger risico op het ontwikkelen van CP werden geïncludeerd, hoofdzakelijk gebaseerd op ernstige hersenbeschadigingen en b) de interventieperiode was langer: een jaar in plaats van drie maanden. Naast kinduitkomsten werden ook uitkomsten voor het gezin meegenomen.

De resultaten van het L2M0-2 onderzoek zijn beschreven in hoofdstuk 6. In het L2M0-2 onderzoek ontwikkelde meer dan de helft van de kinderen CP. Net als in het VIP-onderzoek werden er in de RCT geen verschillen in uitkomsten gevonden tussen de groep die COPCA ontving en de TIP-groep. In tegenstelling tot het VIP-onderzoek, waren er geen relaties tussen de inhoud van de interventie en de uitkomsten van het kind. In het L2M0-2 onderzoek werden echter ook gezinsuitkomsten meegenomen. Een belangrijke gezinsuitkomst was wel gerelateerd aan de inhoud van interventie: de family empowerment was positief geassocieerd met COPCA-elementen van de interventie.

Deel 3: Het evalueren van grof motorisch functioneren bij jonge kinderen met of met een hoog risico op cerebrale parese

Er bestaat geen 'gouden standaard' voor het in kaart brengen van motorisch functioneren bij jonge kinderen. Meetinstrumenten die vaak gebruikt worden bij kinderen met CP zijn de Gross Motor Function Measure (GMFM, meetinstrument grof motorisch functioneren) en de Gross Motor Function Classification System (GMFCS, classificatiesysteem grof

motorisch functioneren). Beide zijn betrouwbare en valide meetinstrumenten, maar worden vooral toegepast bij kinderen die de diagnose CP hebben, dat wil zeggen vaak vanaf de leeftijd van circa 18-24 maanden. In deel 3 van dit proefschrift wordt het gebruik van deze meetinstrumenten op jongere leeftijd geëvalueerd en worden suggesties voor toepasbaarheid op jonge leeftijd gegeven.

Hoofdstuk 7 geeft aan waar tegenaan werd gelopen bij het afnemen van de GMFM bij jonge kinderen, gebaseerd op ervaringen met de GMFM bij de eerste kinderen die geïncludeerd waren in het L2M0-2 onderzoek. Enkele suggesties voor aanpassing van de GMFM op jonge leeftijd werden opgesteld, onder andere het weglaten van elementen die moeilijk uit te lokken zijn op jonge leeftijd en waarbij het kind instructies op moet volgen. De eerste resultaten van de aangepaste GMFM in het pilot onderzoek lijken erop te wijzen dat ze het daadwerkelijk motorisch functioneren beter in kaart kunnen brengen. Er is echter meer onderzoek nodig om te kijken of deze aanwijzingen ook in grote groepen blijven bestaan en om de betrouwbaarheid, validiteit en responsiviteit van de aangepaste GMFM verder in kaart te brengen.

In hoofdstuk 8 wordt de toepassing van de GMFCS op jonge leeftijd besproken aan de hand van een casus. In de afgelopen jaren neemt het vroeg inzetten van ondersteuning van mobiliteit door middel van (gemotoriseerde) hulpmiddelen toe, ook voor het tweede levensjaar. In de huidige GMFCS wordt bij de beschrijving voor kinderen jonger dan twee jaar nog geen aandacht besteed aan mobiliteitsbevorderende hulpmiddelen. Om deze reden is er in dit hoofdstuk aan de hand van de casus een voorstel gedaan om in de GMFCS voor de kinderen van nul tot twee jaar ook het gebruik van hulpmiddelen voor mobiliteit mee te nemen.

Concluderend wordt er in dit proefschrift gezien dat kinderen met een ernstige hersenbeschadiging een hoog risico lopen op het ontwikkelen van CP en dat dit risico hoger is dan voor de kinderen die alleen klinische tekenen laten zien van een disfunctionerend brein. De inhoud van vroege interventie is veranderd in de loop van de jaren. In het begin van de 21e eeuw werd het COPCA-programma ontwikkeld, gericht op vroege interventie voor kinderen die speciale zorg nodig hebben. In de twee interventiestudies in dit proefschrift hadden kinderen die COPCA of TIP kregen vergelijkbare uitkomsten tijdens en na de interventieperiode. Specifieke elementen van de interventies waren echter wel geassocieerd met de uitkomst: in het VIP-onderzoek met uitkomsten van het kind en in het L2M0-2 onderzoek met gezinsuitkomsten. Het meten van motorische uitkomsten bij hoog risico kinderen is een uitdaging, maar een voorwaarde om effecten van interventie goed te kunnen weergeven. Daarom werden er enkele suggesties gedaan voor aanpassingen op jonge leeftijd van twee veel gebruikte meetinstrumenten: de GMFM en de GMFCS.

Voor toekomstig onderzoek zouden de ontwikkelingen op het gebied van beeldvorming van de hersenen, waarbij vroeg kunnen detecteren, exacter kunnen weergeven van hersenbeschadigingen en beter kunnen voorspellen van uitkomst, waardevolle elementen zijn voor het verbeteren van inzicht in vroege ontwikkeling en effecten van interventie. Kennis over inhoud van interventie is nodig om onderliggende werkingsmechanismen te kunnen begrijpen. Om het functioneren van een kind goed weer te kunnen geven, is het verder ontwikkelen en optimaliseren van meetinstrumenten van belang. Bij kinderen met een ernstige hersenbeschadiging is de mate waarin ontwikkeling te beïnvloeden is mogelijk maar beperkt, terwijl het vaak een grote impact heeft op het gezin. Daarom is het bij het onderzoeken van effecten van vroege interventie niet alleen van belang om uitkomsten van het kind te meten, maar ook gezinsuitkomsten hierbij te betrekken.

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OVER DE AUTEUR

Tjitske Hielkema werd geboren op 8 mei 1981 in Dokkum en groeide op in Raard. In 1999 behaalde zij haar VWO-diploma aan het Dockinga College in Dokkum. In 2000 heeft ze haar propedeuse psychologie behaald (cum laude) aan de Rijksuniversiteit Groningen. Daarna is ze begonnen met haar studie geneeskunde, die ze in 2006 heeft afgerond. Van 2006 tot 2008 werkte ze bij het Universitair Centrum voor Kinder- en jeugdpsychiatrie Accare in Groningen, heeft ze vrijwilligerswerk gedaan in Kenia en gewerkt als arts-assistent niet in opleiding bij het Centrum voor Revalidatie van het Universitair Medisch Centrum Groningen (UMCG). Vanaf 2009 begon ze met het promotietraject 'LEARN2MOVE 0-2 jaar' bij de Ontwikkelingsneurologie van het UMCG, afdeling kindergeneeskunde. Vanaf 2011 werd dit promotietraject gecombineerd met de opleiding tot revalidatiearts. In september 2016 rondde ze de opleiding tot revalidatiearts af en is ze werkzaam bij de kinderrevalidatie van het Centrum voor Revalidatie van het UMCG.

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