Measuring motor outcome in childhood

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Measuring motor outcome in childhood:

prognosis and evaluation

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VRIJE UNIVERSITEIT

Measuring motor outcome in childhood:

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Contents

Chapter 1

Introduction

Introduction

The long-term outcome of a child's development is always an intriguing issue. This question keeps many parents busy, often even during pregnancy. When problems arise during pregnancy or delivery of the child, or when a child is treated with a relatively new intervention, parental and professional interest in the outcome is increasing. It is important to identify children with delays or deterioration in their development so that timely referral can be made to the appropriate medical services. Many different clinicians, such as neonatologists, neurologists, physicians, physiatrists, psychologists and paediatric physical and occupational therapists, are involved in the care and follow-up of infants who are at high risk for developmental problems and children with chronic disorders. All these clinicians have their own measurement instruments for the assessment of various areas of development, relating for instance to cognitive, language, behavioural and motor outcome. An area of development can be measured at different levels, for example motor outcome can be assessed by measuring reflexes or muscle strength, by measuring motor abilities (such as crawling, walking or running), or by measuring participation in daily life (e.g. going to school or participation in sports with peers). A framework which is often used in paediatric rehabilitation to describe the consequences of a health condition, is the International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY).[1]

The main aims of this thesis are to describe motor outcome, mainly at the level of activity, in young children who were at risk for developmental problems or who had received an intervention, and to examine the predictive value of the measurement instruments that are most frequently used in childhood to forecast future motor outcome. Many terms can be used to describe motor activities, but in this thesis the term 'motor development' is used when referring to the ongoing process of developing motor abilities during the years, and motor outcome is used to describe the level of motor development (i.e. motor abilities at a certain point in time), which is often assessed with a motor test.

International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY)

The model of the ICF-CY is a theoretical framework designed to record characteristics of health and functioning in children and youth from birth to the age of 18 years. It classifies the consequences of a health condition (disorder or disease) in terms of body function and structures, activity and participation. The model also takes environmental and personal factors into account (see Figure 1). The ICF-CY provides a common and universal language for describing and measuring health and disability in the first two decades of life. It is intended to assist clinicians, educators, policymakers, administrators, family members, consumers and researchers in identifying the health and educational needs of the developing child.

The ICF-CY is derived from, and compatible with the International Classification of Functioning, Disability and Health.[2] The manifestations of functioning, disability and health conditions in children and adolescents are different in nature and impact from those of adults. Therefore, the ICF-CY was developed in such a way that it is sensitive to changes associated with growth and development.[1] An ICF-CY working group provided specific content and additional detail to cover more fully the different domains of ICF for infants, toddlers, children and adolescents. Specific attention was paid to four key issues in the development of the ICF-CY: 1) the child

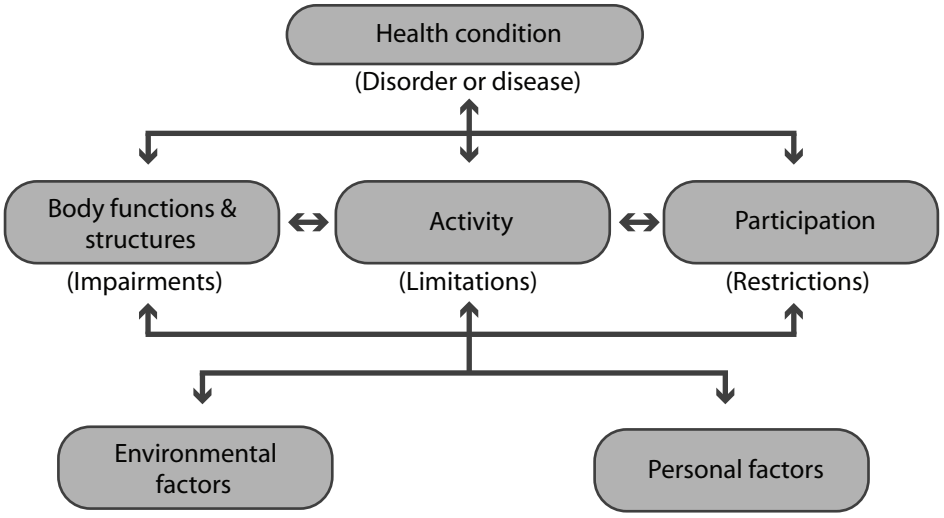

Figure 1 The International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY).[1]

in the context of the family; 2) delay in development; 3) participation and 4) environments. Although all these issues are relevant for the assessment of developmental outcome, identifying developmental delay in motor outcome will be the main focus of this thesis.

Normal motor development in typically developing children

Child development is the progressive ascertainment of new skills over time, and it reflects the integrity of a child's central nervous system, beginning in fetal life and ending in late adolescence or early adulthood.[3] Motor development in the first years is variable.[4] Moreover, motor development is the product of nature and nurture. Especially in early life, factors from all domains of the ICF-CY could affect motor development. For example, not only physical factors such as height and weight,[5] but also environmental factors, such as parental handling can have an influence on motor development.[6] Cultural differences can also influence motor development: it has been reported that the windows of achievement for six gross motor developmental milestones, measured in four different countries, showed great variance.[7] These normal variations and the lack of a 'gold standard' to measure motor outcome makes it difficult to discriminate normal from delayed motor development in one single assessment.

'Normal' motor development in children with a disorder

It is well known that children with a specific disorder also have their own, disease-specific 'normal' development profile. There are a number of examples that support this view. To name a few: prematurely born infants (<32 weeks gestational age) have their own development trajectory according to the Alberta Infant Motor Scale (AIMS)[8] which is different from that of full-term

infants.[9] Children with Osteogenesis Imperfecta also have their own motor development profile,[10] as have blind children.[11] Children with Down syndrome develop differently from typically developing children, but have their own 'normal' gross motor development according to the Gross Motor Function Measure (GMFM).[12] Important for this thesis is that children with cerebral palsy (CP) also have their own 'motor growth curves', which can be measured with the GMFM-66.[13,14]

Assessment of motor outcome in young children

One important feature of children is that they grow and develop over time. Therefore measuring the motor outcome of children poses many challenges. At present, there are various methods for motor assessment, measuring at different levels of the ICF-CY. In paediatric rehabilitation, the main focus is currently on outcome measures at activity level.

The most important decision that must be made in the assessment of motor outcome is the selection of an appropriate measurement instrument. The choice of the instrument will depend on several issues,[15] which will be discussed briefly. It depends on the reason for measuring motor outcome: discrimination, prediction, or evaluation over time. For discrimination purposes, established norms are important. Most instruments have their own norms, established in a certain country in a certain population. In literature, there is debate on the issue of using local or reference norms.[9,16-18] The age of the child is also a very important factor, because most measurement instruments are intended for use within a specific age-range. Unfortunately, there is no single motor measurement instrument that covers all ages. The motor area to be assessed is also important. For example: the AIMS measures gross motor function and the Bayley Scales of Infant Development 2nd version (BSID-II) measures gross and fine motor function. Clinicians should decide whether it is important to make a distinction between capacity (what a child *can* do in a controlled environment) and performance (what a child *does* do in everyday settings).[15] At present, most motor outcome measures assess capacity. Moreover, more practical issues should be considered, such as the time needed to administer a test, the space and equipment which is required, and cost of purchasing a measurement instrument.

Psychometric properties, i.e. evidence of reliability and validity are also important considerations in the selection of an instrument. In recent years, increasing attention is being paid to research on the reliability and validity of measurement instruments. The construct, content and concurrent validity of most instruments are fairly well known, and important for clinical practice. When choosing an instrument, it is important to know its properties: do different tests at the same time classify the same children as having a poor motor outcome, or do they differ? The predictive validity of many instruments, i.e. the extent to which scores will predict future outcomes, is unfortunately still largely unknown.[19] However, for clinical practice, knowledge about the predictive value of measurement instruments is very important for identifying children who are at risk for developmental problems. Infants who are born prematurely, or are small for their gestational age, and infants who suffer from asphyxia during birth are known to be at risk for motor, cognitive and behavioural problems in later life. It is important to try to forecast the outcome of these neonates, and to target those who are at higher risk of developing sequelae, to ensure the timely provision of the necessary rehabilitation services and to facilitate appropriate parental counselling. Early identification also makes it possible to start multidisciplinary intervention programs to improve functional outcome and participation as early as possible.

Paediatric physical therapy

A clinician who assesses a young infant should therefore have knowledge about the normal motor development of typically developing infants, and also knowledge about motor development in children with a specific disorder. Moreover, knowledge about the relationship of body function and structure with motor development, and interaction between contextual factors (i.e. personal and environmental factors) and motor development is important. Furthermore, the clinician should have an understanding of tests and measures, including their psychometric properties, in order to be able to interpret scores correctly. One of the key disciplines involved in the care and follow-up of children who are at risk for problems during motor development, or children with disorders, is paediatric physical therapy. The therapists in this discipline are specialized in the field of movement and movement disorders in children.

In the previous decade, the principles of evidence-based medicine (EBM)[20] have been incorporated in medical and physical therapy education, and knowledge about motor assessment has increased rapidly as an integral part of EBM.

Moreover, there has been a paradigm shift in paediatric rehabilitation[21] from optimizing children's impairments towards optimizing functional abilities, thus activities and participation. This shift is mainly introduced by the acknowledgement that impairments in body function and structures are not linearly associated with limitations in activity or restriction in participation.

Background of this thesis

In the light of the above, this thesis is to contribute to the body of knowledge about the predictive value of measuring motor outcome in children who are at risk for developmental problems, and knowledge about evaluating the effects of an intervention to improve motor outcome in children with CP. Therefore three different cohorts of children were followed longitudinally. One cohort consisted of children, mainly prematurely born and small for their gestational age whose mothers had an early-onset hypertensive disorder of pregnancy, the second cohort consisted of full-term born children with hypoxic-ischemic encephalopathy (HIE) after perinatal asphyxia, and the third cohort consisted of children with CP who underwent an innovative neurosurgical treatment, i.e. Selective Dorsal Rhizotomy (SDR).

The main focus of this thesis is to describe motor outcome in these young children who were at risk for developmental problems or who had received an intervention, and to examine the predictive value of the measurement instruments that are most frequently used in childhood to forecast future motor outcome. The following paragraphs provide background information about the disorders of the children in the studied cohorts (i.e. HIE after perinatal asphyxia and CP) and the SDR treatment. There is also a brief description of the instruments that are most frequently used by paediatric physical therapists in clinical practice to assess motor outcome in children.

Newborns at risk

In the Netherlands, every year approximately 185.000 infants are born alive,[22] mostly full-term (gestational age 37 weeks or more) and after an uncomplicated delivery. However, the incidence of pre-term birth is increasing in the Netherlands, and in 2001 there were approximately 16.000

infants born pre-term (less than 37 weeks of pregnancy), representing 8% of all live births. One of the maternal problems which can interfere with a pregnancy and can result in pre-term birth, are early-onset hypertensive disorders, such as pre-eclampsia (with proteinuria), eclamptic fits, and the hemolysis elevated liver enzymes low platelets (HELLP) syndrome. Hypertensive disorders during a pregnancy are common and occur in 7–10% of all pregnancies.[23,24] Due to placental insufficiency, a high proportion of pre-term newborns and/or infants who are small for gestational age is common after such pregnancies, but thanks to advanced technology in the treatment of these newborns, their rates of survival are improving. Follow-up studies have shown that these infants have higher risk for motor disability in later life, ranging from developmental coordination disorders to CP.[25-28] The neonatal outcome of infants whose mothers had an early-onset hypertensive disorder of pregnancy, as measured by means of neurological examination or General Movements is largely unknown. Moreover, the relationship between early examinations and the subsequent motor outcome of these infants is also not known.

Perinatal asphyxia

After an uncomplicated pregnancy, problems that arise during delivery sometimes cause perinatal asphyxia. Asphyxia is a condition that occurs when there is an impairment in blood gas exchange, resulting in hypoxemia (lack of oxygen) and hypercapnia (accumulation of carbon dioxide). This combination of a decrease in the oxygen supply (hypoxia) and the blood supply (ischemia) results in a cascade of biochemical changes inside the brain and body of the neonate, eventually leading to neuronal cell death and brain damage (neonatal encephalopathy). One to two per 1000 live-born term neonates have HIE[29] (also called post-asphyxia neonatal encephalopathy), which has been defined as 'a clinical syndrome of disturbed neurological function in the earliest days of life in term infants, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness and often by seizures' (p.1325).[30] The severity of the neonatal encephalopathy is commonly classified as stage I (mild), II (moderate) or III (severe) according to the Sarnat criteria.[31] The Sarnat grading is based on the responses of the infants to handling, level of consciousness, changes in tone or reflexes, presence of seizures, and the duration of the symptoms within seven days after birth.[31] Sarnat grading is a widely used predictor of outcome in neonates with HIE. In addition, magnetic resonance imaging (MRI) is often used to predict outcome in children with HIE, although the predictive validity of different scoring systems to evaluate MRI is unclear.

HIE in full-term neonates may have detrimental effects on their motor and mental development, and remains one of the causes of disability, such as CP, in children. Knowledge about the predictive value of neonatal assessments (i.e. Sarnat grading or MRI brain scan findings) for later outcome is important for parental counselling. The relationship between neonatal assessments and later outcome is unclear, and in most cases also ambiguous. Moreover, reports of longitudinal studies on the outcome of children with HIE are scarce. In other words, it is important to obtain more knowledge about the predictive validity of neonatal and motor assessments in these children.

Cerebral palsy

CP is the most common disorder that causes physical disabilities during childhood. The prevalence of CP in the population of the Netherlands was estimated at 2 per 1000 live births.[32] CP is an 'umbrella term' that is used to describe a group of disorders affecting the development

of movement and posture, causing activity limitation, which are attributed to non-progressive disturbances that occurred in the fetal or infant brain. The motor disorders associated with CP are often accompanied by disturbances of sensation, cognition, communication, perception and behavior, and/or seizures.[33] CP can be categorized according to the type of movement disorder (spastic paresis, dyskinetic paresis or ataxic paresis), localization (bilateral or unilateral) and severity (according to the Gross Motor Function Classification System [GMFCS]). Dyskinetic CP, accounting for around 7% of all cases of CP, is reported to occur especially in term-born children,[34,35] and is associated with perinatal adverse events. The most common type of CP (approximately 85%) is spastic paresis, which is more prevalent in pre-term born children.[36] Bilateral spastic CP can be sub-classified in tetra paresis (i.e. all four extremities are equally involved) or diplegia (i.e. the legs are more involved than the arms). Many children with CP are treated by a multidisciplinary rehabilitation team, with the ultimate goal of enhancing the child's participation in society. To reach this goal, the treatment of ambulatory spastic diplegic children is often aimed at improving gait and activities, which are impaired by spasticity, decreased selectivity in muscle activation and reduced strength. There are several local as well as general types of treatment that can reduce spasticity in children with spastic CP. These therapies include oral medication, local botulinum toxin-A injections, and neurosurgery, such as Selective Dorsal Rhizotomy (SDR).

Selective Dorsal Rhizotomy (SDR)

SDR is a neurosurgical procedure aimed at eliminating spasticity in children with spastic diplegia.[37,38] It is hypothesized that this eases the ability to move the lower extremities, thus contributing to improvements in gross motor function and gait. SDR reduces, or even eliminates spasticity by decreasing the facilitory afferent input of the posterior nerve roots to the anterior horn cells involved in the spinal reflex arc. The operation is performed under general anesthesia, with the patient in a prone position. Electrodes are placed on hip adductors, rectus femoris, medial hamstrings and gastrocnemius muscles for intra-operative electromyographic monitoring. A mid-line incision exposures the L2–S1 spinous process and lamina, and after multilevel laminectomy and opening of the dura, the cauda equina is fully exposed. All lumbosacral sensory roots are identified bilaterally, and separated into three or four rootlets, each of which is stimulated electrically. A neurophysiologist and a paediatric physiatrist both assess the patient's motor responses to this electrical stimulation of the sensory roots and rootlets. Rootlets that produce an abnormal muscular and electromyographic response to electrical stimulation are identified and transected. A replacement laminoplasty is performed, and post-operative analgesia is provided. After the operation, the children participate in an intensive physical therapy program, with emphasis on strength training for one hour a day, five days a week, until three months after SDR. Up to six months after SDR, physical therapy is still more intensive than usual care: at least three hours a week. Stability and control of the lower limbs is further enhanced by the judicious use of orthotics.

SDR was introduced in the Netherlands in 1998, and the first nine children to receive this treatment were monitored extensively in a prospective study. In this thesis, the feasibility of SDR is investigated in a single-case research design. Subsequently, the patients were monitored for three to eight years, and long-term effects of SDR on gross motor function and additional treatment were assessed.

PETRA trial

The Preeclampsia Eclampsia TRial Amsterdam (PETRA) was a randomized clinical intervention trial to assess the effect of plasma volume expansion in the management of severe early-onset hypertensive disorders during pregnancy. The study was conducted in collaboration between the Departments of Obstetrics and Gynaecology of the Academic Medical Center and the VU University Medical Center.[39] Between April 1, 2000 and May 31, 2003, 216 patients with severe and early-onset hypertensive disorders during pregnancy were enrolled in the study. Patients were eligible to participate in the trial if they met at least one of the inclusion diagnoses: HELLP syndrome, severe preeclampsia, eclampsia, or severe fetal growth restriction with gestational hypertension. After inclusion, the patients were randomized to a temporizing management strategy with plasma volume expansion (i.e. treatment group) or a strategy without plasma volume expansion (i.e. control group). The primary end-point of the study was the Prechtl neonatal neurological examination score at term age (± one week). Secondary end-points were perinatal mortality, neonatal morbidity and maternal morbidity. The main findings were that neonatal neurological development at term (Prechtl score), neonatal morbidity, and perinatal mortality did not differ between the two groups. Total fetal and postnatal loss was 18%. Major maternal morbidity was equally distributed among the groups, and all maternal morbidity appeared to be reversible.[39]

Motor assessments in young children

General Movements (GMs)

In 1990, Prechtl developed a new, non-invasive assessment technique, based on evaluation of the quality of the spontaneous movements of newborns.[40] It consists of an assessment of the quality of general movements (GMs), which are complex movement patterns involving the head, trunk, arms, and legs, that normally vary in duration and movement trajectories. Complexity, fluency and variation of these involuntary movements are scored in a 'Gestalt' manner. Optimal GMs should reflect an optimally wired brain. The primary purpose of GMs is to predict later outcome. The assessment of GMs by serial videotaped recordings from birth to 16 to 20 weeks of post-term age is known to be a good predictor of neurological outcome. Definitely abnormal GMs at three months post term have a clear relationship with CP at a later date.[41-44]

Alberta Infant Motor Scale (AIMS)

The AIMS assesses spontaneous weight bearing, posture and antigravity movements in four developmental positions (58 items) in children from one month to the age of independent walking. The scale is unidimensial, and measures the construct of motor maturation.[8,9] The score for each developmental position is summed to obtain a total raw score, and converted to an age-based percentile rank, based on Canadian normative data. The AIMS has high degrees of test-retest, intra-rater and inter-rater reliability when it is used to measure typically developing full-term infants[8] and infants born pre-term.[45]

Bayley Scales of Infant Development, second version (BSID-II)

The BSID-II has been developed to assess the development of children between 1 to 42 months, and to discriminate typically from non-typically developing children. The BSID-II contains a motor scale (111 items, gross as well as fine motor items), a mental scale (178 items), and a behavioural rating scale (30 items).[46] Raw scores must be converted to the Psychomotor Developmental Index (PDI) for the motor scale or to the Mental Developmental Index (MDI) for the mental scale, both of which have a mean of 100 and a standard deviation of 15. The reliability and validity of the BSID-II have been established in the United States.[46] There are

American norms as well as Dutch norms, which differ substantially, especially at the age of one year.[16] A new version, the Bayley Scales of Infant and Toddler Development, 3rd edition (BSITD-III), which has recently been introduced in the Netherlands, has different scales for gross and fine motor function.[47]

Gross Motor Function Measure (GMFM)

The GMFM-88 is a criterion-referenced evaluative measure for assessing the gross motor abilities of children with CP. The GMFM consists of 88 items, divided over five dimensions: lying and rolling, sitting, crawling and kneeling, standing and walking, running, jumping. Each item must be scored on a 4-point scale, and total scores are expressed as a percentage of the maximum score. The validity, reliability, and responsiveness of the GMFM have been demonstrated.[48] The GMFM-66 score can be calculated with the Gross Motor Ability Estimator,[49] this score addresses the linearity of the individual item scores across the entire range of GMFM scores.[50] The GMFM-66 is known to be a reliable and responsive measure.[49] In combination with the Gross Motor Function Classification System (GMFCS), motor growth curves are described.[13] Percentile rankings of GMFM-66 per GMFCS level have recently been published,[14,51] and these can be used to compare the development of a child within a certain GMFCS level with the development of other children with CP.

Outline of this thesis

The main aims of this thesis are to describe motor outcome in young children who were at risk for developmental problems or who had received an intervention, and to examine the predictive value of the measurement instruments that are most frequently used in childhood to forecast future motor outcome.

Chapter 2 describes the motor outcome of 175 infants, mostly small for their gestational age, and born prematurely from women with early-onset hypertensive disorders of pregnancy. We studied the results of GMs and neurological examinations at term and at three months corrected age, and their relationship with neurodevelopmental outcome at one year, measured by means of neurological examination and the motor and mental scales of the BSID-II. This prospective cohort study was part of a randomized controlled trial of two pre-birth management strategies, the PETRA study.

Chapter 3 describes the motor outcome at the age of one year of a cohort of 32 surviving children who were born full-term with perinatal HIE. Motor outcome was measured by means of neurological examination, the AIMS and the BSID-II motor scale, respectively. Moreover, we examined the relationships between the motor outcome tests (AIMS and BSID-II) and the neurological examination at one year. We also investigated the association of these three tests with neonatal brain MRI.

Chapter 4 focuses on the additional predictive value of the motor tests (AIMS and BSID-II) and neurological examination at one year compared with prediction based on Sarnat staging and neonatal MRI for both motor and mental outcome at two years, assessed with the BSID-II in the same children with perinatal HIE.

Chapter 5 describes the effects of SDR on gross motor function as well as on self-care and gait in nine ambulatory children with spastic diplegia one year after SDR.

Chapter 6 presents the short-term (one year after SDR) and long-term (3 to 8 years after SDR) results of gross motor function, compared to reference percentile data for the cohort of 33 children who had undergone SDR. In addition, the side effects and additional treatment after SDR will be discussed.

The final part of this thesis, Chapter 7, is the general discussion, in which the impact of the findings presented in this thesis is further emphasized. Subsequently, recommendations are made for future research and clinical implications are formulated.

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Chapter 2

General movements in infants born from mothers with early-onset hypertensive disorders of pregnancy in relation to one year's neurodevelopmental outcome

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J.I.P. de Vries, for the Petra investigators

Abstract

Background: Assessment of general movements (GMs) at three months is considered useful for prediction of adverse neurological outcome in high risk infants.

Aims: To study the prevalence of abnormal GMs in infants born from women with early-onset hypertensive disorders of pregnancy and the association of GMs with neurodevelopmental outcome at one year.

Study design: Prospective study, part of a randomised controlled trial of pre-birth management strategies.

Subjects: Infants born from women with early-onset hypertensive disorders of pregnancy.

Outcome measures: GMs observation and neurological examination at term and three months corrected age; at one year neurological examination and Bayley Scales of Infant Development.

Results: From 216 women included, 175 of 178 surviving infants (mean gestational age 31.6 weeks [SD 2.3], mean birth weight 1346 grams [SD 458]), were examined at three months. At term age normal, mildly abnormal and definitely abnormal GMs were observed in 54%, 36% and 10% respectively; and at three months in 47%, 40% and 13%. Mildly or definitely abnormal GMs at three months were not associated with abnormal neurological examination at one year, however, they were associated with delayed psychomotor development at one year (p=0.01).

Conclusions: In this prospective study, including small for gestational age, preterm infants about half of them did not have normal GMs at term and three months. There was no association of GMs at term nor three months with neurological outcome at one year, but there was a significant association of GMs at three months with one year psychomotor development.

Introduction

Early-onset hypertensive disorders of pregnancy are associated with increased perinatal morbidity and mortality.[1] Contributing factors are fetal growth restriction and (iatrogenic) preterm delivery.[1,2] Neonatal neurological outcome can be described by neurological examination, but also by observation of the quality of spontaneous motility of the infant, the general movements (GMs).[3] GMs are spontaneous movements involving all parts of the body. Particularly the quality of GMs at 2 to 4 months post term (so called fidgety GMs) has been found to have a high predictive value for later development of neurological deficits.[3-11] In these studies on GMs, the populations were relatively small, and the selection of infants was generally based on their risk of adverse neurological outcome, e.g. abnormal neonatal brain imaging,[3,4,6,7] growth restriction,[5,8] being preterm with transient periventricular echodensity[6] or repeated abnormal general movements up to 22 weeks post term.[10] It has been reported recently that even in healthy term born infants mildly abnormal GMs were observed in 18–24% and definitely abnormal GMs in 0–7% of the infants at three months.[12,13] Cohort studies of infants who are characterised by well defined obstetric pathology are absent.

We here report GMs of infants, born from women with early-onset hypertensive pregnancy disorders, participating in the Pre-eclampsia Eclampsia TRial Amsterdam (PETRA). In this randomised trial we studied the effect of plasma volume expansion on maternal and perinatal outcome in women with early-onset preeclampsia undergoing temporising management. No significant differences were observed in the primary study end-point (neurological

Table 1 Definitions of included hypertensive disorders of pregnancy

Hypertensive disorder of pregnancy	
Severe preeclampsia[15]	Diastolic blood pressure ≥110 mm Hg and proteinuria ≥0.3 g/24 h
HELLP syndrome[16]	Platelet count b100×109/L and aspartate aminotransferase ≥70 U/L and lactate dehydrogenase ≥600 U/L
Fetal growth restriction and pregnancy induced hypertension[17]	Estimated fetal weight bp10 and diastolic blood pressure ≥90 mm Hg

examination), nor in secondary end-points (neonatal survival, neonatal and maternal morbidity) both at term age.[14]

The aim of the present prospective study was to describe GMs at term age and three months post term, and their association with neurological examination performed at the same ages. Furthermore, the predictive validity of GMs at three months for the observed neurological outcome (neurological examination) and psychomotor development (Bayley scales) at one year corrected age was evaluated.

Subjects and methods

Subjects

The PETRA trial was a randomised trial that consecutively enrolled 216 women at a gestational age between 24 and 34 completed weeks with a singleton pregnancy and with severe preeclampsia, HELLP syndrome or fetal growth restriction with pregnancy-induced hypertension or preeclampsia.[14] Inclusion criteria are specified in Table 1.[15–17] The study was conducted at the Departments of Obstetrics of the Academic Medical Center and the VU University Medical Center in Amsterdam, the Netherlands, between April 1 2000 and May 31 2003. Methods have been described in full previously.[14] In line with the institutional review board approval of both hospitals, informed consent was obtained prior to inclusion. Patients were subjected to a temporising management strategy with plasma volume expansion (treatment group) or a strategy without plasma volume expansion (control group). In all cases, management consisted of intensive monitoring of fetal (twice daily fetal non-stress tests by means of cardio tocography and twice weekly Doppler ultrasound) and maternal condition (among others blood pressure at least four times daily, and laboratory testing at least twice weekly). Hypertension was managed with fixed protocols (80% of patients receiving one or more medications). Magnesium sulphate was prescribed for treatment of eclampsia and in patients with clinical signs of imminent eclampsia. Corticosteroids were administered to patients, if delivery was thought to be imminent before 33 weeks, based on maternal disease deterioration or fetal Doppler abnormality. All but three mothers of infants, who were delivered alive before 33 weeks, had been given corticosteroids. Fetal indications for delivery were repeated decelerations or prolonged low variability on fetal heart rate tracings. Maternal indications were therapy-resistant hypertension, pulmonary edema and recurrent HELLP syndrome.

During the first four weeks of life sonographic examinations of the brain were made assessing periventricular leukomalacia (PVL)[18] and intraventricular haemorrhages (IVH).[19] Two

neonatologists (WPFF and LvS), unaware of treatment allocation, reviewed and classified all individual cases of neonatal morbidity.

Methods

Assessment of spontaneous motor activity, general movements (GMs)

At term age and three months, an observation of 15 minutes of spontaneous GMs was recorded on videotape. The observations were performed in the outpatient clinic of the Academic Medical Center, the VU University Medical Center, or the referring hospital, on the neonatal ward in case the infant was still admitted to the hospital, or at home in case the infant was recently discharged.

The infants were in supine position, dressed in a diaper, 30 minutes after a feed, in a quite room at a comfortable temperature. The infants were not exposed to extraneous sensory stimuli. When infants were distressed, efforts as extra feeding, change of diapers, parental comforting or applying a pacifier up till 30 minutes for each parent–infant pair were made to calm them down.

GMs were analysed 'off-line' during replay of the videotape recording by one highly trained paediatric physical therapist (VS), unaware of the medical history of the infants and the treatment regime of their mothers. GMs were examined during an awake, active, non-crying behavioural state (state 4).[20] GMs were categorised as normal, mildly abnormal or definitely abnormal based on the qualitative judgement of their complexity, variation and fluency as described at first by Prechtl,[21] and further specified by Hadders-Algra et al.[22] At three months, if fidgety movements were abnormal, GMs were classified as mildly abnormal, and if fidgety movements were absent as definitely abnormal.

Neurological examination

At term age and at three months, a neurological examination was performed.[23,24] Both scores were expressed by a numerical score with a maximum of 60, where 58 or higher was considered normal, 54–57 suspect and below 54 as abnormal.

At one year a neurological examination according to Touwen et al. was performed.[24] This test was classified as normal when there were no abnormalities of tone and posture, as suspect when there were mild abnormalities of tone and posture, with no or moderate delay in motor development, and as abnormal when there were definite abnormalities in tone and posture, resulting in a delayed motor development. During the same visit the mental and psychomotor development of the child were assessed according to the Bayley Scales of Infant Development II.[25] The standardised mental (MDI) and psychomotor development indices (PDI) of these scales have a mean of 100 and a standard deviation of 15. A MDI or PDI score equal or above 85 was classified as normal development, a score of 70 to 84 was classified as moderately delayed and a score below 70 as severely delayed development.

Statistical procedures

Statistical analysis was performed by Chi-square tests. It was intended that if no differences were observed between randomisation groups, further analysis would be performed in the complete study group. All test results were analysed by comparison of normal outcome with moderate or severe abnormal outcome. Statistical analysis was performed with SPSS software (version 11.5 SPSS Inc, Chicago). All comparisons were tested two-sided with p=0.05 as level

of significance.

Results

During the study period, 216 women were assigned randomly to the control group (105 women) or to the treatment group (111 women). At term age 180 infants were alive, of which one infant died due to chronic lung disease before three months, and two women refused follow-up. At three months 177 infants came for examination. Two infants had to be excluded due to a non-operating video system. In 175 infants GMs could be evaluated. One of these infants died due to chronic lung disease at the age of 142 days, two women refused further participation and three could not be traced at one year. The Bayley test was performed on 169 of the 175 included infants (97%). The PDI was unavailable in one infant due to a spica cast for neonatal hip dysplasia and in one infant because of non-cooperativeness. Baseline characteristics were comparable between randomisation groups[14] and are depicted in Table 2. The mean gestational age at delivery was 31.6 weeks (SD 2.3) and mean birth weight was 1346 (SD 458); 158 infants (89%) were small for gestational age. Twenty six infants (15%) had neonatal morbidity with

Table 2 Baseline characteristics of the mothers (*n*=175)

Maternal age (year)	30.4 (5.0)
Non-Caucasian	47 (26)
Nulliparity	121 (69)
Non-smoking	163 (93)
Body mass index	24 (4.4)
Educational level	
High	52 (30)
Average	54 (36)
Low	61 (34)
Gestational age at inclusion (weeks)	30.2 (2.2)
Corticosteroid for fetal lung maturation	131 (75)
Maternal diagnoses at discharge	
Severe preeclampsia[#]	133 (76)
HELLP syndrome[#]	72 (41)
Fetal growth restriction[#]	158 (90)
AREDF	29 (17)
Maximal measured PI umbilical artery	1.73 (0.61)
Maximal U/C-ratio	1.38 (0.64)
Prolongation of pregnancy (days)	11.6 (10.2)
Caesarean section/ fetal indication	163 (93) / 141 (81)
Major maternal morbidity[‡]	59 (34)
Treatment regime mother without/with PVE	89 (51) / 86 (49)

Values presented as mean (SD) or numbers (%) as appropriate.

[#]Categories not mutually exclusive; [‡]Major maternal morbidity: eclampsia, encephalopathy, pulmonary edema, liver haematoma, abruptio placentae, severe infectious morbidity, and severe thrombotic morbidity.

AREDF, absent or reversed end-diastolic flow of the umbilical artery; HELLP, hemolysis, elevated liver enzymes and low platelets; PI, pulsatility index; PVE, plasma volume expansion; U/C-ratio, umbilical artery pulsatility index divided by middle cerebral artery pulsatility index.

Table 3 Neonatal morbidity and test results at term age, three months and one year, specified for the three months general movements (GMs) results (*n*=175)

	Total group	GMs three months		
		Normal	Mildly abnormal	Definitely abnormal
		n=83 (47%)	*n*=70 (40%)	*n*=22 (13%)
PVE	86 (49)	43 (52)	30 (43)	13 (60)
Neonatal outcome				
Male gender	85 (49)	39 (47)	35 (50)	11 (50)
GA at delivery	223 (17)	223 (16)	224 (17)	221 (18)
Birth weight	1346 (458)	1358 (450)	1355 (441)	1266 (549)
Neonatal morbidity	26 (15)	11 (13)	11 (13)	4 (18)
CLD >36 weeks GA	15 (9)	5 (6)	9 (13)	1 (5)
Brain sonography				
PVL gr I	7	5	1	1
PVL gr II	2	1	–	1
IVH gr I	21	9	8	4
IVH gr II	–	–	–	–
IVH gr III	1	–	1	–
IVH gr IV	1	–	–	1
GM at term age (*n*=175)				
Normal	95 (54)	47 (57)	38 (54)	10 (46)
Mildly abnormal	63 (36)	29 (35)	27 (39)	7 (32)
Definitely abnormal	17 (10)	7 (8)	5 (7)	5 (23)
Neurol exam at term age (*n*=174)				
Normal	127 (73)	60 (73)	51 (73)	16 (73)
Suspect	37 (21)	17 (21)	15 (21)	5 (23)
Abnormal	10 (6)	5 (6)	4 (6)	1 (5)
Neurol exam at 3 months (*n*=175)				
Normal	112 (64)	58 (70)	46 (66)	8 (36)
Suspect	52 (30)	23 (28)	19 (27)	10 (46)
Abnormal	11 (6)	2 (2)	5 (7)	4 (18)
Neurol exam at 1 year (*n*=169)				
Normal	147 (84)	70 (84)	58 (83)	19 (86)
Suspect	18 (10)	8 (10)	8 (11)	2 (9)
Abnormal	4 (2)	2 (3)	1 (1)	1 (5)
Missing	6 (3)	3 (4)	3 (4)	0
PDI at 1 year (*n*=167)		83.87 (13.7)	78.40 (13.4)	75.55 (10.9)
Normal	57 (33)	34 (41)	18 (26)	5 (23)*
Mildly delayed	83 (47)	34 (41)	36 (51)	13 (59)
Significantly delayed	27 (15)	10 (12)	13 (19)	4 (18)
Missing	8 (5)	5 (6)	3 (4)	0
MDI at 1 year (*n*=169)		89.84 (9.6)	87.03 (9.7)	85 (7.8)
Normal	105 (60)	52 (63)	42 (60)	11 (50)
Mildly delayed	61 (35)	27 (32)	23 (33)	11 (50)
Significantly delayed	3 (2)	0	3 (4)	0
Missing	6 (3)	4 (5)	2 (3)	0

Values presented as mean (SD) or numbers (%) as appropriate.

*Difference statistically significant at $p<0.05$ (PDI normal versus mildly and significantly delayed).

PVE, plasma volume expansion; GA, gestational age; PVL, periventriculair leukomalacia; IVH, intraventricular haemorrhage; Neurol exam, neurological examination; PDI, psychomotor developmental index; MDI, mental developmental index.

one or more of the following diagnoses: chronic lung disease (*n*=15), PVL grade I (*n*=7), PVL grade II (*n*=2), IVH grade III (*n*=1) or IVH grade IV (*n*=1).

Prevalence of normal, mildly abnormal and definitely abnormal GMs

GM categories were not statistically different between the two maternal management strategies (*p*=0.331), thus all intended analyses were performed for the whole group.

At term age, 95 (54%) of the 175 infants had normal GMs, 63 infants (36%) had mildly abnormal and 17 infants (10%) had definitely abnormal GMs. At three months, 83 infants (47%) had normal GMs, 70 infants (40%) had mildly abnormal and 22 infants (13%) had definitely abnormal GMs (Table 3). Less than half of the infants (*n*=79; 45%) did not change in GM categories from term age to three months, while 55 infants (31%) deteriorated and 41 infants (23%) improved over time. GMs at term age were not correlated with GMs at three months.

Relation between GMs and neurological examination at term age and three months

The distribution of neurological examination at term age and three months is depicted in Table 3. Infants with mildly or definitely abnormal GMs at term age had significantly more often a suspect or abnormal neurological examination at term age (*p*=0.001). GMs at three months were not related to neurological examination at three months (*p*=0.12).

GMs at three months and outcome at one year

Mildly or definitely abnormal GMs at three months were not related to neurological examination at one year (*p*=0.85) or MDI (*p*=0.41) (Table 3). However, infants with mildly or definitely abnormal GMs at three months had significantly more frequently a moderately or severely delayed PDI at one year than infants with normal GMs at three months (*p*=0.01). Neurological examination at three months was related to PDI at one year (*p*=0.04), but not with neurological examination (*p*=0.16) or MDI (*p*=0.07).

In Table 4 the individual developmental trajectories are presented for those infants with abnormalities on neonatal brain sonography (PVL I–IV and IVH III–IV). These trajectories demonstrate that GM categorisation and neurological examination change during development. From the four infants with higher grading PVL II or IVH III–IV, three had mildly or definitely abnormal GMs at three months, two had suspect neurological examination at three months and two had abnormal neurological examination at one year.

Abnormalities on neonatal brain sonography were not significantly correlated to neurological examination at one year (*p*=0.15) or MDI (*p*=0.07) or PDI (*p*=0.69).

Discussion

This is the first large prospective study on the quality of general movements in infants from mothers with early-onset hypertensive disorders of pregnancy. Because of placental insufficiency a high proportion of preterm and/or small for gestational age infants is common after such pregnancies. In our cohort, indeed 98% was born prematurely, while 89% was small for gestational age. In this patient group, with high perinatal risk, we found a high (about 50%) prevalence of mildly and definitely abnormal GMs both at term and three months.

Table 4 Individual trajectory of GMs and neurological examination at term and three months, and outcome at one year in infants with abnormalities in neonatal brain sonography from PVL and IVH III–IV

		Term age		3 months		1 year		
No.	PVL and/or IVH	GM	Neur ex	GM	Neur ex	MDI	PDI	Neur ex
1	IVH IV	n	n	a	n	ma	n	n
2	IVH III	n	n	ma	ma	n	ma	n
3	PVL II + IVH I	a	a	a	ma	n	ma	a
4	PVL II	n	a	n	n	ma	a	a
5	PVL I + IVH I	n	n	n	n	n	n	n
6	PVL I + IVH I	ma	a	n	ma	n	ma	n
7	PVL I	n	ma	n	n	ma	ma	ma
8	PVL I	ma	n	n	ma	ma	n	n
9	PVL I	n	n	ma	n	ma	a	n
10	PVL I	n	n	a	n	ma	ma	n
11	PVL I	n	ma	n	ma	ma	ma	n

PVL, periventricular leukomalacia; IVH, intraventricular haemorrhage; GM, general movement; Neur ex, neurological examination; MDI, mental developmental index; PDI, psychomotor developmental index; n, normal; ma, suspect neurological examination / mildly abnormal GM / mildly delayed MDI or PDI; a, abnormal neurological examination / definitely abnormal GM / severely delayed MDI or PDI.

The prevalence of abnormal GMs varies considerably between studies, depending on the characteristics of the studied populations. Studies in high risk populations, based on growth restriction or sonographic brain lesions, reported a prevalence of 45%[8] to 100%.[4] In two low-risk populations, one characterised by preterm and term infants with at most transient echodensities or IVH grade I, and another by preterm infants born after an uncomplicated pregnancy and delivery and uneventful neonatal period, a prevalence of 0–17%[3,4] was found. In healthy term infants at the age of three months a prevalence of definitely abnormal GMs was observed of 0%[13] to 7%[12] and of mildly abnormal GMs of 18%[12] to 24%.[13]

The results of our study group of preterm, growth restricted infants selected on maternal hypertensive disorders of pregnancy were comparable to the low-risk population as mentioned above (at three months definitely abnormal GMs 13%). The high prevalence of mildly abnormal GMs at three months (40%) is in agreement with the study of Hadders-Algra[7] in a mixed high-low-risk population.

The prevalence of abnormal GMs is highly influenced by the severity of cerebral damage as visualized on ultrasound (PVL and IVH).[3,4,7,26,27] For this reason we reported the individual trajectories of the infants with these sonographic brain abnormalities. Seven infants in our study had PVL grade I. At the age of three months, one of them had abnormal GMs and one mildly abnormal GMs (29%). This is lower than the 52% abnormal GMs in infants with PVL grade I as observed by Bos et al.[6] The individual trajectories between term age and one year appeared to vary substantially, not only in infants with the same cerebral ultrasound diagnosis but in all infants with respect to outcome on the different neurodevelopmental tests we performed during the first year post term.

The prevalence of abnormal GMs is also dependent on the severity of fetal growth restriction. In two studies, including 31[8] and 19[5] small for gestational age infants the prevalence varied from 41%[8] to 78%.[5] Our results are closer to those of Zuk et al.[8] Like in their study, we also

included growth restriction below the 10th percentile like Zuk et al.,[8] and not only below the 5th percentile, like Bos et al.[5]

Moreover, there is an ongoing discussion on the influence of prematurity itself on the quality of GMs. Preterm infants, even in good condition, more often have affected quality of GMs than term infants,[28] which also can explain the high prevalence of especially mildly abnormal GMs in our study. This was not confirmed by Zuk et al.[8] however, who reported that low-risk preterm infants have identical quality of GMs as term infants, indicating that GM quality is not affected by prematurity itself, but by the neurological status of the infant.

Abnormal GMs at three months were not related with neurological examination at one year. Moreover, GMs at term age and three months were also not related to each other, while GMs at term, but not at three months, were related to neurological examination at the same time point. GMs at three months were, however, related to one year psychomotor development.

GMs measure the quality of spontaneous motor activity, whereas neurological examination especially focuses on elicited motor output. Our observation that abnormal GMs can normalise and vice versa has been shown by others.[7] However, especially GMs at three months, the fidgety age, have been found to be most predictive, not only for cerebral palsy at age two[21] but for infants with mildly abnormal GMs for all sorts of minor neurological dysfunctions even up to puberty.[7,28,29] Deviations found at early ages are often transient to reappear later when a new function is established. A reduced primary repertoire of the neural network early in life may lead to inappropriate processing of afferent information which at a later age may be recognisable as restrictions of variability of the nervous system.[30,31] Not only sonographically visible brain abnormalities are important attributing factors in neurological outcome, but prematurity also induces more subtle anomalies like reduced cerebellar growth with consequences for neurological outcome.[32]

In follow-up studies, the mildly abnormal GMs group often shows variable outcomes.[7] One year of age is probably a too young age to differentiate between more subtle neurodevelopmental abnormalities and is also too young to diagnose cerebral palsy. As mentioned above, GMs at three months were related to psychomotor development. The PDI measures the achievement of a broader set of motor milestones, and in our cohort 65% of the infants had a mildly or significantly delayed psychomotor development. We are currently performing follow-up in our cohort at the age of 4.5 years. It will be interesting to know whether the infants with both a subnormal GM registration at three months and a subnormal PDI at one year are those at risk for (minor) neurological dysfunction at early school age. GMs at three months then might discriminate between infants that improve spontaneously and those in which delay is one of the markers of neurological damage.

In conclusion, this prospective study indicates a high prevalence of mildly and definitely abnormal GMs at three months in small for gestational age, preterm infants. Abnormal GMs at three months had no association with neurological examination at one year, but were related to PDI at one year. The GM assessment in this perinatal high risk population should be seen as an additional tool in the evaluation of the dynamic process of neurological development. Further follow-up of this cohort is necessary to assess a possible association of GMs with more subtle neurological abnormalities which become only detectable at a later age.

Appendix

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Chapter 3

Motor outcome at the age of one after perinatal hypoxic-ischemic encephalopathy

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Abstract

Objective: The aim of this report is to describe the motor outcome in one year old children who were born at full-term with perinatal hypoxic-ischemic encephalopathy (HIE). Relationships between motor ability tests and neurological examination at one year, and between these tests and neonatal brain magnetic resonance imaging (MRI) were investigated.

Participants and methods: 32 surviving children, born full-term with perinatal HIE, are included in this report. All children had a neonatal MRI. At one year, motor ability was assessed with the Alberta Infant Motor Scale and the Bayley Scales of Infant Development (2nd version). Neurological examinations included the neurological optimality score (NOS).

Results: At one year, 14 children (44%) had normal motor ability, nine (28%) had mildly delayed, and nine had significantly delayed motor ability. The NOS ranged from 14.6–27.0 points. All children with normal motor ability had (near) optimal NOS, however, not all children with high NOS had normal motor ability. Eleven children (34%) had normal neonatal MRI; at one year, six of them had normal, and five had mildly delayed motor ability. Eight children with normal motor ability showed abnormalities on neonatal MRI.

Conclusion: Neonatal brain MRI does not predict motor outcome at one year. Motor ability tests and neurological examination should be used in a complementary manner to describe outcome after HIE.

Introduction

Acute hypoxic-ischemic encephalopathy (HIE) in the full-term newborn is a major cause of neurodevelopmental abnormalities in childhood.[1-3] To describe outcome after perinatal HIE, various outcome measures are available. According to the International Classification of Functioning, Disability and Health (ICF),[4] outcomes can be described in terms of diseases (such as cerebral palsy [CP]), in terms of body function and structures (such as (impaired) muscle tone or involuntary movements), or in terms of activities (such as motor ability or motor performance). The relations between these domains (i.e., diseases versus activities) are not linear, and largely unknown.

The vast majority of outcome studies have documented outcomes with an emphasis on severe neurological morbidity, such as CP or mental retardation. Neurological function, measured with different neurological examinations at different ages,[1,5-7] has been the most frequently used outcome measure in previous studies of HIE.[8-15] In other studies, outcome has been described in terms of mental development[16-18] or in terms of more overall, multi-dimensional development.[5,6,17,19-21] Unfortunately, only a few studies have described the outcome in terms of activities, as motor ability.[13,22]

Several instruments are available for the assessment of motor ability at the age of one year. Most of these instruments distinguish children with normal motor ability from children with delayed motor ability. A valid and precise assessment of motor ability can be of added value for targeting rehabiliation services and making a proper functional prognosis. Moreover, a functional prognosis in terms of ability is clearer and more understandable for parents than a neurological diagnosis alone.

Early diagnosis and prediction of outcome is important, not only for clinical decision-making,

and referral of the children to services but, in particular, for providing information to the parents. Therefore, it is important to have knowledge about the relationship between neonatal prognostic factors, such as the Sarnat score, and outcome in terms of motor ability. The outcome of children with Sarnat stage 2, in particular, is quite variable.[1,9] More recently, magnetic resonance imaging (MRI) has been introduced to detect brain damage in infants with HIE. However, the predictive value of MRI for functional outcome needs further validation.

The main aim of the present study was to describe motor outcome in one year old children, who were born full-term with a perinatal hypoxic-ischemic event. Secondly, the relationship between motor ability (activity level of ICF) and neurological function (level of body function of ICF) at the age of one year was assessed, and thirdly, the relationship between motor ability, Sarnat score and neonatal MRI was investigated.

Materials and methods

Patients and methods

All full-term (gestational age 37 weeks or more) neonates suffering from HIE, born between August 2000 and November 2002, who had been referred for neonatal intensive care to the VU University Medical Center, were enrolled consecutively in this prospective study. The study group consisted of 46 neonates, who all fulfilled the first mentioned criterion of HIE (see 1. below), and at least one of the other inclusion criteria:

1. clinical status of HIE within 24 hours: lethargy, hypotonia, hyperreflexia, convulsions, segmental myclonics;
2. signs of intra-uterine asphyxia, such as late decelerations or meconium-stained amniotic fluid;
3. umbilical cord artery pH <7.10;
4. respiratory insufficiency at birth, with need of mechanical ventilation;
5. APGAR score of less than 5 at 5 minutes.

Children with dysmorphic syndromes, malformations, evidence of intrauterine or perinatal infections, intracranial hemorrhage, and those who required surgical intervention in the neonatal period were excluded. The research protocol was approved by the hospital Medical Ethics Committee, and all parents gave their informed consent.

Measurements

Neonatal assessment

The degree of neonatal encephalopathy was classified during the first week of life, according to Sarnat,[14] as mild (stage 1), moderate (stage 2) or severe (stage 3). When the Sarnat stage changed within the first week of life, the most severe stage was used in this study. The Sarnat stages included assessment of the level of consciousness, tone, complex and tendon reflexes, autonomic function, and the presence of myoclonics and seizures.

To determine brain damage, all infants had a brain MRI as soon as possible in the neonatal period, upon stabilisation of the clinical situation of the infant.

Assessment at the age of one year

At the age of one year, the children were assessed in the outpatient clinic of the VU University Medical Center. Motor ability was assessed with the Alberta Infant Motor Scale (AIMS) and the motor scale of the Bayley Scales of Infant Development 2nd version (BSID-II), in that order, and in case of children with CP with the Gross Motor Function Measure (GMFM) by a trained paediatric physical therapist (PEMS). She was not involved in the neonatal and postnatal care of the children under investigation, and was blinded for the clinical status, histories and neonatal brain MRI scores of the children. A neurological examination (Neurological Optimality Score; NOS)5 was performed by a paediatric neurologist (RJV). The AIMS and motor scale of the BSID-II were tested in one examination in 30–40 minutes. This examination took place at a time which was chosen by the mother as being the most optimal time for the child to cooperate, mostly around 11 a.m.

1. Alberta Infant Motor Scale (AIMS)

The AIMS is an observational assessment tool that is used to measure the gross motor maturation of infants from birth through the age of independent walking. It consists of 58 items that are arranged in four subscales: prone (21 items), supine (9 items), sitting (12 items), and standing (16 items). For each test item, the examiner must identify and observe three key descriptors: weight-bearing, posture, and antigravity movement. The content and key descriptors for each item have been described in detail elsewhere.[25] The scoring system entails a dichotomous choice for each test item, scored as 'observed' or 'not observed', resulting in one total score. Normative data are available to determine whether the motor performance differs from typically developing infants. Normal motor development was defined as a *z* score above −1; mildly delayed motor development as a *z* score between −2 and −1, and significantly delayed motor development as a *z* score below −2.

The AIMS has been investigated for its practicality, and for the reliability and validity of its scores,[23,24] and it has high degrees of test-retest, intra-rater and inter-rater reliability when it is used to measure typically developing full-term infants[25] and pre-term born infants.[26] The AIMS can be administered in approximately 20 minutes.

2. Bayley Scales of Infant Development, 2nd version (BSID-II)

The BSID-II has been developed to assess the psychomotor development of children between the age of 1–42 months. The revised BSID-II contains the motor scale (111 items), the mental scale (178 items), and the behavioral rating scale (30 items).[27] In this study only the motor scale was used. The BSID-II specifies sets of items to be assessed, depending on the child's chronological age. For the 12-month age-period, at least 15 items must be assessed: 3 fine motor skill items and 12 gross motor skill items. The content and criteria for each item are described in the manual. Raw scores must be converted to the Psychomotor Developmental Index (PDI), which has a mean of 100 and a standard deviation of 15. Outcomes are defined as 'within normal limits' if the PDI is 85 or above (= *z* score above −1), as 'mildly delayed performance' if the PDI is between 70 and 84 (= *z* score between −2 and −1), and as 'significantly delayed performance' if the PDI is 69 or below (= *z* score below −2).[27] The recently established normative data for the Dutch population[28] were used in this study, although reliability and validity studies of the Dutch translation of the BSID-II are still under investigation. The reliability and validity of the BSID-II have been established in the United States.[27] For children under 15 months, the

motor scale test will take 10–15 minutes.

3.1 Gross Motor Function Measure (GMFM)

Children with a clear neurological disorder such as CP can not fulfil the criteria for AIMS and BSID-II, and will score below –2 standard deviations. Therefore, for these children (also) the GMFM was used. The GMFM-88[29] is a criterion-referenced evaluative measure that was developed and validated to assess the gross motor abilities of children with CP. All test items can usually be accomplished by a five-year-old with normal motor abilities.

The GMFM consists of 88 items, divided over five dimensions: lying and rolling (17 items), sitting (20 items), crawling and kneeling (14 items), standing (13 items) and walking, running, jumping (24 items). Each item must be scored on a 4-point scale, where 0 means 'does not initiate' and 3 'completes the item'. The scores are expressed as a percentage of the maximum score. The validity, reliability, and responsiveness of the GMFM have been demonstrated in a population of children with CP.[30] Assessment with the GMFM will take between 30 and 60 minutes, depending on the child's ability.

3.2 Gross Motor Function Classification System (GMFCS)

The GMFCS[31,32] is a condition-specific 5-level classification system, based on self-initiated movement of children with CP, in which I is the highest functional level and V the lowest. For the youngest age group (below the age of 18 months), it is recommended to use only two GMFCS categories: one for levels I–II–III (these children have a prognosis of walking) and one for levels IV and V (these children will probably be wheelchair-bound).[33] The inter-rater and test-retest reliability of the GMFCS is high,[34] and the inter-rater reliability of the two categories for children under the age of 18 months is also high.[33] Classification according to the GMFCS will only take a few minutes.

4. Neurological Optimality Score (NOS)

The results of the standardized neurological examination[5] were expressed in an NOS, according to Prechtl.[35] The NOS consists of nine subgroups of items (spontaneous motility, posture, involuntary movements, muscle tone, tendon reflexes, primitive responses, quality of motor behaviour, vision, and hearing) with a total of 47 items. Each item is separately scored as normal (3 points), moderately abnormal (2 points) or severely abnormal (1 point). The score of a subgroup is obtained by calculating the mean of all individual items in that subgroup. The total score is the sum of the scores of the 9 subgroups, and ranges from 9 points (indicating severe neurological impairment) to 27 points (indicating complete neurological integrity). There are no normative data or reliability data available.

5. Magnetic Resonance Imaging (MRI)

The MRI protocol included transverse T1, multi-echo T2 and FLAIR and diffusion-weighted sequences. All images were reviewed for abnormalities by an experienced radiologist (FB), who was unaware of the clinical condition of the children.

We used the scoring system for basal ganglia/watershed scores as proposed by Barkovich,[16] with the following scores: 0 = no abnormalities in the basal ganglia or cortex; 1 = an abnormal signal in the basal ganglia or thalamus; 2 = an abnormal signal in the cortex; 3 = an abnormal signal in the cortex and basal nuclei (basal ganglia or thalami); 4 = an abnormal signal in the

entire cortex and basal nuclei. Special attention was paid to the posterior limb of the internal capsule (PLIC), knowing that presence or absence of a normal signal from myelin in the PLIC in the term infant following a perinatal hypoxic-ischemic insult is a very good predictor of normal or abnormal motor outcome.[36,37]

Statistical analyses

Correlation between the *z* scores of the AIMS and BSID-II was tested non-parametrically by calculating a Spearman rank order correlation coefficient. The difference between the mean GMFM scores of the two GMFCS categories was tested by means of the non-parametric Kruskal-Wallis one way of analysis of variance test. All analyses were performed with SPSS for windows, version 11.5, and tested two-tailed with a *p* value lower than 0.05 as the level of statistical significance.

Results

Clinical neonatal data

All consecutive newborn children who met the inclusion criteria entered the study. No family refused to participate. The study group consisted of 46 full-term born neonates, of whom 11 died within one week after birth and three were lost to follow-up at the age of one year. Two of these children had been moved to an unknown new address, and were investigated considerably later than at the age of one year, and were therefore not included in the analysis. The parents of one child withdrew consent. Therefore 32 children (20 boys, 12 girls) were assessed when they were one year old, most of them before the age of 13 months, although three children with severe CP and one child with normal motor development were assessed later (mean age at assessment: 54 weeks, range: 52–66 weeks).

The neonatal data of the surviving children are presented in Table 1. Their gestational age ranged from 37–42 weeks (mean age 40 2/7 weeks, SD 1 3/7 weeks), which was all considered full term, and their birth weight varied between 2060 and 4140 g (mean birth weight 3211 g, SD 443). According to Sarnat's HIE stages, seven children had mild HIE (stage 1) and 25 had moderate HIE (stage 2). There were no surviving children with severe HIE (stage 3).

Motor ability at the age of one year: AIMS and BSID-II

Of the 32 children, 15 (47%) had normal motor ability according to the AIMS, 3 (9%) had mildly delayed while 14 (44%) had significantly delayed motor ability. According to the Dutch norms of the BSID-II, 20 children (63%) had normal motor ability (PDI 85 or above = *z* score >−1), three (9%) had mildly delayed motor ability and nine (28%) had significantly delayed motor ability.

In 23 of the 32 children (72%), the two scales showed agreement with respect to the classification: 14 children were classified as having normal motor ability and nine children were classified as having a significantly delayed motor ability on both scales. Nine children were classified as having mildly delayed motor ability because their classification according to the two scales differed; one child was mildly delayed according to the BSID-II but normal on the AIMS, three children were mildly delayed on the AIMS, but normal on the BSID-II, three children were significantly delayed on the AIMS, but normal on the BSID-II, and two children were significantly delayed on the AIMS but only mildly delayed on the BSID-II. Spearman rank

Table 1 Neonatal characteristics and outcome at the age of 1 year (*n*=32)

No.	Sex	Ga	BW	pH	Apg5	Conv	Sarnat	Day	MRI	Plic	Age	AIMS		BSID-II		NOS	GMFM	GMFCS	Diagn
												Raw	*z* score	PDI	*z* score				
1	M	39 5/7	2895	–	6	yes	1	7	0	0	53	57	0.53	121	1.40	27			Normal
2	F	42	3200	7.03	4	no	1	18	2	0	56	57	0.53	117	1.13	27			Normal
3	M	39	3070	–	–	no	1	24	0	0	61	54	−1.47	102	0.13	27			Mild d
4	M	41	3560	–	7	no	1	37	2	0	52	51	−0.80	99	−0.07	27			Normal
5	F	41 4/7	2600*	6.81	6	no	1	12	3	0	54	52	−0.58	99	−0.07	27			Normal
6	M	38 2/7	2380*	6.79	4	yes	1	2	3	0	53	52	−0.57	99	−0.07	26.60			Normal
7	M	40 3/7	3630	7.08	4	no	1	18	0	0	52	29	−5.66	92	−0.53	26.20			Mild d
8	M	41	3530	–	7	yes	2	12	2	2	52	52	−0.57	106	0.40	27			Normal
9	F	40 4/7	4140	6.81	4	yes	2	2	0	0	55	54	−0.13	105	0.33	27			Normal
10	M	40 2/7	3060	7.19	4	yes	2	6	0	0	52	52	−0.57	102	0.13	27			Normal
11	M	41 3/7	3280	6.88	6	no	2	41	0	0	52	51	−0.80	99	−0.07	27			Normal
12	F	40 3/7	3250	6.80	6	yes	2	45	0	0	55	51	−0.80	98	−0.13	27			Normal
13	M	41	3120	–	5	no	2	6	0	0	52	50	−1.02	95	−0.33	27			Mild d
14	F	38 4/7	3320	7.24	5	yes	2	9	3	2	52	52	−0.58	95	−0.33	26.90			Normal
15	F	39 5/7	3540	–	5	yes	2	3	2	0	52	52	−0.58	95	−0.33	26.90			Normal
16	F	39 6/7	3660	–	5	no	2	8	0	0	52	48	−1.46	92	−0.53	27			Mild d
17	M	38	2750	6.70	4	no	2	5	3	0	53	35	−4.33	92	−0.53	26.63			Mild d
18	M	39 2/7	3700	6.94	5	yes	2	4	4	0	56	53	−0.35	91	−0.60	27			Normal
19	F	40 6/7	2895	6.99	4	yes	2	4	0	0	57	51	−0.92	87	−0.87	26.70			Normal
20	F	41 3/7	2930	–	4	yes	2	7	2	0	52	38	−3.67	85	−1.0	26.08			Mild d
21	M	42	3980	7.11	3	yes	2	11	0	0	55	53	−0.35	84	−1.07	27			Mild d
22	F	38	2885	6.85	7	yes	2	7	3	0	52	33	−4.78	78	−1.47	25.50			Mild d
23	M	40 5/7	3580	6.80	6	yes	2	8	1	0	52	28	−5.88	74	−1.73	26.40			Mild d
24	M	38 2/7	2060*	7.03	3	yes	2	3	3	2	54	23	−6.99	66	−2.27	25.70	25.0	I–III	Hemi
25	M	41 1/7	3250	7.13	6	yes	2	6	4	0	52	17	−8.32	<55	<−3.0	23.67	20.6	I–III	Di/dys
26	F	40 2/7	3220	6.96	3	no	2	4	1	0	52	26	−6.34	<55	<−3.0	24.30	18.6	I–III	Di/dys
27	M	39	3350	–	4	no	2	2	3	0	53	18	−8.10	<55	<−3.0	26.58	16.2	I–III	Dyst
28	M	42	3350	–	4	yes	2	3	3	0	66	9	−10.00	<55	<−3.0	19.60	7.8	IV/V	Tetra
29	F	40 2/7	3025	–	4	yes	2	11	3	1	54	10	−9.87	<55	<−3.0	18.27	7.2	IV/V	Tetra
30	M	37 1/7	2900	–	6	no	2	7	3	2	61	8	−10.00	<55	<−3.0	19.90	5.6	IV/V	Tetra
31	M	42 1/7	3500	6.84	4	yes	2	1	3	1	64	7	−10.00	<55	<−3.0	14.55	4.0	IV/V	Tetra
32	M	42 1/7	3335	7.23	5	yes	2	3	3	0	52	8	−10.31	<55	<−3.0	19.95	3.4	IV/V	Tetra

AIMS, Alberta Infant Motor Scale; Age, age in weeks on assessment; Apg5, APGAR at 5 minutes (–, missing); BSID-II, Bayley Scales of Infant Development second version (Dutch norms); BW, birth weight (*<p10 Dutch norms for birth weight); Conv, convulsions during first week; Day, day of neonatal MRI; Diagn, diagnosis and/or classification; Di/dys, diplegia and/or dystonia; F, female; Ga, gestational age; GMFCS, level of gross motor function classification system; GMFM, total score in % on GMFM; Hemi, hemiplegia; M, male; Mild d, mildly delayed motor ability; MRI, magnetic resonance imaging (0, normal; 1, basal ganglia; 2, cortex; 3, basal ganglia and cortex; 4, basal ganglia and entire cortex); NOS, neurological optimality score; PDI, psychomotor developmental index on BSID-II; pH, umbilical cord artery pH (–, missing); Plic, posterior limb of internal capsule (0, normal; 1, mildly abnormal/suspect; 2, abnormal); Raw, raw score on AIMS; Tetra, tetraplegia.

Table 2 Relationship between outcomes on AIMS and BSID-II (*n*=32)

	AIMS *z* score >−1 (normal; *n*=15)	AIMS *z* score −2<−1 (mildly delayed; *n*=3)	AIMS *z* score <−2 (significantly delayed; *n*=14)
BSID-II: *z* score ≥−1 (normal) (*n*=20)	14 (44%)	3 (9%)	3 (9%)
BSID-II: *z* score −2<−1 (mildly delayed) (*n*=3)	1 (3%)	0	2 (6%)
BSID-II: *z* score <−2 (significantly delayed) (*n*=9)	0	0	9 (28%)

AIMS, Alberta Infant Motor Scale; BSID-II, Bayley Scales of Infant Development, 2nd version (motor scale); *n*, number.

Table 3 MRI score per motor ability category (combined AIMS and BSID-II scores)

	Motor ability		
	Normal	Mildly delayed	Significantly delayed
MRI score	(*n*=14)	(*n*=9)	(*n*=9)
Normal (*n*=11)	6	5	0
Basal ganglia (*n*=2)	0	1	1
Cortex (*n*=5)	4	1	0
Basal ganglia and cortex (*n*=12)	3	2	7
Basal ganglia and entire cortex (*n*=2)	1	0	1

AIMS, Alberta Infant Motor Scale; BSID-II, motor scale of Bayley Scales of Infant Development 2nd version; MRI, magnetic resonance imaging; *n*, number.

order correlation coefficients between the raw scores and between the *z* scores of the AIMS and the BSID-II (of children without CP) were 0.83 and 0.61 respectively (both $p<0.01$). The combined results of the AIMS and the BSID-II are shown in Table 2.

Motor ability at the age of one year: GMFM

The total GMFM score for nine children with CP (all with significantly delayed motor ability) ranged from 3.4%–25% (mean 12%). These nine children were sub-divided into two groups, according to their GMFCS level. The mean GMFM score for the GMFCS I–II–III group (*n*=4) was 22% (range 16–28%), and for the GMFCS IV–V group (*n*=5) it was 5.6% (range 3–7%). The mean GMFM scores for these two groups also differed significantly ($p<0.001$).

Results of NOS

At the age of one year the NOS ranged from 14.6–27.0 points. Fourteen children (44%) had an NOS of 27 points; 10 of them were classified as having normal motor ability, and four as having mildly delayed motor ability. The other four children with normal motor ability scored between 26.6 and 26.9 points on the NOS. For the group of children with mildly delayed motor ability the NOS ranged from 25.5–27.0 points. The nine children with significantly delayed motor

ability had an NOS ranging from 14.6–26.6 points, most of them (*n*=7) had values lower than 25 (Table 1). The five children in GMFCS level IV and V (diagnosed as severe tetraplegics) all had an NOS of less than 20 points. The four children in GMFCS level I–II–III had an NOS between 23.7 and 26.6 points. One of these children was diagnosed as hemiplegic and three children were diagnosed as a mixed type of spastic/dystonic bilateral (legs more involved than arms) CP. Table 1 shows that all children with normal motor ability had a high NOS (>26.5).

Results of MRI

To determine brain damage, a brain MRI was made as soon as possible (mean 11 days after birth, SD 11 days, median 7 days, range 1–45 days).

Eleven children (34%) had normal brain MRI, but the MRI of 21 children showed abnormalities (Table 3). Six of the 11 children with normal brain MRI had normal motor ability and five had mildly delayed motor ability. Of the 14 children with normal motor ability, six had normal MRI, and eight had abnormalities in the cortex (*n*=4), the basal ganglia and cortex (*n*=3) or the basal ganglia and the entire cortex (*n*=1). Of the nine children with mildly delayed motor ability, five had a normal brain MRI, one had abnormalities in the basal ganglia, one in the cortex and two in the basal ganglia and cortex. Most children (*n*=7) with significantly delayed motor ability had abnormalities in the basal ganglia and cortex, one had abnormalities in the basal ganglia only, and one had abnormalities in the basal ganglia and the entire cortex.

Results of the Sarnat score

Of the seven children with a mild Sarnat score (stage 1), five (71%) had normal and two had mildly delayed motor ability (of whom one was mildly delayed and one significantly delayed on the AIMS) at the age of one year. Of the 25 children with a moderate Sarnat score (stage 2), nine (36%) had normal, seven (28%) had mildly delayed and nine (36%) significantly delayed motor ability.

Discussion

This study describes the motor ability and neurological function of well-documented children with neonatal HIE at the age of one year. Of our cohort of 32 surviving children, all seven children with mild HIE had normal or mildly delayed motor ability, which is in agreement with the literature.[9] Of the 25 children with moderate HIE, nine (36%) had significantly delayed motor ability at the age of one year. This finding is also in line with the conclusion of Dilenge and collegues,[9] who showed that children with moderate HIE had a 30–50% risk of major deficits. In the present study, nine children (36%) with moderate HIE showed normal motor ability.

Acknowledging that it is not clear which test is most valid to describe motor ability at the age of one year, we used two different assessments in the present study. In our study, in 72% of the cases, the two scales identified the same children with normal or significantly delayed motor ability. Spearman rank correlation coefficient between the raw scores of AIMS and BSID-II was in agreement with that of Piper et al., who found a correlation coefficient of 0.85 between AIMS and BSID-II in 43 children between age 8–13 months, suggesting good concurrent validity.[25] However, the AIMS seems to be more stringent, and classified more children as significantly delayed. The different classification of nine children can be explained by the difference in the items of the two tests. Both instruments measure gross motor ability, but the BSID-II also assesses fine motor ability. Children with good fine motor ability can be classified as having

normal motor ability, even though their gross motor ability is delayed. A limitation of this study is that children are only assessed once. It is known that normally developing infants are not stable in the rate of emergence of gross motor delay.[23] To date, a low percentile ranking at one assessment does not necessarily indicate delayed motor development in the long term. Therefore, serial assessments are recommended. In addition, long-term follow-up is needed to determine whether the infants with mildly or significantly delayed motor ability at the age of one year, still have a motor delay when they are older.

Furthermore, children with the diagnosis CP cannot be assessed with these instruments, but their motor ability should preferably be described by means of the GMFCS, or more precisely (for therapy purposes) according to the GMFM. In particular, the combination of GMFCS and GMFM using 'motor growth curves'[38] enables clinicians to make a valid functional prognosis.

Although there are no normative data or clear cut-off points for NOS, it was apparent that the sensitivity of the NOS is lower than its specificity. Our findings are in line with the study by Kuenzle and co-workers,[5] in which 37% of the children with a high NOS (26–27 points), showed motor impairment, such as spastic diplegia (n=1) and discrete asymmetry (n=6). In our study, 39% of the children with a high NOS (26–27 points) had delayed motor ability such as dystonic cerebral palsy (n=1) or mildly delayed motor ability without a specific diagnosis (n=8). Acknowledging that neurological examination is always necessary to diagnose a neurological disease, NOS and motor ability tests should be used as complementary tests for describing outcome.

Of the 11 children who had no abnormalities on the brain MRI, five had mildly delayed motor ability. As reported by others, (mild) neurological abnormalities can occur in the absence of lesions or abnormalities in the first year of life.[1] In contrast, more than half of the children with normal motor ability at the age of one year had abnormalities on the MRI. Children with mildly delayed motor abilities had a wide range of abnormalities on the MRI. Thus, at the age of one year the relationship between neonatal MRI and motor ability is still ambiguous.

In our opinion, especially for the subgroup representing children with mildly delayed motor ability, the age of one year is too young to appreciate the full spectrum of neurological deficits. Relatively normal motor ability, with regard to the achievement of motor milestones at the age of one year, does not preclude the possibility that some children might have a very mild hemiplegia or diplegia. Other children, although they do not have CP, might be clumsy when they reach school age. Barnet et al.[39] demonstrated that even children with neonatal HIE who had a normal outcome at the age of two years had motor problems such as minor neurological dysfunction, at the age of 5–6 years. Dilenge[9] also stated that, although it has not been well documented to date, it is suspected that a good proportion (50–75%) of children presenting with neonatal neurological symptoms, secondary to neonatal HIE, will manifest difficulties at school later on. Therefore follow-ups at the age of two years, and also at school age, might provide further insight into the relationship between neonatal brain damage and motor outcome. Due to the initial design of the study, we did not include assessment of mental outcome at the age of one year. As a consequence, data on the correlation between mental outcome and motor ability are lacking. In future studies, in this cohort, assessment of mental outcome will also be investigated.

Conclusion

Neonatal brain MRI does not predict motor outcome at the age of one year. Motor ability tests and neurological examination at the age of one year should be used complementary to describe outcome after HIE.

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Chapter 4

Motor testing at one year improves the prediction of motor and mental outcome at two years after perinatal hypoxic-ischemic encephalopathy

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Abstract

The aim of this study was to investigate the predictive value of motor testing at one year for motor and mental outcome at two years after perinatal hypoxic-ischemic encephalopathy (HIE) in full-term neonates. Motor and mental outcome at two years was assessed with the Bayley Scales of Infant Development 2nd version (BSID-II) in 32 surviving children participating in a prospective cohort study on HIE. The predictive value of three motor tests (Alberta Infant Motor Scale [AIMS], BSID-II and neurological examination [NOS]) at one year was analyzed, in addition to prediction based on neonatal Sarnat staging and MRI.

Twelve children (38%), all with Sarnat II, had a poor motor outcome and 12 children (38%), of which one with Sarnat I, had a poor mental outcome at two years. Motor tests at one year increased the probability of a poor motor outcome from 71% to 92–100%, and a poor mental outcome from 59% to 77–100% in children with Sarnat grade II and abnormal MRI, assessed with the AIMS and BSID-II or NOS respectively.

In conclusion, additional motor testing at one year improves the prediction of motor and mental outcome at two years in children with Sarnat grade II and abnormal MRI.

Introduction

One to two per 1000 live full-term neonates have hypoxic-ischemic encephalopathy (HIE).[1] HIE in full-term neonates is one of the main causes of disability in children. It is important to assess the outcome of full-term neonates with HIE and to target those with a higher risk of developing sequelae to ensure the provision of early and appropriate rehabilitation services and to facilitate parental counselling. Knowledge about the predictive value of neonatal assessments, the stage of clinical encephalopathy according to Sarnat grading[2] or magnetic resonance imaging (MRI) brain scan findings is important for later outcome. The Sarnat grading is a widely used predictor of outcome in neonates with HIE. However, follow-up studies have demonstrated a lower predictive value of Sarnat grading for the outcome in infants with moderate (Sarnat grade II) encephalopathy, in contrast to the high predictive value of Sarnat grading in infants with mild (Sarnat grade I) and severe (Sarnat grade III) encephalopathy.[3-7]

Neonatal MRI has high sensitivity, but lower specificity for the prediction of good motor outcome in surviving children with HIE.[8-10] Children with normal MRI usually have a favourable motor outcome,[3,11,12] but children with abnormal MRI have a variable outcome. Thus, Sarnat grade I and normal neonatal MRI accurately predict a good motor outcome after neonatal HIE, whereas Sarnat II and abnormal MRI predict a poor outcome with less accuracy.

Motor development in the first year is routinely assessed in the clinical follow-up of children with neonatal HIE.

The aim of this study was to investigate whether motor testing at one year can improve the accuracy of the prediction of motor and mental outcome at two years after HIE, especially in children with Sarnat II and abnormal MRI. For this purpose we prospectively studied motor and mental outcome at two years in a cohort of full-term born neonates with neonatal HIE.[13-15] First of all, we established the predictive value of Sarnat staging and neonatal MRI findings for the outcome at two years. Secondly, we investigated the additional predictive value of three different motor tests at one year (the Alberta Infant Motor Scale [AIMS][16], the Bayley Scales of Infant Development 2nd version [BSID-II][17] and Neurological Optimality Score [NOS][18]) for poor motor or mental outcome at two years.

Methods

Participants

This is an ongoing study[13-15] of full-term neonates who were admitted to the neonatal intensive care unit of the VU University Medical Center between August 2000 and November 2002. All had symptoms of HIE within 24 hours (defined as a clinical status of HIE: lethargy, hypotonia, hyperreflexia, convulsions and segmental myclonics). Moreover, they met one of the following criteria: signs of intra-uterine asphyxia, such as late decelerations or meconium-stained amniotic fluid; umbilical cord artery pH <7.10; respiratory insufficiency at birth, in need of mechanical ventilation; or an Activity, Pulse, Grimace, Appearance and Respiration (APGAR) score of less than 5 at five minutes. Excluded were children with dysmorphic syndromes, malformations, and evidence of intra-uterine or perinatal infections, intracranial hemorrhage or requiring surgical intervention in the neonatal period. The research protocol was approved by the hospital Medical Ethics Committee, and all parents gave informed consent.

Neonatal assessment

During the first week of life, the degree of neonatal encephalopathy was classified according to Sarnat[2] as mild (grade I), moderate (grade II) or severe (grade III). If there was a change in the Sarnat grade, the most severe grade was included in the analysis. All infants had a brain MRI as soon as possible in the neonatal period, to determine brain damage. The neonatal brain MRI consisted of a transverse T1-weighted and multi-echo T2-weighted MRI, a Fluid-attenuated inversion recovery MRI (FLAIR), and diffusion weighted imaging. All images were scored for abnormalities according to the Barkovich[19] basal ganglia/watershed system, by an experienced radiologist (FB), who was blinded for all clinical parameters and outcomes of the children. For the present study, MRI scores were defined as 'normal' in the absence of abnormalities or 'abnormal' if the MRI showed any abnormality.

Assessment at one year

At one year, motor outcome was assessed by means of the AIMS and the motor scale of the BSID-II. Poor motor outcome was defined as significantly delayed motor outcome, i.e. if the *z* score of the AIMS was below −2, or if the Psychomotor Developmental Index (PDI) of the BSID-II was below 70. The neurological assessments were performed by a paediatric neurologist (RJV) according to the Neurological Optimality Score (NOS). Poor neurological outcome was defined as a NOS lower than 26.

Motor and mental ability at two years

At two years, the children were (re-)assessed in the out-patient clinic of the VU University Medical Center according to both the motor and the mental scale of the BSID-II by an experienced paediatric physical therapist (PEMS). She was not involved in the neonatal or postnatal care of the children under investigation, and was blinded for their clinical status, medical history and neonatal MRI scores.

The raw BSID-II scores were converted to the PDI for the motor scale, and to the Mental Developmental Index (MDI) for the mental scale. These indexes have a mean of 100 and a standard deviation of 15. The normative data for the general population[20] in the Netherlands were used in this study. The reliability and validity of the BSID-II have been established in the

United States.[17] In all of the analyses, all children with normal (PDI or MDI ≥ 85) and mildly delayed performance (PDI or MDI between 70 and 84) were assigned to the good outcome group, and children with significantly delayed performance (PDI or MDI 69 or below) were assigned to the poor outcome group.

A paediatric neurologist (RJV) performed an age-adequate neurological examination to identify children with cerebral palsy (CP), which were then classified according to the Gross Motor Function Classification System (GMFCS).[21]

Statistical analysis

The predictive values of neonatal Sarnat grade I and II, and normal or abnormal neonatal MRI scores for poor motor and mental outcome, measured with the BSID-II at two years, were calculated by using contingency tables. The additional predictive values of the AIMS, BSID-II and NOS scores at one year were investigated for their ability to predict poor motor or mental outcome at two years. The resulting probability scores and their 95% confidence intervals (95% CI) were calculated with Confidence Interval Analysis Software (version 2.0.4).

Results

Clinical neonatal data

Forty-six neonates met the inclusion criteria, of whom 11 (24%) died within one week after birth. The one-year assessment of two children was missing, and the parents of one child withdrew consent. Therefore, data on 32 children (20 boys, 12 girls) were included in the analyses. The assessment at two years was usually performed within one month after the child's second birthday (mean age at assessment: 24 months and 3 weeks, standard deviation (SD) 6 weeks, range: 23–30 months). Seven children had mild HIE (Sarnat grade I) and 25 children had moderate HIE (Sarnat grade II). Neonatal brain MRI was normal in 11 children and abnormal in 21 children. The clinical neonatal data are presented in more detail in Table 1.

Motor outcome at one year

According to the AIMS at one year, 14 (44%) children had a poor (significantly delayed) motor outcome and 18 (56%) had a good motor outcome (15 normal; 3 mildly delayed). According to the BSID-II motor scale, 9 (28%) children had a poor (significantly delayed) motor outcome and 23 (72%) had a good motor outcome (20 normal; 3 mildly delayed) at one year. According to the NOS, 9 (28%) children had a poor outcome and 23 (72%) had a good outcome (Table 2).

Motor and mental outcome at two years

Twelve children (38%) had a poor motor outcome (according to the BSID-II motor scale) at two years, and 12 (38%) had a poor mental outcome (according to the BSID-II mental scale). Ten children (31%) had both poor motor and mental outcomes; nine of these children were diagnosed with CP, with the following GMFCS classifications: five spastic bilateral type (quadriplegia; GMFCS level V), three dyskinetic type (GMFCS level II) and one spastic unilateral type (right hemiplegia; GMFCS level I) (see for more details Table 2). Data on the two children who missed the assessment at one year were not included in the analyses. Both of these children had Sarnat stage I, normal MRI, a good motor outcome and a poor mental outcome.

Table 1 Summarized clinical neonatal data (*n*=32)

	Number or mean (SD)
Boy:girl	20:12
APGAR at 5 minutes <5	15
Meconium-stained amniotic fluid	20
Decelerations	20
Umbilical cord artery pH of <7.10	15 (12 missing)
Epileptic seizures	17
Sarnat	
Mild (grade I)	7
Moderate (grade II)	25
Severe (grade III)*	0
MRI	
Normal	11
Basal ganglia	2
Cortex	5
Basal ganglia and cortex	12
Basal ganglia and entire cortex	2
Gestational age (weeks)	40.2 (1.4)
Birth weight (g)	3217 (435)

n, number; SD, standard deviation; MRI, magnetic resonance imaging; g, gram.
*all infants with Sarnat III of the original cohort of 46 infants died in the neonatal phase.

Table 2 Motor and mental outcome at two years, according to neonatal Sarnat staging and MRI, and AIMS, BSID-II and NOS scores at one year (*n*=32)

	Good motor outcome (*n*=20)	Poor motor outcome (*n*=12)	Good mental outcome (*n*=20)	Poor mental outcome (*n*=12)	Total (*n*=32)
Sarnat					
Stage I	7	0	6	1	7
Stage II	13	12	14	11	25
Neonatal MRI					
Normal	11	0	10	1	11
Abnormal	9	12	10	11	21
AIMS at one year					
Normal and mildly delayed (*z* score ≥−2)	18	0	16	2	18
Significantly delayed (*z* score <−2)	2	12	4	10	14
BSID-II at one year					
Normal and mildly delayed (PDI ≥70)	20	3	20	3	23
Significantly delayed (PDI ≤69)	0	9	0	9	9
NOS at one year					
Good (≥26)	20	3	20	3	23
Poor (<26)	0	9	0	9	9

AIMS, Alberta Infant Motor Scale; BSID-II, Bayley Scales of Infant Development 2nd version; MRI, magnetic resonance imaging; *n*, number; NOS, Neurological Optimality Score; PDI, Psychomotor Developmental Index.

Prediction of motor outcome at two years

In the entire study population the (pre-test) probability of a poor motor outcome was 38%. In children with Sarnat grade I (*n*=7) the probability of a poor motor outcome decreased to 0%, but in children with Sarnat grade II (*n*=25) the probability of a poor motor outcome increased to 48%. In children with normal MRI the probability of a poor motor outcome decreased to 0%, but in children with abnormal MRI the probability of a poor motor outcome increased to 57%.

In children with Sarnat grade II and abnormal MRI, the probability of a poor motor outcome at two years increased from 48% to 71%. This probability increased to 92% if the AIMS indicated a poor outcome at one year, and increased to 100% if the BSID-II or the NOS indicated a poor outcome at one year. The post-test probability of a negative test (= good motor outcome at one year according to the BSID-II or the NOS) was 37%, indicating that 37% of the children with a good motor outcome at one year had a poor motor outcome at two years (see Table 3).

Prediction of mental outcome at two years

In the entire study population the (pre-test) probability of a poor mental outcome was 38%. In children with Sarnat grade I (*n*=7) the probability of a poor mental outcome decreased to 14%, but in children with Sarnat grade II (*n*=25) the probability of a poor mental outcome increased to 44% (Table 4). In children with normal MRI the probability of a poor mental outcome decreased to 9%, but in children with abnormal MRI the probability of a poor mental outcome increased to 52%.

Table 3 Predictive value of neonatal Sarnat and MRI, and motor testing at one year for poor motor outcome at two years

Population	*n*	Pre-test probability %	Test*	Sensitivity (95% CI)	Specificity (95% CI)	Post-test probability, % (95% CI)	
			Neonatal			For positive test*	For negative test
All	32	38% (12/32)	Sarnat	100 (82–100)	35 (24–35)	48 (40–48)	0 (0–30)
All	32	38% (12/32)	MRI	100 (81–100)	55 (44–55)	57 (46–57)	0 (0–20)
Sarnat II	25	48% (12/25)	MRI	100 (83–100)	62 (46–62)	71 (58–71)	0 (0–26)
			+ 1 year				
Sarnat II + abn MRI	17	71% (12/17)	AIMS	100 (87–100)	80 (48–80)	92 (80–92)	0 (0–40)
Sarnat II + abn MRI	17	71% (12/17)	BSID-II	75 (60–75)	100 (65–100)	100 (80–100)	37 (37–60)
Sarnat II + abn MRI	17	71% (12/17)	NOS	75 (60–75)	100 (65–100)	100 (80–100)	37 (37–60)

Abn, abnormal; AIMS: Alberta Infant Motor Scale; BSID-II, Bayley Scales of Infant Development 2nd version; CI, confidence interval; MRI, magnetic resonance imaging; NOS, Neurological Optimality Score.

*Positive test Sarnat = Sarnat II; Positive test MRI = abnormal MRI; Positive test AIMS = *z* score < –2; Positive test BSID-II = PDI <70; Positive test NOS = score <26.

In children with Sarnat grade I and normal MRI the probability of a poor mental outcome decreased to 0%, but in children with Sarnat I and abnormal MRI the probability of a poor mental outcome increased to 25%. In children with Sarnat grade II and normal MRI the probability of a poor mental outcome decreased to 12%, but in children with Sarnat grade II and abnormal MRI the probability of a poor mental outcome increased to 59%.

In the few children with Sarnat grade I and abnormal MRI (*n*=4) the AIMS, BSID-II and NOS scores at one year were all normal, thus the probability did not change. In children with Sarnat grade II and abnormal MRI (*n*=17) the probability of a poor mental outcome increased from 59% to 77% if the AIMS indicated a poor outcome at one year. The probability of a poor mental outcome increased to 100% if the BSID-II or the NOS indicated a poor outcome at one year. However, the post-test probability of a negative test result (= good motor outcome at one year according to the BSID-II or the NOS) was 12%, indicating that 12% of the children with a good motor outcome at one year had a poor mental outcome at two years.

Discussion

The aim of this study was to investigate whether motor testing at one year can improve the accuracy of the prediction of motor and mental outcome at two years after HIE, especially in children with Sarnat II and abnormal MRI. With Sarnat and MRI findings alone we were able to predict motor outcome slightly better than mental outcome. Motor testing at one year had

Table 4 Predictive value of neonatal Sarnat and MRI, and motor testing at one year for poor mental outcome at two years

Population	*n*	Pre-test probability %	Test*	Sensitivity (95% CI)	Specificity (95% CI)	Post-test probability, % (95% CI)	
			Neonatal			For positive test*	For negative test
All	32	38% (12/32)	Sarnat	92 (73–99)	30 (19–34)	44 (35–47)	14 (3–47)
All	32	38% (12/32)	MRI	92 (71–99)	50 (38–54)	52 (41–56)	9 (2–42)
Sarnat I	7	14% (1/7)	MRI	100 (23–100)	50 (37–50)	25 (6–25)	0 (0–26)
Sarnat II	25	44% (11/25)	MRI	91 (70–98)	50 (34–56)	59 (46–64)	12 (2–41)
			+1 year				
Sarnat II + abn MRI	17	59% (10/17)	AIMS	100 (83–100)	57 (33–57)	77 (64–77)	0 (0–42)
Sarnat II + abn MRI	17	59% (10/17)	BSID-II	90 (73–90)	100 (75–100)	100 (81–100)	12 (12–34)
Sarnat II + abn MRI	17	59% (10/17)	NOS	90 (73–90)	100 (75–100)	100 (81–100)	12 (12–34)

Results for Sarnat I and abnormal MRI are not shown because all motor test outcomes were good, and thus did not have any additional predictive value.

Abn, abnormal; AIMS, Alberta Infant Motor Scale; BSID-II, Bayley Scales of Infant Development 2nd version; CI, confidence interval; MRI, magnetic resonance imaging; NOS, Neurological Optimality Score.

*Positive test Sarnat = Sarnat II; Positive test MRI = abnormal MRI; Positive test AIMS = *z* score <–2; Positive test BSID-II = PDI <70; Positive test NOS = score <26.

additional predictive value for motor as well as mental outcome at two years in children with Sarnat stage II and abnormal MRI. All three motor tests at one year performed almost equally well in predicting poor motor and mental outcome, although the AIMS had higher sensitivity but lower specificity than the BSID-II and the NOS.

Prediction of motor outcome

In our study, 38% of the children had a poor motor outcome at two years. All children with Sarnat stage I (*n*=7) and those children with Sarnat stage II and normal MRI (*n*=8) had a good motor outcome at two years. Therefore motor testing at one year did not have any additional predictive value for these children. This finding is in line with reports in the literature, in which the motor outcome of children with Sarnat I and children with normal MRI was usually found to be good.[5,22] Motor testing at one year improved the prediction of outcome in children with Sarnat stage II and abnormal MRI. A poor motor outcome on the AIMS, the BSID-II or the NOS at one year increased the probability of a poor motor outcome at two years, and a good motor outcome at one year increased the probability of a good motor outcome at two years. This finding indicates that motor testing at one year is useful for the prediction of motor outcome at a later age, for example for parental counselling and referral to medical services. The choice of test dependents on preference: high sensitivity (AIMS) or high specificity (BSID-II or NOS). For parental counselling this implies that the BSID-II or the NOS results would have incorrectly reassured some parents of a normal outcome at one year (one third of the children with good results on the BSID-II or the NOS had a poor motor outcome at two years). On the other hand, the AIMS results would have caused some parents unnecessary worries at one year, because 8% of the children with poor results on the AIMS at one year had a good motor outcome at two years. Although the AIMS is more stringent at one year than the BSID-II and the NOS, the significance of the results are tempered because the 95% CI of the post-test probability of a poor motor outcome on the three instruments are overlapping. A definite diagnosis of CP can not be made until a child is five years of age, and therefore a longer follow-up period might make it possible to detect developmental abnormalities that might not be detected at a younger age. Barnett et al. (2002)[23] studied 34 children who survived HIE, and were classified as normal at two years; 25% of these children had minor neurological dysfunctions at 5½–6½ years of age, although they were not diagnosed with CP. The authors concluded that continued surveillance is recommended for children with an apparently normal outcome two years after HIE, particularly when abnormalities are detected with brain MRI.

Prediction of mental outcome

In our study, 38% of the children had a poor mental outcome at two years. Sarnat grading or MRI findings alone, or combinations of these two changed the pre-test probability of a poor mental outcome less than that of a poor motor outcome. Motor testing at one year had no additional predictive value for mental outcome at two years in children with Sarnat grade I who had abnormal MRI, because in all cases the results of the motor testing were good. However, motor testing improved the prediction of a poor mental outcome in children with Sarnat grade II and abnormal MRI. In these children the probability of a poor mental outcome increased if the results of the motor testing at one year were poor, and decreased if these results were good. Thus motor testing at one year is useful for the prediction of mental outcome at two years. For mental outcome, the BSID-II and the NOS have better specificity than the AIMS. All children with a poor score on the BSID-II or the NOS at one year and 77% of the children with a poor

score on the AIMS at one year had a poor mental outcome at two years. On the other hand, 12% of the children with a good score on the BSID-II or the NOS at one year, and none of the children with a good score on the AIMS at one year, had a poor mental outcome at two years. An explanation for the finding that motor testing improves the prediction of mental outcome could be that achieving good results on a motor test at this young age is also dependent on the mental ability of the child. Lindström et al.[24] (2008) found that 81% of the children with moderate neonatal encephalopathy (although not only HIE) had cognitive dysfunctions at the age of 15–19 years. More long-term follow-up studies are needed to investigate whether the results of mental testing at a young age can predict the outcome at a later age.

Limitations of the study

Our study cohort was relatively small, although well documented and prospective: children with Sarnat stage I and II were included, and all children were assessed with validated measurement instruments at regular follow-up points. Although we previously reported more detailed information on MRI and outcome in neonatal HIE, we think that our simplification (i.e. normal or abnormal MRI) in the analysis adds to the clarity of this paper.

The AIMS and the BSID-II were assessed by a blinded paediatric physical therapist, and although the NOS was scored by the paediatric neurologist who was not blinded for the medical history of the children, the NOS and the BSID-II had the same predictive value.

Although the BSID-II motor scale and the NOS at one year predicted mental outcome at two years quite well, it would probably have been better if we had also assessed the BSID-II mental scale at one year.

Conclusion

All children with Sarnat II and abnormal neonatal MRI should be monitored for a longer, systematic follow-up period, and undergo validated motor and mental testing, at least until school-age, and preferably into adolescence. Based on our results, we recommend motor testing of infants with neonatal HIE at one year to improve prediction of the outcome at two years, and subsequently facilitate adequate referral to the relevant services.

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Chapter 5

Selective Dorsal Rhizotomy in cerebral palsy to improve functional abilities: Evaluation of criteria for selection

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Abstract

Objectives: The aim of this study is to evaluate the effect of selective dorsal rhizotomy (SDR) on functional abilities in a well-defined group of ambulatory children with spastic diplegia.

Methods: Nine children were selected for SDR (mean age 65 months, range 43–82 months). Gross motor function was measured with the Gross Motor Function Measure (GMFM-88). Self-care was assessed with the Pediatric Evaluation of Disability Inventory (PEDI) and gait pattern was measured with the Edinburgh Visual Gait Score (EGS). There were nine single-case research designs with a 12-month follow-up after surgery.

Results: After 12 months the mean improvement in the total GMFM-88 scores was 8.8%. On an individual level, all patients improved significantly in comparison with baseline. Functional skills and care-giver assistance measured with the PEDI showed significant improvement. Improvement in gait was also found; in particular, better initial contact and heel-lift resulted in a decreased EGS.

Conclusion: In this well-defined group of ambulatory children SDR had a small but significant positive effect on gross motor function, self-care and gait pattern.

Introduction

Cerebral palsy (CP) is the most common motor disorder that can occur during childhood. The incidence of CP is estimated at 1.5–2.5 per 1000 in the general population.[1] CP is the collective name given to a group of disorders of the development of posture and motor control, occurring as a result of a non-progressive lesion of the developing central nervous system. This definition encompasses a wide variety of pathological and clinical entities, due to differences in aetiology, manifestation, severity, prognosis and co-morbidities.

Spastic paresis is the most common motor disorder in CP, with spasticity as the most prominent symptom. Spasticity is generally defined as a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome.

It is a general assumption that spasticity interferes with a child's motor abilities, including gait. Therefore, several treatment strategies aim to ameliorate gait performance by reducing the spasticity itself or the consequences of spasticity. These strategies include physiotherapy, orthoses, antispastic medications, orthopaedic surgery and neurosurgery such as selective dorsal rhizotomy (SDR).[2] The goal of SDR is to reduce spasticity, which occurs predominantly in the lower limbs, and hence to improve motor function. Non-controlled studies reported that SDR results in an acute and often dramatic decrement in spasticity in the lower limbs of children with CP. However, it should be emphasised that the improvement in abilities after SDR is more important than the changes in spasticity. Three randomised clinical trials that have been conducted reported conflicting results on the outcome of the Gross Motor Function Measure (GMFM-88).[3-5] Meta-analysis of the pooled Ashworth data revealed a dramatic decrement in spasticity, whereas GMFM-88 data showed modest improvement after SDR and physical therapy (PT) compared with PT only.[2] However, it should be noted that these three randomised trials included patients with different levels of ability, i.e. ambulant and non-ambulant children. In addition, the heterogeneity between children with CP may have masked effects in randomised clinical trials executed. Finally, spasticity itself may contribute to standing and walking. Therefore, it can be postulated that SDR could cause deterioration of standing and walking

ability by lack of residual voluntary muscle force. At present, it is therefore unclear which individual CP patients will benefit in terms of functional abilities from treatment with SDR. To address the above-mentioned problems several suggestions have been made, such as a better selection of appropriate candidates and goals for SDR, and more responsive measurements to detect functional improvement.[6] The aim of the present study was to investigate the effects of SDR on functional abilities (gross motor function, self-care and gait pattern) in a well-defined group of ambulatory children with spastic diplegia.

Methods

Participants

The study population consisted of nine children with spastic diplegia. All candidates were evaluated by a physician, a paediatric neurologist, a neurosurgeon and a physiotherapist to assess whether they were eligible for the SDR operation. Eligibility criteria for SDR were:

1. Spastic diplegic CP with a periventricular leucomalacia on magnetic resonance imaging
2. Age 3–7 years
3. Spasticity (defined as velocity-dependent resistance to passive stretch) in at least six groups of muscles in both legs
4. No contractures limiting function at hip, knee or ankle (<20° flexion contracture, popliteal angle less than 80°)
5. No structural orthopaedic deformities
6. At least able to crawl, sit for a short time independently, kneel tall (support for balance allowed) and squat seven times
7. Gross Motor Function Classification System (GMFCS) level II or III (i.e. walking ability with or without walking aid) in crouch gait
8. Good support from parents and rehabilitation setting

Design of the study

The study consisted of nine single-case research designs. Single-case research designs provide a quasi-experimental approach to evaluating the effectiveness of treatment in a small group of subjects, who serve as their own controls.[7] The baseline phase consists of repeated measurements of the dependent variable (target behaviour or outcome) during a period of time prior to treatment. Subsequently, the intervention phase commences with the introduction of the treatment. The target behaviour continues to be measured repeatedly over time. Data are plotted on a graph and analysed for change in level, trend and variability between the baseline and intervention measurements. In the present study the target behaviour was gross motor function, measured by means of the Gross Motor Function Measure (GMFM-88). For a period of 4 months before SDR, all children were assessed monthly, whereas after the operation they were re-assessed with the GMFM-88 bi-monthly during a follow-up period of 1 year. All other measurements (Pediatric Evaluation of Disability Inventory [PEDI], Edinburgh Visual Gait Score [EGS], Ashworth Score and Repetitive Movement test [RM]) were assessed at baseline (1 day before surgery) and 6 and 12 months after surgery. During follow-up, the investigator (PEMS) had no access to the child's previous assessment data. The study was conducted at

the VU University Medical Center in Amsterdam and approved by the local Medical Ethical Committee, according to the Helsinki convention. Informed consent was obtained from the parents.

Functional outcome measures

Because functional ability has many aspects, such as gross motor function, self-care in daily life and gait, it was measured by means of different instruments.

Assessment of gross motor function

The primary outcome measure for this study was the GMFM-88.[8] The GMFM-88 is a criterion-referenced observational measure that was developed and validated to assess children with CP. The five gross motor dimensions of the GMFM are: lying and rolling (A, 17 items), sitting (B, 20 items), crawling and kneeling (C, 14 items), standing (D, 13 items) and walking, running, jumping (E, 24 items). The scores are expressed as a percentage of the maximum scores, and are computed for each of the five dimensions as well as for the total score. The validity, reliability and responsiveness of the GMFM have been demonstrated in a population of patients similar to the participants in the present study.[8]

Assessment of self-care

For the assessment of self-care, use was made of the functional skills (FS) and care-giver assistance (CA) scales for the self-care domain of the PEDI.[9] The PEDI is a comprehensive clinical assessment instrument that samples key functional capabilities and performance in children from the age of 6 months to 7.5 years. The PEDI is a judgment-based tool, administered in the form of a structured interview with the child's parents. The PEDI measures both capability and performance with regard to functional activities in three content domains: self-care (81 items), mobility (66 items) and social function (50 items). The FS scale focuses on the patient's ability to perform various tasks; each item is scored 0 for incapability or 1 for capability to perform the task in most situations without assistance. The CA scale, concerning 20 complex functional activities, is used to assess the amount of assistance a child requires to complete a task. Each activity is scored on a six-point ordinal scale, ranging from 0 = complete dependence to 5 = complete independence. Raw scores for individual items and content areas were transformed into scaled scores (SS) using the PEDI conversion tables.[9] The reliability and validity of the PEDI have been demonstrated[9,10] and its sensitivity to change in functioning after SDR combined with PT has also been studied.[6]

Assessment of gait pattern

Gait pattern was measured by the Edinburgh Visual Gait Scale (EGS).[11] Gait analysis was performed using a SYBAR system, a digital video in sagittal and frontal plane.[12] A video recording was made of the children during each session, while walking barefoot on a 10-meter free walkway across the gait laboratory at a comfortable, self-selected speed. The EGS was assessed from the digitalised video recording on a 5-point scale, scoring the movements of the trunk, pelvis, hip, knee and ankle. The total score for normal walking is 0 and the highest score for deviation is 34; the higher the total score, the greater deviation in the gait pattern. Good intra-observer and inter-observer reliability has been reported.[11]

Assessment of spasticity

The Ashworth Score was used for the clinical assessment of spasticity and all children were assessed by the same independent investigator. For the instrumental measurement of spasticity the RM test in the ankle was performed.[13] The RM test consists of passive, alternating flexion and extension movements in the ankle, imposed by an investigator, keeping pace with a metronome at 100 beats per minute for a period of 30 seconds. This frequency was chosen because it is the most comfortable speed while still fast enough to elicit spasticity, as was assessed in a previous study.[13] Range of motion (ROM) in the ankle joint was recorded on a potentiometer-based goniometer. Muscle activity was recorded by surface electromyography (EMG) of a flexor muscle (the tibialis anterior muscle) and an extensor muscle (the medial head of the gastrocnemius muscle). The RM test has been described more extensively in a previous publication.[13] It can be expected that a reduction in spasticity will cause a decrease in the Ashworth Score and in the RM test a decrease of the maximum muscle activity during stretching, and an increase in the ROM.

Treatment procedure

Surgical technique

The operation was performed according to the method described by Steinbok et al.[4] by the same neurosurgeon for all patients. A laminotomy of L1–L5 was performed and the dura was opened to expose dorsal roots L1–S2. Each dorsal root was separated in three to four rootlets. Subsequently, each rootlet was stimulated separately in order to reveal abnormal, exaggerated responses of the muscles. The responses caused by electro-stimulation were recorded by EMG. Low threshold of muscle response and eradiation of the muscle responses was used as criterion to select rootlets for the rhizotomy. If stimulation of the penis or clitoris evoked an electrical response in a selected rootlet (S1, L5), this rootlet was preserved to prevent bladder and sexual disturbances.

Rehabilitation period

Post-operative treatment was standardised: 4 days of bed rest, and mobilisation in a wheelchair from the 5th day onwards, three times a day for 1 hour. On day 6, standing and (if possible) walking was exercised, with a rigid ankle–foot orthosis in 0° of dorsiflexion (floor reaction orthosis [FRO]) to stimulate knee extension during walking. All children were discharged home on the 7th day after the operation.

Physiotherapy (PT) started immediately after surgery. During the first few days it consisted of passive ROM exercises of the lower limb joints and strengthening of the hip abductors and extensors, knee extensors and ankle dorsiflexors. Much emphasis was placed on strength training and practising normal patterns of movement, standing and walking. The children received PT 5 days a week for 1 hour for the first 3 months, and 4 days a week for 1 hour in the period 3–6 months post-operatively. In the period 6–12 months post-operatively they received half an hour of PT at least three times a week. The children were encouraged to walk as much as possible every day. From 6 weeks onwards most of them started with hydrotherapy treatment and horseback riding. It should be noted that this is a more intensive program than regular PT, which consisted mostly of 1.5–2 hour of therapy per week.

Statistical analysis

The non-parametric Wilcoxon signed rank test was used to analyse the differences between baseline and the 12-month follow-up in the GMFM-88, PEDI, EGS, Ashworth Score and RM. On an individual level, the change in GMFM-88 baseline and follow-up scores was tested with C-statistics.[14] In addition to visual inspection of the individual time series, the C-statistic was used to evaluate the dataset of GMFM-88 scores for each patient separately. This C-statistic controls for serial dependency of successive measurements over time. The C-statistic is a test that calculates the trend of the baseline data, and then compares this with the trend of the baseline and intervention data combined. If the difference between the two calculations is significant, the scores during the intervention phase are considered to differ from those observed at baseline.[7] SPSS for Windows (11.5) was used for the statistical analysis. The level of significance was set at 0.05.

Results

Participants

Nine children (five girls, four boys) were included. The mean age at the time of operation was 5 years and 5 months (range 43–82 months, median 67 months). Eight children were classified as level III of the GMFCS and one as level II (Table 1).

Table 1 Characteristics of the nine children and effect of selective dorsal rhizotomy (SDR) on functional abilities and Edinburgh Visual Gait Score 1 year after SDR

Patient	Gender	Gestational age	Birthweight (grams)	Age (months)	GMFM-88 (%)		Self-care FS/sc		Self-care CA/sc		EGS	
					Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	Girl	40	2500	67	51.2	63.6	67.6	74.7	54.6	60.1	28	29
2	Boy	31	1650	80	52.8	60.0	42.0	51.0	57.9	62.2	33	22
3	Boy	33	2270	59	56.8	65.6	59.9	63.9	61.1	63.4	30	33
4	Girl	30	1345	43	58.4	65.2	na	na	na	na	26	22
5	Girl	28	1285	59	60.0	68.4	58.6	64.6	79.5	83.2	41	25
6	Girl	30	2000	67	62.4	72.0	58.5	62.5	66.9	72.7	33	29
7	Girl	40	3450	68	67.8	72.0	73.6	77.3	35.0	41.1	32	27
8	Boy	27	1285	82	70.8	87.0	79.0	85.1	56.8	60.1	32	25
9	Boy	26	1000	63	84.6	90.0	66.8	74.7	60.1	64.5	32	15
Mean (SD)		31.7	1865	65.3	62.8	71.5*	63.3	69.2*	59.0	63.4*	31.89 (4.17)	25.22* (5.22)

Patient numbers do not refer to the children's actual assigned study number. Age denotes age and time of operation. *Significant difference ($p<0.05$).

FS/sc, functional skills, scaled scores of the Pediatric Evaluation of Disability Inventory (PEDI); CA/sc, care-giver assistance, scaled scores of PEDI; EGS, Edinburgh Visual Gait Score; Pre, pre-operation; Post, post-operation; SD, standard deviation; na, not available.

Treatment

The mean percentages of the posterior roots cut were 56% for L2, 43% for L3, 44% for L4, 60% for L5 and 51% for S1 (mean 50% per child, range 31–68%). The percentage of rhizotomy per level and the improvement in the GMFM-88 were not significantly related and are presented in Table 2. All children were discharged on the 7th day after surgery.

Adverse effects

No major adverse effects were detected after the SDR operation. Although there were some temporary complaints about hypersensitivity in the legs, no permanent loss of sensibility in the legs was observed. No bladder dysfunction occurred, and no spinal deformities could be seen on the lumbar spine X-rays 12 months after SDR.

Functional outcome

Gross motor function

The mean increase in the GMFM-88 total scores was 8.8% (range 4.2–16.2%). The difference between the GMFM-88 total score at baseline and one year after SDR was statistically significant (z=−2.67, p=0.008; Table 1). The mean improvements in the dimensions of crawling, standing and walking/running/jumping were 11.9% for crawling, 12.8% for standing and 8.2% for walking/running/jumping.

Individual changes in gross motor function

One year after SDR one child had risen from GMFCS level III to level II. To correct for the effect of maturation C-statistics were used on the GMFM-88 scores to test whether the change in functional abilities during the period before SDR (4 months) differed from the change in the period after SDR. A statistically significant improvement (C-statistics; range of p values, 0.0143–0.0006) was found for all children in the total score (Figure 1) and the separate domains of crawling and walking/running/jumping.

Table 2 The percentage of rhizotomy per level and the improvement in the GMFM-88

Patient	L2 right	L2 left	L3 right	L3 left	L4 right	L4 left	L5 right	L5 left	S1 right	S1 left	Mean %	Diff GMFM
1	55	50	40	50	60	0	50	60	50	50	47	12.4
2	75	70	60	60	70	70	60	70	66	80	68	7.2
3	60	60	30	40	50	60	60	70	0	0	43	8.8
4	40	60	40	55	50	50	50	60	75	60	54	6.8
5	70	66	50	50	40	75	66	60	66	70	61	8.4
6	50	50	50	0	0	50	60	50	0	0	31	9.6
7	60	50	33	30	33	0	60	65	65	70	47	4.2
8	50	50	50	50	0	50	50	50	65	75	49	16.2
9	50	50	40	50	66	65	75	70	60	60	59	5.4
Mean	57	56	44	43	41	47	59	62	50	52	51	8.8

Diff GMFM, improvement in GMFM-88 score between baseline and one-year follow-up.

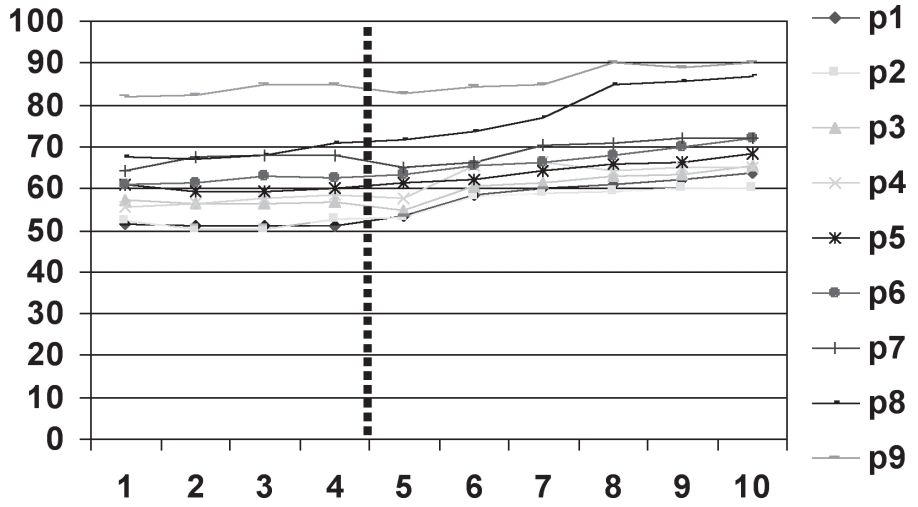

Figure 1 Changes in total GMFM-88 scores 1 year after SDR. 0–100, total GMFM-88 score in %; 1–10, number of measurement; p1–p9, patients; dotted line, moment of surgery.

Assessment of self-care

For the self-care domain of the PEDI, both the mean scaled scores of the FS scale (increasing from 63.3 to 69.2) and the CA scale (increasing from 59.0 to 63.4) improved significantly (both p=0.012) one year after SDR, compared with baseline (Table 1).

Assessment of gait pattern

The mean total EGS (for both legs) changed significantly (p=0.021) from 31.9 (SD 4.17) before the operation to 25.2 (SD 5.22) after the operation (Table 1). A clear improvement in initial contact and in the heel-lift position of the ankle was observed.

Assessment of spasticity

Spasticity, as measured by the Ashworth scale in five muscle groups (gluteus, adductors, hamstrings, quadriceps and the gastrocnemius muscle) in both legs, decreased significantly after SDR (p=0.008).

The RM test results also showed a significant improvement between the baseline and the 12-month follow-up ROM of the ankle joint (p=0.011) and a decrease in the maximum muscle activation during stretching of the gastrocnemius muscle (p=0.024).

Discussion

The present findings demonstrate significant improvements of SDR combined with exercise therapy on gross motor function by applying single-case research designs. We preferred this design to overcome existing heterogeneity between children with diplegia and with that, the lack of statistical power to reveal significant effects. As we stated in the introduction, this is in our opinion a good instrument to lead the clinician to choose the most appropriate treatment for each individual patient.

We observed a mean improvement of 8.8% in the total GMFM-88 scores after 12 months, which is almost similar to the results of other studies[3-5] and the meta-analysis of the three randomised clinical trials on SDR.[2] On an individual level, all children improved significantly, indicating that the development of abilities after surgery improved more compared with baseline measurements. Single-case research designs are particularly useful when recruiting large numbers is not feasible. However, maturation, testing and instrumentation are important confounders that should be controlled in these experiments. Besides visual analysis by observing a rise in the patient's performance after surgery, C-statistics were used to reveal that the change after surgery was significantly different statistically from the 4-month baseline phase. In the present study, self-care, gait pattern and spasticity were tested in a pre–post design, which does not control for spontaneous development. Nevertheless, the improvements observed in the functional skills and care-giver assistance scaled scores for the self-care domain of the PEDI were almost identical to the outcomes of two previous studies.[6,15] The EGS decreased significantly for the whole group, showing a change in gait pattern towards more "normal" gait, especially with regard to initial contact and heel-lift position of the ankle. This finding is also almost similar to the results of previous studies.[16-18] Importantly, none of the children's gait performance deteriorated after SDR.

Comparable to other studies, a strong decrease was found in spasticity, measured with the Ashworth scale, which is a widely used scale for clinical assessment.[2] Since the validity of the Ashworth scale to assess spasticity is a matter of debate,[19,20] the RM test was also performed as an objective measurement of spasticity. The RM data confirmed the Ashworth data, and showed a decrease in stretch activity of the gastrocnemius and tibialis anterior muscles during passive movement.

With regard to the present therapeutic options, SDR seems to be a suitable therapy for young children with spastic diplegia, walking in a crouch pattern, who show good improvement after multi-level botulinum toxin treatment, but relapse after recurrence of spasticity. Treatment options are repeated botulinum toxin injections, or an SDR procedure. Children who can stand with support but have insufficient muscle strength to meet the selection criteria for SDR can benefit from intrathecal baclofen therapy (ITB). Children without any standing ability and with severe spasticity, causing problems in daily care, may also be candidates for SDR or ITB.

Conclusion

Selective dorsal rhizotomy combined with exercise therapy has a significant positive effect on gross motor function, self-care and gait pattern, one year after operation in a well-defined group of ambulatory CP children with spastic diplegia. In these ambulatory children the proposed criteria for selection was found to be adequate to achieve improvement in gross motor function, comparable with the conclusion of the meta-analysis.

Further follow-up measurements are needed, because final assessment of the results with regard to functional abilities and necessary orthopaedic interventions can only be made in adulthood.

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Chapter 6

Short-term and long-term effects of Selective Dorsal Rhizotomy on gross motor function in ambulatory children with spastic diplegia

Submitted for publication

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Abstract

Aim: The aim of this prospective cohort study was to evaluate the short-term (1 year) and long-term (3-8 years) effects of Selective Dorsal Rhizotomy (SDR) on gross motor function in ambulatory children with spastic diplegia.

Methods: Thirty-three children who had undergone SDR (mean age 6 years and 7 months, standard deviation [SD] 2 years) were included. Gross motor function was assessed with the Gross Motor Function Measure-66 (GMFM-66) and spasticity was measured according to a modified Tardieu scale. Any additional treatment was recorded by the parents in a questionnaire.

Results: At the one year follow-up, mean GMFM-66 scores improved significantly by 4.3 (SD 4.1), with significantly more improvement in children with GMFCS levels I–II (7.2), compared to level III (2.9). In the long term (mean 6 years [SD 22 months]), mean GMFM-66 scores improved significantly by 6.5 (SD 5.9), without difference between children in GMFCS levels I–II and III. No relapse of spasticity was noted. Ten children (30%) needed orthopedic surgery and 13 children (39%) had botulinum toxin-A (BTX-A) treatment after SDR.

Interpretation: SDR resulted in short-term and long-term improvements in gross motor function, with no relapse of spasticity. However, additional surgery or BTX-A treatment was still needed.

Introduction

Cerebral palsy (CP) is the most common disorder causing disability in childhood. CP includes a group of disorders that affect the development of movement and posture, causing activity limitations which are attributed to non-progressive disturbances that occurred in the fetal or infant brain.[1] Spastic paresis is the most common motor disorder associated with CP, and spasticity is the most prominent symptom. Spasticity is defined as hypertonia in which one or both of the following signs are present: 1) resistance to externally imposed movement increases with increasing speed of stretch, and varies with the direction of joint movement, and/or 2) resistance to externally imposed movement rises rapidly above a threshold speed or joint angle.[2,3] Spasticity is considered to be a cause of discomfort, gait abnormalities and functional limitations in children with spastic CP.[4] Both local as well as general forms of treatment are used to reduce spasticity in children with spastic CP, such as oral medication, intrathecal baclofen therapy, intramuscular botulinum toxin-A (BTX-A) injections and neurosurgery, such as Selective Dorsal Rhizotomy (SDR).[4]

SDR is a neurosurgical procedure in which selected sensory nerves in the lumbar spine are transected to reduce the excitatory input entering the spinal cord via the lumbosacral posterior nerve roots.[5] The aim of SDR is to eliminate spasticity in the lower limbs, and thus improve the walking ability of children with spastic diplegia. In a meta-analysis of three randomised controlled trials (total number of patients = 90) in which SDR plus physical therapy was compared to physical therapy only, reduced spasticity and a small but significant mean difference of 2.66 was found in change scores on the Gross Motor Function Measure-66 (GMFM-66) between the two groups (SDR and control) at 9 to 12 months after SDR.[4] Several studies of the long-term effects of SDR have reported a significant reduction in spasticity,[6,7] improved gait parameters,[7,8] and improvements in functional movements,[6] mobility[7] and self-care.[7,9] Although the GMFM-88 is often used in studies on SDR, only limited long-term data are available on gross motor function measured with the GMFM-66[6] and the Gross Motor Function Classification

System (GMFCS).[7,10]

Side effects of SDR (such as spondylolistesis[11] or scoliosis[12]) are reported frequently. Although one of the positive outcomes of SDR could be a reduction in the need for orthopedic procedures,[13] reports on the rate of additional treatments such as BTX-A injections and orthopedic surgery after SDR differ.[6,9] Therefore, the possible long-term benefits of SDR on the rate of orthopedic procedures are still unclear.

Since 1998, 33 ambulatory children with spastic diplegia have been treated with SDR in the Netherlands. The short-term effects one year after SDR were investigated extensively in the first nine children,[14] showing reduced spasticity in the lower limbs and an improvement in gross motor function, self-care and gait pattern.

The main aim of the present study was to evaluate the short-term (1 year) and long-term (3–8 years) effects of SDR on gross motor function and spasticity in ambulatory children with spastic diplegia. Secondary aims were to investigate side effects, additional treatment and surgery, and parental satisfaction.

Methods

Participants

Between August 1998 and December 2005, 33 children underwent SDR treatment in the VU University Medical Center in the Netherlands. Inclusion criteria for SDR were: spastic diplegia; age 2.5 years or older; spasticity (defined as velocity-dependent resistance to passive stretch) in at least six groups of muscles in both legs; no contractures limiting function at hip, knee or ankle (<20° flexion contracture in knee, popliteal angle <80°, at least 0° dorsal flexion in the ankle possible); no structural bony deformities; at least able to crawl, to sit independently >10 seconds, to maintain tall knee position (support for balance allowed) and to squat seven times; GMFCS level I, II or III; good motivation and support after surgery from parents and the rehabilitation setting.

Procedure

All children were invited to participate in this follow-up study with extra measurements, although most of them had also been seen on a regular basis for follow-up. One paediatric physiatrist (JB) and two paediatric physiotherapists (PEMS/MS) assessed the children during their visit to the outpatient clinic between April 2006 and April 2007. The assessments included GMFCS, GMFM-66, physical examination for spasticity, X-rays of lumbar spine and hips, and parental questionnaires for side effects, additional treatment and surgery, and the opinion of the parents about improvement in their child's functioning after SDR. GMFCS and GMFM-66 measurements at baseline and one year after SDR were reviewed retrospectively from medical records and earlier research. The study was conducted at the VU University Medical Center in the Netherlands and the protocol was approved by the Local Medical Ethics Committee. Informed consent was obtained from all parents and from children over 12 years of age.

Outcome measures

GMFCS

The GMFCS provides a 5-level classification of the functional severity of CP, based on age-adjusted clinical descriptors.[15] For the analysis, two groups were formed: children in GMFCS levels I and II versus children in GMFCS level III.

Gross Motor Function Measure

Gross motor function was measured with the GMFM, a measure that was specifically designed to assess the functional abilities of children with CP.[16] The GMFM-66 score, calculated with the Gross Motor Ability Estimator, addresses the linearity of the individual item scores across the entire range of GMFM scores.[17]

Recently, tabulated reference percentiles have been published for GMFM-66 scores per GMFCS level for children up to 12 years of age.[16-19] These percentiles were used to compare the individual short-term and long-term GMFM-66 scores with baseline scores for each child, in order to differentiate between natural course and improvement due to SDR. The percentile which was closest to the GMFM-66 score of a child in his or her GMFCS level was chosen for the analysis. For children over 12 years of age, percentile ranking for the age of 12 years was taken for the analysis. The short-term and long-term effect of SDR per individual child was classified as 'improvement' or 'worsening' if the change in percentile ranking was 20 or more from baseline, and as 'no change' if the change in percentile ranking was less than 20.

Physical examination

Spasticity was assessed according to a modified Tardieu scale in m. rectus femoris, mm. hamstrings, short adductors, soleus and gastrocnemius muscles of both legs by the paediatric physiatrist. First, the muscle was stretched three times with very slow velocity (>3 seconds) to record the maximum range of motion (ROM) of each muscle. Spasticity was assessed by stretching the muscle at a high velocity (full ROM within 1 second). If there was a clear catch within the ROM, with or without blocking further movement, this was recorded as spasticity.

An X-ray of the spine was made, and scoliosis was defined as a Cobb's Angle of 20° or more. At baseline and at the long-term follow-up an X-ray of the pelvis was made. The Anterior Posterior (AP) pelvic radiographs were scored according to the Migration Index (MI),[20] a MI >50% was classified as subluxation of the hip.

Parental questionnaires

A parental questionnaire was used to obtain information about side effects and additional treatment such as BTX-A or orthopaedic surgery after SDR. In addition, all medical records were checked retrospectively for this information. Moreover, the parents rated their child's functioning compared to baseline on a 7-point scale (no change, or slightly, moderately or very much improved or worse).

Statistical analysis

The statistical analyses were performed in SPSS (15.0) for Windows. A paired t-test was used to analyze the difference between GMFM-66 at baseline and in the short term (1 year) as well as the long term (3–8 years) after SDR. The independent *t*-test was used to analyze the difference in short-term and long-term improvements in GMFM-66 between children in GMFCS levels I–II and level III. We considered $p<0.05$ to be statistically significant.

Results

Since 1998, 33 children had undergone SDR, two of whom had spastic familial paraparesis and 31 had CP. Between April 2006 and April 2007, 31 of these 33 children were re-assessed in the VU University Medical Center. One child could not be traced due to an unknown change of address; therefore we used the last available data from a regular follow-up visit three years after SDR in our analyses. The other child did not show up for several appointments due to instable social circumstances, but regular follow-up data were available one year after SDR. At the long-term follow-up only GMFCS data for this child were available from medical records.

In total, six children only had short-term follow-up data, and 27 children had SDR more than 3 years previously (mean 6.0 years [SD 22 months]) at the time of their visit. The patient characteristics at baseline are presented in Table 1.

GMFCS

At baseline, seven children were classified as GMFCS level I, seven children as level II and 19 children as level III. At the one-year follow-up, two children had improved one GMFCS level (one from level III to II, and one from level II to I), and one child had dropped one level (from level II to III), but had recovered at the long-term follow-up. However, 30 out of the 33 children (91%) remained in the same GMFCS level. At the long-term follow-up (*n*=27), one child had improved from level III at the short-term follow-up to level II at the long-term follow-up, and one child had dropped from level III at the short-term follow-up to level IV at long-term follow-up. All the other 25 children remained stable.

Table 1 Patient characteristics at baseline (*n*=33)

Patients	N or mean
Boys/girls	21/12
Age at operation	6 years 7 months (SD 2 years; range 2 years 9 months – 12 years 1 month)
GMFCS pre-operative	
I	7
II	7
III	19
GMFM-66 pre-operative (*n*=28)	58.6 (SD 11.4)

Diff GMFM, improvement in GMFM-88 score between baseline and one-year follow-up.

Table 2 Short-term and long-term effects of SDR on GMFM-66

GMFCS level patients	Pre-operative GMFM-66 score (SD)	Short-term follow-up (SD)	Mean improvement (SD)	*P* value (dependent *t*)	*P* value* (independent *t*)
Total group (*n*=24)	56.6 (10.5)	60.9 (12.4)	4.3 (4.1)	<0.001 (5.18)	
Level I–II (*n*=8)	69.0 (8.9)	76.2 (8.5)	7.2 (4.0)		0.012 (2.74)
Level III (*n*=16)	50.4 (3.0)	53.3 (3.9)	2.9 (3.4)		
		Long-term follow-up (SD)			
Total group (*n*=23)	57.5 (11.4)	64.0 (12.8)	6.5 (5.9)	<0.001 (5.28)	
Level I–II (*n*=7)	73.0 (7.3)	79.0 (8.5)	6.0 (4.4)		n.s.
Level III (*n*=16)	50.7 (3.0)	57.4 (7.8)	6.7 (6.6)		

GMFM-66, Gross Motor Function Measure-66; n.s., not significant; SD, standard deviation; SDR, Selective Dorsal Rhizotomy; *t*, *t* value.

*Difference in GMFM-66 scores between levels I–II and III was significant at short-term follow-up (p=0.012; t=2.74), but not at long-term follow-up.

Table 3 Short-term and long-term results after SDR based on change in percentile ranking of GMFM-66 scores

	Long-term result (*n*=33)				
	Improvement (*n*=11)	Stable (*n*=10)	Worsening (*n*=3)	Missing (*n*=3)	Not yet available (*n*=6)
Short-term result (*n*=33)					
Improvement (*n*=7)	4	0	0	0	3
Stable (*n*=17)	6	6	3	1	1
Worsening (*n*=1)	0	1	0	0	0
Missing (*n*=8)	1	3	0	2	2

GMFM-66, Gross Motor Function Measure-66; SDR, Selective Dorsal Rhizotomy.

Improvement = >20 percentile increase; Stable = change is <20 percentile increase or decrease; Worsening = >20 percentile decrease; Not yet available = no long-term follow-up yet.

GMFM-66

At baseline, GMFM-66 data were available for 28 children, of whom 24 also had data available at the short-term follow-up, and 23 at the long-term follow-up after SDR (for details see Table 2). At the short-term follow-up, the mean GMFM-66 scores improved significantly with 4.3 (range −2.53 to 12.31; t=5.18, p<0.001). The eight children in GMFCS levels I–II (mean improvement 7.2) improved significantly more than the 16 children in level III (mean improvement 2.9; t=2.74, p=0.012).

At the long-term follow-up, the mean GMFM-66 scores of 23 children improved significantly with 6.5 (range −0.35 to 23.66; t=5.28, p<0.001). No significant difference in improvement was found between the children with GMFCS levels I–II versus the children with GMFCS III.

GMFM-66 scores at individual level; percentile ranking

At the short-term follow-up after SDR, seven out of 24 children (29%) showed an improvement of more than 20 percentile on their GMFM-66 score, while 17 children did not change according to the cut-off point of 20 percentile (Table 3). At the long-term follow-up, 10 out of 23 children (43%) showed an improvement of more than 20 percentile, and three children (13%) showed a decrease of more than 20 percentile on their GMFM-66 score since baseline. Ten children changed less than 20 percentile in score.

Spasticity

At the short-term follow-up, seven children had residual spasticity: two children in the mm. hamstrings in one leg, and five children in the gastrocnemius muscle, three of them in both legs. In the latter children only limited rhizotomy of S1 could be performed, because the S1

Table 4 Side effects, surgery and additional treatment after SDR

Child	Age at SDR in years	GMFCS level	Spinal deformities (years after SDR)	Type of surgery (years after SDR)	BTX-A in years after SDR
1	9;11	III	Fusion of proc. spinosi L2–L5 (6)		–
2	5;8	III	Spondylolysis + listhesis L3–L4 (8)	Fulford both feet + re-arthrodesis left (5, 7)	5
3	8;9	III	Scoliosis (Cobb Angle 21°)(5)		
4	3;8	III		Fulford + FDO (2) for hipsubluxation (1)*	–
5	4;1	III		DVIO (5) for hipsubluxation (2) both hips	–
6	7;3	II		Fulford (3)+ hipsurgery for progressive dysplasia (6)	4
7	4;11	III		Fulford + TEO (5)	7
8	5;2	III		Fulford + TEO (3, 5)	1, 3
9	2;9	II		Fulford + GM (5)	2, 5
10	6;5	III		Fulford (3)	–
11	5;2	III		Fulford (4)	1, 3, 4
12	5;0	III		Fulford + GM (5)	1, 4
13	6;0	III			1
14	10;11	II			1, 2
15	8;1	III			3
16	5;7	III			5
17	6;11	III			7
18	5;9	II			4, 8

BTX-A, Botulinum toxin-A treatment; DVIO, Derotation Varisering Intertrochanter (femur) Osteotomy; FDO, Femur Derotation Osteotomy; Fulford, subtalar arthrodesis for flexible hind foot deformities; GM, Gastrocnemius Myotenotomy; proc., processi; SDR, Selective Dorsal Rhizotomy; TEO, Tibia Endorotation Osteotomy.
*Pre-operative radiographs showed a subluxation.

rootlets contained bladder function as tested per-operatively. Apart from the residual spasticity, at the long-term follow-up spasticity did not relapse.

Long-term side effects after SDR

Three children had long-term spinal side effects after SDR (Table 4). One child had fusion of processi spinosi L2–L5, one child had spondylolysis and listhesis L3–L4, and one child had scoliosis (Cobb angle 21°). No other side effects were found in the medical records.

Additional treatment after SDR

Thirteen children (39%) had BTX-A treatment of the gastrocnemius muscle or mm. hamstrings because of muscle shortening, five of whom needed two treatment sessions and one child needed three treatment sessions. Nine of these children had GMFCS level III and four had level II. BTX-A treatment took place between 1 and 8 years (mean 3.5 years) after SDR (Table 4).

Ten children (30%) needed orthopedic surgery between 2 to 7 years (mean 4 years and 4 months [SD 16 months]) after SDR to maintain walking ability (19 operations in total) (Table 4). Nine children had calcaneotalar desis (Fulford technique), sometimes combined with soft tissue surgery (medial hamstring lengthening and/or gastrocnemius myotenotomy). Three children (two of whom also had calcaneotalar desis) developed hip subluxation (MI >50%), at respectively one, two and seven years after SDR, and underwent surgery. Eight of these children had GMFCS level III and two had level II.

Parental opinion about their child's improvement

The parents of six children who only had short-term follow-up data rated the improvement in their child as moderate (n=3) and very much improved (n=3). Twenty two of the 27 parents (response rate 81%) of the children with long-term follow-up data gave their opinion about the improvement in their child's functioning. Twenty parents (91%) thought that their child's functioning had improved since baseline (slightly [n=5], moderately [n=11] and very much [n=4]), and two parents thought that their child's functioning was worse (slightly [n=1] and moderately [n=1]).

Discussion

In the present study we evaluated the short-term and long-term effects of SDR on gross motor function and spasticity. In addition, we investigated long-term side effects, additional treatment and surgery, and parental opinion about improvement in their child's functioning after SDR.

The children in our cohort improved significantly in gross motor function in the short term (one year) and long term after SDR. This is in line with the results of other studies.[7,21] This improvement in gross motor function resulted in only a few children in a change in GMFCS level. This stability in GMFCS level is in agreement with the findings of Chan et al. (2008)[7] who reported that only one out of 21 children changed GMFCS level one year after SDR. However, this is in contrast with the findings of Cole et al. (2007)[10] who reported that 79% of the children improved in GMFCS level after SDR, a difference for which we have no explanation.

It is important to find out whether SDR has a beneficial effect above the natural course of development in children with CP, as is indicated by the results of McLaughlin et al. (2002),[4] who reported a mean difference in change score of 2.66 between the SDR plus physiotherapy

group and the physiotherapy-only group. In our opinion, comparing the percentile rankings of an individual child is the best way so far to interpret the changes in gross motor function after SDR, when there are no available data from a control group receiving usual care. At individual level, 29% and 43% of the children improved more than 20 percentiles in GMFM-66 scores between baseline and the short-term and long-term follow-up, respectively. In a representative cohort of children with CP, the chance that a child in GMFCS level I or II had a change of more than 20 percentiles in one year was 20%.[18] We therefore consider the effect of SDR in our study to be an improvement above the expected natural course in some children, especially in the long term. Unfortunately however, there were some children who had a decrease of more than 20 percentiles in the long term.

Our finding, that children in GMFCS levels I–II improved significantly more than children in GMFCS level III during the first year of follow-up, is in contrast with the results of the meta-analysis[4] in which GMFCS classification was not related to outcome. However, it can be hypothesised that children in GMFCS levels I and II have better initial neuromuscular control, and can benefit from the release of spasticity faster than children in GMFCS level III. At the long-term follow-up, mean GMFM-66 scores changed significantly from baseline in the entire study group, with no difference in change in GMFM-66 between children in GMFCS levels I–II and III, indicating that children in level III can achieve the same improvement as children in levels I–II.

Like in other studies,[6,8] we found that spasticity had disappeared completely in the majority, although not in all children, and no relapse of spasticity occurred in the long term. However, abnormal movement patterns in the lower extremities did persist, indicating that spasticity is only one component of the spastic motor disorder. Abnormal muscle activation is obviously persistent after SDR, although spasticity has disappeared.

In our study, a low percentage (9%) of children developed spinal deformities after SDR, compared to other studies in which percentages of 12–20% for spondylolysis or grade–I spondylolisthesis[11,12] and 24–55% for scoliosis[12,22] were reported. An explanation for the low percentage we found could be that only ambulatory children were treated.

Our finding, that 39% of the children had BTX-A treatment after SDR, is in line with reports in the literature.[6,23] Treatment with BTX-A after SDR was only partly used to decrease residual spasticity. For most children, the reason for BTX-A treatment in combination with serial casting was to maintain ROM of the ankle joint.

The percentage of children who underwent orthopaedic surgery after SDR in our study (30%) was also within the range of percentages in previous studies,[6,11,24,25] and is low in comparison with the 65% reported by Steinbok.[13] The hindfoot stabilizing operation was the most frequently performed operation, although foot deformity also frequently develops in children with CP children who do not have SDR treatment. Of the children who had orthopedic surgery, 80% had GMFCS level III. This is in line with the results of an earlier study, in which it was found that children who walked independently after SDR underwent fewer orthopedic operations than children who walked with assistance.[24]

Conclusion

Comparing baseline data with short-term and long-term follow-up data, significant improvement in gross motor function after SDR has been demonstrated. At individual level, the children seemed to improve more in the long term than would be expected by natural course. However, the disappearance of spasticity did not prevent secondary orthopedic deformity. Ongoing follow-up and treatment is necessary to maintain mobility, especially in children using walking aids.

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Chapter 7

General discussion

Introduction

The main aims of this thesis are to describe motor outcome, mainly at the level of activity, in young children who were at risk for developmental problems or who had received an intervention, and to examine the predictive value of the measurement instruments that are most frequently used in childhood to forecast future motor outcome.

Therefore, three different cohorts of children were followed longitudinally. One cohort consisted of children, mostly born prematurely and small for their gestational age from mothers with early-onset hypertensive disorders of pregnancy, the second cohort consisted of children born full-term with hypoxic-ischemic encephalopathy (HIE), and the third cohort consisted of children with cerebral palsy (CP) who received an innovative neurosurgical treatment i.e. Selective Dorsal Rhizotomy (SDR).

The results of this thesis should be considered in the light of the paradigm shift in paediatric rehabilitation that took place in recent decennia. Since introduction of the model of the International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY)[1] as a theoretical framework in paediatric rehabilitation, a shift can be observed from optimizing a child's impairments towards optimizing the child's functional abilities, thus focussing on motor assessment (and treatment) at the level of activity.[2] Moreover, clinicians acknowledge more and more that the relationship between body functions and activity is non-linear, and not always direct. By adopting Evidence Based Practice as leading concept, although perhaps with some hesitation,[3] interest in and use of motor assessment instruments increased in clinical practice. More knowledge is becoming available about normal development, not only in typically developing children, but also in children with a neurological disorder.[4] Other shifts that can be observed are the focus on better understanding of the determinants for functional outcome,[5] and a shift from cross-sectional to longitudinal research.[5] The main results of this thesis will be discussed in line with some of these changing paradigms in paediatric rehabilitation research and care.

Measuring motor outcome

Motor development in childhood is very variable, especially in the first years of life. This finding was also observed in our study of GMs, in which we did not find a significant association between GMs on term and three months of age, but observed that abnormal GMs normalised, and vice versa, indicating variability in early motor development. In the same study cohort, the individual developmental trajectories of children with abnormalities on neonatal brain sonography appeared to vary substantially between term age and one year.

To describe motor outcome, measures at different levels of the ICF-CY can be used. It is known that the relationship between test results in different ICF-CY levels (i.e. the level of body structure and function versus the level of activity) is not straight forward. In our HIE study, we found that not all infants with significantly delayed motor outcome in terms of activities had poor neurological examination results in terms of body structure and function at the age of one year. All children with normal or mildly delayed motor outcome, and also two children with significantly delayed motor outcome had high scores for the neurological examination. In our SDR study, despite the elimination of spasticity in most of the children after SDR, not all children improved to the same extent in gross motor function in terms of activity. The above findings suggest that the relationships between body functions and activity are not straight-

forward, and measurements at different ICF-CY levels should be combined to describe motor outcome in children.

The relationship between measurement instruments which measure at the same ICF-CY level is also often not linear. In the PETRA study, we found that neurological examination and assessment of General Movements (GMs) were significantly related at term, whereas at the corrected age of three months, no significant association was found. Snider et al. (2008)[6] also found no evidence of the concurrent validity of GMs with traditional neurological assessment. They stated that these findings support Prechtl's suggestion that GMs reflect a unique neurological construct, different from traditional tests, and reinforce the complementary perspective which the GMs brings to neonatal assessment.

In our study on HIE, we used both the Alberta Infant Motor Scale (AIMS) and the Bayley Scales of Infant Development (BSID-II) motor scale to measure motor outcome at one year. The AIMS and the BSID-II motor scale both identified approximately three quarters of the children with normal or significantly delayed motor outcome. Spearman's rank-order correlation coefficient between *z* scores on the AIMS and the BSID-II motor scale (of children without CP) was 0.61 ($p<0.01$), suggesting that the two motor tests did not measure the same underlying construct. Depending on which test was used, different children were classified as having normal, suspect or abnormal outcome. The AIMS classified more children with a delayed outcome at one year than the BSID-II. In other words, if the clinician does not want to miss a child who is suspected of delayed motor outcome, the AIMS is the preferential method with which to assess motor outcome at one year, whereas beyond the age of independent walking only the BSID-II can be used.

Normal motor development in typically developing children

To obtain valid information about a child's development and to interpret results of motor assessments correctly, reliable and up-to-date reference data are needed. Because Dutch norms are not always available, the question arises if reference norms from US or Canadian study populations can be applied to children in the Netherlands without problems.[7,8] In our HIE study, the AIMS (with Canadian norms) classified more children as delayed than the BSID-II (with Dutch norms). Is this difference introduced by differences in contents of the tests, or by the norms which were used? Suppose that if, in general, children in the Netherlands have a slower rate of development than children in Canada, they will be wrongly classified as delayed according the Canadian reference norms. The question that arises is: are Dutch norms for the AIMS necessary and will they result in an improvement in the accuracy of classifying children?[7,8]

The BSID-II has US norms, and recently Dutch norms have also been formulated.[9] When applying both Dutch and US BSID-II norms for the same population, large, clinically relevant Dutch-US differences were found in motor scores, especially at the age of 6 and 12 months.[10] This gives rise to the question of whether or not there was a bias in the Dutch normative data, or whether the difference between US and Dutch norms reflects a generally slower rate of development in children in the Netherlands. There have been many reports of significant differences in the rate of early development in children in different bio-sociocultural groups.[11] If US norms would have been used in our HIE study, probably the relationship between results on the AIMS and the BSID-II at one year, and the relationship between BSID-II at one and

two years would have been higher.

At this moment, it is recommended that local norms are used when making clinical decisions in the local context, such as referral to special medical services, and that reference norms derived from a broader context are used in research to enable comparison with the results of other studies.[11] This choice should be taken into account when drawing conclusions about a child's development based on one single outcome measurement.

Moreover, the ability to assess motor outcome in children is continually evolving, with new information regarding specific assessment methods and new norms emerging all the time.[12] A new version (with new norms) of the Movement Assessment Battery for Children,[13] and the third edition of the BSID has recently been developed: the Bayley Scales of Infant and Toddler Development (BSITD-III).[14] New editions of these motor measurement instruments are currently being introduced in the Netherlands, and are recommended for standard use by all paediatric physical therapists.

Predictive value of motor assessments

One of the psychometric properties of motor assessments is their predictive value for a poor or abnormal outcome. In the following paragraphs this issue will be discussed for each instrument separately.

General Movements (GMs)

Definitely abnormal GMs at three months corrected age are reported to have a high predictive value for CP at later age.[15-18] In our study of 175 mostly pre-term born infants, small for their gestational age, with no severe brain sonography abnormalities, we found no relationship between definitely abnormal GMs at three months and a diagnosis of CP at one year. Nevertheless, there was a weak association between GMs at three months and motor outcome as measured with the BSID-II motor scale at one year. We found a relatively high percentage of children with mildly abnormal GMs at term or at three months; most of these children had a normal outcome at one year. Mildly abnormal GMs at three months have been found to be predictive for all sorts of minor neurological dysfunctions, even up to puberty.[19-21] Therefore it will be interesting to monitor these children at a later age, to find out whether they will develop minor neurological dysfunctions. We are at the opinion that conclusions about the future development of a newborn should not be based solely on GM observations alone, but should also depend on the results of an age-specific neurological examination. Moreover, the children should be assessed again at later age to take into account the dynamic process of neurological development.

AIMS and BSID-II

The potential role of the AIMS and the BSID-II motor scale in the prognosis of future motor outcome has not yet been established. When assessing children with HIE at the age of two years, we found that all children with good outcome by means of the AIMS at one year had good motor outcome at two years as measured by the BSID-II, but some of children with good outcome by means of the BSID-II motor scale at one year had poor motor outcome at two years. In the subgroup of children with Sarnat grade II and abnormal MRI, both the AIMS and the BSID-II motor scale at one year had a predictive value for poor motor outcome at two years. Also in this subgroup, the AIMS had higher sensitivity, and the BSID-II motor scale had

higher specificity. In terms of parental counselling, this means that according to the BSID-II motor scale, some parents would have been incorrectly reassured of a normal outcome at one year, whereas one third of the children with good results on the BSID-II had a poor motor outcome at two years. On the other hand, according to the AIMS, a few parents would have had unnecessary concerns at one year, since 8% of the children with poor results on the AIMS at one year had a good motor outcome at two years. We found that motor testing at age one improved the prediction of motor outcome at two years. Thus, children with HIE should be followed frequently. Moreover, children should be assessed again at a later age to determine the predictive value of both instruments for motor outcome, for example, at school age.

'Normal' motor development in children with CP

Children with CP have their own profile of motor development, as has recently been established with the 'motor growth curves' for children from 1 to 12 years, based on Gross Motor Function Measure 66 (GMFM-66) scores per GMFCS level.[22-24] Rosenbaum and colleagues, working at CanChild in Canada, made a big step forward in evidence-based prognosis of gross motor development in children with CP.[22,23,25] It is known that three quarters of the children with CP, once classified in a GMFCS level (after the age of 2 years), will not change their GMFCS level.[26] At every GMFCS level there is substantial variation in gross motor development. Percentile data of GMFM-66 per GMFCS level have recently been published.[27,28] Hanna et al. (2008)[27] found that the chance of changing more than 20 percentiles in one year is 20% for children in GMFCS levels I and II. These percentile data can be very helpful in interpreting the effects of interventions, when the research design is not a randomized clinical trial. Therefore, knowledge of GMFCS, GMFM-66 and the reference percentiles is essential for all clinicians who work with children with CP. This enables them to monitor the motor development of these children and see whether they develop as expected. These data provide accurate prognostic information, which can be used as a basis for the counselling of parents and for the planning of clinical management.

Short-term and long-term outcome after SDR

In our study of the effects of SDR on gross motor function in children with CP, we found significant short-term and long-term improvements in gross motor function measured with the GMFM-66 for the entire study population. Despite this improvement in mean GMFM-66 scores, only a few children changed GMFCS level after SDR. In order to establish whether the improvement in the GMFM-66 score was higher than could be expected for the natural course, we used reference percentiles. We found that in the long term 43% of the children showed a change in percentile ranking, compared to baseline, that was higher than would be expected from the natural course.

The disappearance of spasticity did not prevent secondary orthopedic deformity. Ongoing follow-up and treatment is necessary to maintain mobility, especially in children using walking aids.

Recommendations for future research

Discussing the results of this thesis, some recommendations for future research can be made with respect to motor assessment and follow-up of children who are at risk for developmental problems or have been treated with SDR.

Knowledge about motor assessments

The psychometric properties of (new) motor assessments should be examined extensively. The prognostic value of many early motor assessments is still questionable. In clinical practice some instruments are used for prognosis, although that was not their main purpose. Therefore, especially the prognostic value of a test should be assessed, so that clinicians will know whether it is possible to predict later outcome from early assessments. As long as this is not clear, predictions of future outcome based on only one single motor assessment should be made with great caution.

Adequate norms are needed for the interpretation of the results of motor tests. If it is decided to establish Dutch national norms, the necessary research should be done quickly after the introduction of the test, and with great care, also taking into account potential differences in development between different social cultural groups.

In order to gain more knowledge about the (possible) relationship between the different ICF-CY levels, determinants not only at the level of body function, but also at the level of personal and environmental factors for outcome at activity level, should be examined longitudinally to determine whether certain impairments in specific domains are prognostic for future outcome. There is a need to develop functional measures that reflect children's abilities, not typical development, and their performance.

The GMFCS has recently been extended to assess children from 13 to 18 years; it would be very helpful if also motor growth curves and reference percentiles came available for this age.

Longer follow-up is needed

A longer follow-up of children who are at risk for developmental problems is necessary, not only for research purposes but also to improve care. In prematurely born children and children born full-term with HIE, it is well known that minor neurological dysfunctions or cognitive problems only become detectable at a later age. If these new problems arise, timely referral to the relevant medical services is important. Associations between early and later assessment should also be studied, adding to the body of knowledge about motor development, and the predictive value of early assessments.

A longer follow-up of children who are treated with SDR is necessary, to further examine long-term results. It would be very helpful if all studies on SDR should use the GMFCS and the GMFM-66 to assess the effects of SDR on gross motor function. This would make it possible to combine and compare the results of different studies. Cohort studies with a long-term follow-up should also focus on identifying the characteristics of children who benefit most from SDR.

Recommendations for clinical implications

Children who are at risk for developmental problems (i.e. born very prematurely or born full-term with HIE) should be monitored frequently during the first years of life because motor development is very variable. Moreover, they should be monitored until at least school-age, or preferably until adulthood. They should preferably be assessed with a core-set of motor measurement instruments during childhood, about which there is consensus, including timing of assessment in the Netherlands.

Children with CP, and especially those who are treated with SDR, should be monitored yearly to ensure that they develop according to their predicted motor growth curve, until they reach adulthood. Moreover, the assessment should also include tests at different ICF-CY levels.

All clinicians working with children with CP in multidisciplinary teams, including paediatric physical therapists, should use the GMFM-66 in the assessment of children with CP, and should have the necessary knowledge about using the GMFCS and reference percentiles. We therefore recommend promotion of the knowledge and use of these new methods in clinical practice in the Netherlands.

The body of knowledge about motor assessment and the motor development of children with or without neurological disorders is growing rapidly. Therefore, new motor instruments or the results of research should be used as a basic element of clinical practice in the Netherlands. Preferably, these assessments should be included in basic medical and physical therapy education programme. Paediatric physical therapy training should include, in addition to extensive knowledge about 'normal' motor development in children, practical and theoretical information about motor assessments during childhood. Therapists should know not only how to use a measurement instrument, but also understand the psychometric properties and understand the underlying construct of the instruments, in order to interpret the results.

Paediatric physical therapists, among other specialists, assess the level of motor development in children. They have extensive knowledge about normal and deviant motor development in children, the psychometric properties of tests and prognosis. With emphasis on the assessment of motor development at the level of activity, including knowledge about the assessment of body functions and structure, they can play an important role in (joint) diagnostics and the evaluation of interventions in multidisciplinary rehabilitation teams.

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Summary

The long-term outcome of a child's development is always an intriguing issue, especially if the child was born after problems during pregnancy or delivery, or if the child has been treated with a relatively new intervention.

This thesis describes the results of studies focusing on the motor outcome of three different cohorts of children: 1) children, mostly small for their gestational age and born prematurely, from mothers with early-onset hypertensive disorders of pregnancy; 2) children born full-term with hypoxic-ischemic encephalopathy (HIE) due to perinatal asphyxia; 3) and children with cerebral palsy (CP) who were treated with Selective Dorsal Rhizotomy (SDR).

The main aims of this thesis are to describe motor outcome, mainly at the level of activity, in young children who were at risk for developmental problems or who had received an intervention, and to examine the predictive value of the measurement instruments that are most frequently used in childhood to forecast future motor outcome.

Chapter 1, the Introduction, describes the aims and outline of the thesis. In this chapter the International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) is introduced, and 'normal' motor development and issues concerning motor assessments are discussed. It also provides background information on the disorders in the study population (HIE and CP) and the SDR treatment. This is followed by a brief outline of the motor tests that are commonly used in clinical paediatric physical therapy practice to measure motor outcome in children.

Chapter 2 describes a study of the motor outcome of 175 infants. The aim of the study was to describe General Movements (GMs) at term age and three months post term, and their association with neurological examination performed at the same ages. Furthermore, the predictive validity of GMs at three months for outcome at one year corrected age was evaluated. Most infants were small for their gestational age and born prematurely from women with early-onset hypertensive disorders of pregnancy. This prospective study was part of a randomised controlled trial of pre-birth management strategies, the PETRA study (Pre-eclampsia and Eclampsia TRial Amsterdam), executed in a collaboration between the Departments of Obstetrics and Gynaecology of the Amsterdam Medical Center and the VU University Medical Center. We examined the prevalence of normal, mildly abnormal and definitely abnormal General Movements (GMs) and the results of neurological examination at term and three months corrected age in these infants. We investigated the association of GMs with neurodevelopmental outcome at one year, measured with the motor and mental scales of the Bayley Scales of Infant Development second version (BSID-II). We found an association between GMs and neurological examination results at term age, but at three months corrected age, GMs and neurological examination results were not related. GMs at three months were also not associated with abnormal neurological examination at one year, but they were associated with delayed motor outcome at one year. Neurological examination at three months was related to motor outcome at one year, but there was no association with neurological examination or mental outcome at one year. We concluded that, although reports in the literature suggest that the assessment of GMs at three months is useful for the prediction of adverse neurological outcome in high risk infants, we were not able to confirm this in our study. The assessment of GMs can be useful in the examination of high risk children, but should preferably be combined with other assessments such as neurological examinations.

In **Chapter 3** we investigated motor outcome at the age of one year in a cohort of 32 surviving children who were born full-term with perinatal HIE. Motor outcome was measured according to the Alberta Infant Motor Scale (AIMS), the motor scale of the BSID-II and a neurological examination (Neurological Optimality Score; NOS). We studied the relationships between, on the one hand, motor tests (AIMS and BSID-II motor scale) and neurological examination at one year, and on the other hand, the outcome of these tests and neonatal brain Magnetic Resonance Imaging (MRI).

We found that the AIMS and the BSID-II motor scale agreed in the classification of normal, mildly delayed or significantly delayed motor outcome at one year in approximately 75% of the children. All children with a normal motor outcome had a (near) optimal NOS, but not all children with a high NOS had a normal motor outcome. Children with a normal neonatal MRI had a normal or mildly delayed motor outcome at one year, but in children with abnormalities on the MRI motor outcome was variable at one year. We concluded that the two motor tests agreed on classification of motor outcome in the majority of cases, but not in all cases. Normal brain MRI is a good predictor for a normal or mildly delayed motor outcome, but abnormal MRI did not predict motor outcome at the age of one year. In line with these findings we suggest that a combination of motor tests and neurological examination at the age of one year should be used to assess outcome after HIE.

In **Chapter 4** we investigated motor and mental outcome at two years in our cohort of 32 children with HIE. We assessed the additional predictive value of the different tests (AIMS, BSID-II and NOS) at one year, in addition to prediction based on neonatal Sarnat staging and MRI, for both motor and mental outcome (measured with the BSID-II) at two years. We found that all children with Sarnat grade I had a good motor outcome, but 14% had a poor mental outcome. All children with normal MRI had a normal motor outcome, but 9% had a poor mental outcome. In children with Sarnat II or with neonatal MRI abnormalities the outcome was variable: approximately 50% had a normal motor outcome. Sarnat I and normal neonatal MRI were good predictors of a normal or only mildly delayed motor outcome. For children with Sarnat grade II and abnormal MRI, additional motor testing at one year improved the accuracy of predicting a poor motor and mental outcome at two years. In line with this finding, our conclusion was that motor testing at one year is helpful for the prediction of a poor motor outcome at two years. Nevertheless, a longer follow-up of these children is needed to establish how they will develop in the long term, acknowledging that a few studies suggest that even children with a good outcome at two years may have minor neurological dysfunctions or cognitive problems in later life.

In **Chapter 5** we evaluated the effect of SDR on gross motor function, self-care and gait pattern in a well-defined group of nine ambulatory children with spastic diplegia. These children were the first to undergo this operation in the Netherlands and were monitored extensively during the first year after SDR. Outcome was measured in the different levels of the ICF-CY. Gross motor function was measured with the Gross Motor Function Measure (GMFM-88) every two months, from 4 months before until one year after SDR. Self-care was assessed with the Pediatric Evaluation of Disability Inventory (PEDI) and gait pattern was assessed with the Edinburgh Visual Gait Score (EGS) at baseline and one year after SDR.

We found a significant improvement in the mean total GMFM-88 score between baseline and one year after SDR, indicating an improvement in gross motor function. These results were comparable to the effects reported in the literature. Using a single-subject research design, with repeated measurements over time, visual plots of individual cases showed significant change in GMFM-88 scores after SDR, compared to baseline measurements. These findings were confirmed by within-subject analysis with C-statistics. Functional skills and care-giver assistance for self-care, measured with the PEDI, also showed significant improvement in the entire study population. Improvement in gait pattern was found, in particular with respect to initial contact and heel-lift, resulting in a more normal EGS. We concluded that in this well-defined group of ambulatory children, SDR had a small but significantly positive effect on gross motor function, self-care and gait pattern.

In **Chapter 6** we evaluated the short-term (1 year) and long-term (3–8 years) effects of SDR in all 33 ambulatory children with spastic diplegia who had undergone SDR in the Netherlands. Gross motor function was assessed according to the Gross Motor Function Classification System (GMFCS) and GMFM-66. Spasticity was measured according to a modified Tardieu scale. Information about additional treatment and the opinion of the parents with regard to improvement in their child's functioning was obtained from questionnaires. We found that in both the short term (one year) and the long term (mean 6 years) after SDR, the mean GMFM-66 score had improved significantly from baseline, indicating improved gross motor function. However, most children had a stable short-term and long-term GMFCS level. In the short term, the children in GMFCS levels I–II improved significantly more on the GMFM-66 than the children in level III. In the long term there was no significant difference in mean GMFM-66 improvement between the children in GMFCS level I–II and III. Reference percentile data were used for comparison with the 'natural course' of gross motor development in children with CP. It has been stated that the chance of a change of more than 20 percentile data in one year in a cohort of children with CP is 20%. When comparing the individual percentile rankings, 29% of the children improved more than 20 percentiles in their GMFCS level between baseline and the one year follow-up, and 43% had improved more than 20 percentiles at the long term. We considered the effect of SDR to be an improvement on the expected natural course of gross motor development in a subgroup of children with CP, especially in the long term.

Spasticity had disappeared in the majority, although not in all children, and no relapse of spasticity was noted at the long-term follow-up. Almost one third of the children, mostly children in GMFCS level III, needed orthopedic surgery, especially operations to stabilise the feet. Approximately 40% of the children were treated with botulinum toxin-A injections after SDR, and most of these children were in GMFCS level III.

We concluded that SDR resulted in small short-term improvements, in particular for children in GMFCS levels I–II. In the long term, approximately 40% of the children showed improvements in their gross motor function, which was considered to be more than what could be expected, according the percentile ranking of their individual motor growth curve. Approximately 50% of the children needed additional surgery or botulinum toxin-A treatment. This also suggests that final conclusions about the effectiveness of SDR can only be drawn after the child reaches adulthood.

In **Chapter 7** the main findings described in the thesis were discussed, suggestions were made for future research, and clinical implications were formulated. Recommendations for future research include obtaining more knowledge about motor assessments, especially about the prognostic value of tests, and the development of adequate norms. A longer follow-up of children who are at risk for developmental problems is necessary, not only for research purposes, but also for the provision of care. Moreover, a longer follow-up of children is needed after SDR, acknowledging that the long-term effects of SDR are largely unknown. Cohort studies with a long-term follow-up should also focus on identifying the characteristics of children who benefit most from SDR.

Recommendations for clinical implications included longer follow-up for children who are at risk for developmental problems and children who are treated with SDR, which a core-set of measurement instruments, about which there is consensus in the Netherlands.

We recommend that all clinicians working with children with CP in multidisciplinary teams use the GMFM-66 in the assessment of children with CP, and should have the necessary knowledge about using the GMFCS and reference percentiles. Paediatric physical therapists can play an important role in (joint) diagnostics and the evaluation of interventions in multidisciplinary rehabilitation teams.

Het meten van motoriek bij kinderen:

prognose en evaluatie

Samenvatting

Hoe een kind zich op lange termijn gaat ontwikkelen is altijd een boeiende zaak, maar met name als het kind geboren is na problemen tijdens de zwangerschap of bevalling, of als het kind behandeld wordt met een relatief nieuwe interventie.

Dit proefschrift beschrijft de resultaten van onderzoeken die zich concentreren op de motorische uitkomst van drie verschillende cohorten kinderen: 1) kinderen die vrijwel allemaal te vroeg geboren zijn en die te licht zijn voor hun zwangerschapsduur, en wiens moeder ernstige vroege hypertensieve aandoeningen in de zwangerschap ('zwangerschapsvergiftiging') had; 2) op tijd geboren kinderen met hypoxisch-ischemische encephalopathie (HIE) door zuurstoftekort tijdens de bevalling; en 3) kinderen met cerebrale parese (CP) die behandeld werden met Selectieve Dorsale Rhizotomie (SDR).

De belangrijkste doelen van dit proefschrift zijn om de motorische uitkomst te beschrijven van jonge kinderen met een verhoogd risico op ontwikkelingsproblemen en van kinderen na een specifieke interventie, en dan met name op het gebied van activiteiten. Daarnaast wordt van de meetinstrumenten die het meest gebruikt worden tijdens de kinderjaren de predictieve waarde voor het voorspellen van de toekomstige motorische uitkomst onderzocht.

Hoofdstuk 1, de Introductie, beschrijft de doelen en de opbouw van het proefschrift. In dit hoofdstuk wordt de International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) geïntroduceerd. Tevens worden de 'normale' motorische ontwikkeling en zaken rond het meten van motoriek bediscussieerd. Daarnaast geeft dit hoofdstuk achtergrondinformatie over de aandoeningen van de bestudeerde groepen kinderen (HIE en CP) en over de SDR-behandeling. Daarna volgt een korte samenvatting van de motoriektesten die gangbaar zijn in de klinische kinderfysiotherapeutische praktijk om motoriek bij kinderen te meten.

Hoofdstuk 2 beschrijft een onderzoek naar de motorische uitkomst van 175 kinderen op de leeftijd van 0, 3 en 12 maanden. Het doel van de studie was om General Movements (GMs) op de uitgerekende datum en de gecorrigeerde leeftijd van drie maanden te beschrijven, en hun relatie met de uitkomsten van neurologisch onderzoek op dezelfde leeftijden. Tevens werd de predictieve waarde van GMs op de gecorrigeerde leeftijd van drie maanden voor de motorische uitkomst op de gecorrigeerde leeftijd van één jaar geëvalueerd. De meeste kinderen waren te vroeg geboren en te licht voor hun zwangerschapsduur, en hun moeders hadden ernstige vroege hypertensieve aandoeningen in de zwangerschap. Deze prospectieve studie maakte deel uit van de gerandomiseerde gecontroleerde trial van behandeling van ernstige vroege hypertensieve aandoening in de zwangerschap, de PETRA-studie (Pre-eclampsie Eclampsie TRial Amsterdam), uitgevoerd in een samenwerking tussen de afdelingen Obstetrie en Gynaecologie van het Amsterdam Medisch Centrum (AMC) en het VU medisch centrum (VUmc). De prevalentie van normale, licht afwijkende en duidelijk afwijkende GMs werd onderzocht, evenals het resultaat van het neurologisch onderzoek op de a terme leeftijd en de gecorrigeerde leeftijd van drie maanden. Daarnaast werd de associatie van GMs met de ontwikkeling op één jaar, gemeten met de motorische en mentale schalen van de tweede versie van de Bayley Scales of Infant Development (BSID-II) onderzocht. Er werd een verband gevonden tussen GMs en het resultaat van het neurologisch onderzoek op de a terme leeftijd, maar niet op de gecorrigeerde leeftijd van drie maanden. GMs geobserveerd op de leeftijd van drie maanden vertoonden geen samenhang met abnormaal neurologisch onderzoek op de leeftijd van één jaar, maar wel met een vertraagde motorische ontwikkeling op één jaar. Het neurologisch onderzoek op de leeftijd

van drie maanden vertoonde samenhang met de motorische ontwikkeling op één jaar, maar er was geen relatie met het neurologisch onderzoek of de mentale ontwikkeling op één jaar. Hoewel de literatuur suggereert dat de GMs op drie maanden bruikbaar zijn voor de predictie van een slechte neurologische uitkomst bij kinderen met een hoog risico op ontwikkelingsproblemen, concludeerden wij dat onze studieresultaten deze bevindingen niet konden bevestigen. De beoordeling van GMs kan bruikbaar zijn bij het onderzoek van kinderen met een hoog risico op ontwikkelingsproblemen, maar zal bij voorkeur gecombineerd moeten worden met andere onderzoeksmethoden, zoals het neurologisch onderzoek.

In **hoofdstuk 3** werd de motorische uitkomst op de leeftijd van één jaar van een cohort van 32 overlevende kinderen die a terme geboren waren met perinatale HIE onderzocht. De motorische uitkomst werd gemeten met de Alberta Infant Motor Scale (AIMS), de motorische schaal van de BSID-II en een neurologisch onderzoek (Neurological Optimality Score; NOS). De relaties tussen enerzijds de motorische testen (AIMS en motorische schaal van de BSID-II) en het neurologisch onderzoek op één jaar, en anderzijds de relatie tussen de uitkomst van deze testen en de neonatale Magnetic Resonance Imaging (MRI)-bevindingen werden bestudeerd.

We vonden dat de AIMS en de BSID-II in ongeveer 75% van de kinderen overeen kwamen in hun classificatie van een normale, licht vertraagde of duidelijk vertraagde motorische ontwikkeling op een jaar. Alle kinderen met een normale motorische uitkomst hadden een (bijna) optimale NOS, maar niet alle kinderen met een hoge NOS hadden een normale motorische uitkomst. Kinderen met een normale neonatale MRI hadden een normale of licht vertraagde motorische ontwikkeling op één jaar, maar de kinderen met afwijkingen op de MRI hadden variabele motorische uitkomsten op één jaar. We concludeerden dat de classificatie van de motorische uitkomst op basis van de twee motorische testen bij de meerderheid van de kinderen overeen kwam. Een normale MRI is een goede voorspeller voor een normale of licht vertraagde motorische ontwikkeling, maar afwijkingen op de MRI konden de motorische uitkomst op één jaar niet voorspellen. In het verlengde van deze bevindingen adviseren wij om een combinatie van een motorische test en het neurologisch onderzoek te gebruiken om de uitkomst na HIE vast te stellen. Echter, het moet duidelijk zijn dat deze testen verschillende onderliggende constructen meten.

In **hoofdstuk 4** worden de motorische en mentale uitkomst op de leeftijd van twee jaar van ons cohort van 32 kinderen met HIE beschreven. We onderzochten de additionele predictieve waarde van de verschillende testen (AIMS, motorische schaal van de BSID-II en NOS) op de leeftijd van één jaar, bovenop de voorspelling die gebaseerd is op neonatale Sarnat- en MRI-classificaties, voor zowel de motorische als de mentale uitkomst (gemeten met de BSID-II) op twee jaar. We vonden dat alle kinderen met Sarnat I een goede motorische uitkomst hadden, maar 14% had een slechte mentale uitkomst. Ook alle kinderen met een normale MRI had een goede motorische uitkomst, hoewel 9% van deze groep een slechte mentale uitkomst had. Van de kinderen met Sarnat II en met afwijkingen op de neonatale MRI was de uitkomst variabel; ongeveer 50% had een normale motorische uitkomst. Een Sarnat I-classificatie en een normale neonatale MRI zijn goede predictoren voor een normale of slechts licht vertraagde motorische uitkomst. Voor kinderen met Sarnat II en afwijkingen op de MRI verbetert een motoriektest op de leeftijd van één jaar de accuratesse van voorspellen van de motorische en mentale uitkomst op twee jaar. Onze conclusie is dat het testen van de motoriek op de leeftijd van één jaar helpt bij het voorspellen van een slechte motorische uitkomst op twee jaar. Toch

is lange termijn follow-up van deze kinderen nodig om vast te stellen hoe zij zich over een langere periode ontwikkelen, daar een aantal studies suggereren dat zelfs kinderen met een goede uitkomst op twee jaar lichte neurologische disfuncties of cognitieve problemen kunnen ontwikkelen op latere leeftijd.

In **hoofdstuk 5** worden de effecten van SDR geëvalueerd op de grove motoriek, de zelfverzorging in het dagelijks leven en de kwaliteit van het looppatroon in een duidelijk gedefinieerde groep van negen lopende kinderen met spastische diplegie. Deze kinderen waren de eersten die in Nederland een SDR ondergingen, en zij werden uitgebreid gevolgd gedurende het eerste jaar na de operatie. Uitkomsten werden gemeten op de verschillende niveaus van het ICF-CY. De grove motoriek werd elke twee maanden gemeten met de Gross Motor Function Measure (GMFM-88) vanaf 4 maanden voor de operatie tot een jaar na de SDR. De mate van zelfverzorging werd vastgelegd met behulp van de Pediatric Evaluation of Disability Inventory (PEDI), en de kwaliteit van het looppatroon werd gescoord met behulp van de Edinburgh Visual Gait Score (EGS), zowel op baseline als één jaar na de SDR.

We vonden een significante verbetering van de gemiddelde totaalscore van de GMFM-88 tussen de baseline en één jaar na SDR, hetgeen een verbetering in grove motoriek aanduidt. Deze resultaten waren vergelijkbaar met de effecten zoals die beschreven zijn in de literatuur. Gebruikmakend van een single-subject onderzoeksdesign, met herhaalde metingen over de tijd, toonden individuele grafieken een significante verandering in GMFM-88-score na de SDR vergeleken met de baselinemetingen. Deze bevindingen werden bevestigd door within-subject analyses met C-statistics. De gehele groep liet een significante verbetering zien voor functionele vaardigheden en verzorgerassistentie voor zelfverzorging, gemeten met de PEDI. Daarnaast werd een verbetering in de kwaliteit van het looppatroon gevonden, in het bijzonder betreffende initial contact en heel-lift, hetgeen resulteerde in een 'normalere' EGS. We concludeerden dat SDR in deze duidelijk omschreven groep van lopende kinderen een klein maar significant positief effect heeft op zowel de grove motoriek, de zelfverzorging als de kwaliteit van het looppatroon.

In **hoofdstuk 6** werden zowel de korte termijn- (1 jaar) als lange termijneffecten (3-8 jaar) van SDR in alle 33 lopende kinderen met spastische diplegie die een SDR hebben ondergaan in Nederland geëvalueerd. De grove motoriek werd gemeten met behulp van het Gross Motor Function Classification System (GMFCS) en de GMFM-66. Spasticiteit werd onderzocht met behulp van een gemodificeerde Tardieuschaal. Informatie over bijkomende behandelingen na SDR en de mening van de ouders over de verbetering van het functioneren van hun kind werd verzameld door middel van vragenlijsten. We vonden dat zowel op korte (1 jaar) als lange termijn (gemiddeld 6 jaar) de gemiddelde GMFM-66 score na SDR significant verbeterde ten opzichte van de baseline, hetgeen wijst op een verbetering van de grove motoriek. De meeste kinderen functioneerden echter in hetzelfde GMFCS-niveau op zowel korte als lange termijn. Op de korte termijn verbeterden kinderen in GMFCS-niveau I-II significant meer op de GMFM-66 dan kinderen in GMFCS-niveau III. Op de lange termijn was er geen verschil tussen de gemiddelde vooruitgang op GMFM-66 tussen de kinderen in GMFCS-niveau I-II en III. Om de vooruitgang in grove motoriek te vergelijken met de 'natuurlijke ontwikkeling' van kinderen met CP werd gebruik gemaakt van de onlangs gepubliceerde referentie-percentielscores. Het is bekend dat de kans op een verandering van meer dan 20 percentielen in één jaar voor een kind met CP 20% is. Wanneer de individuele percentielscores van de kinderen binnen hun

GMFCS-niveau werden vergeleken, bleek dat 29% van de kinderen meer dan 20 percentielen verbeterde tussen baseline en de meting op 1 jaar na SDR. Op de lange termijn verbeterde 43% van de kinderen meer dan 20 percentielen. We beschouwen het effect van SDR dan ook als een verbetering ten opzichte van de verwachte natuurlijke ontwikkeling van grove motoriek in een subgroep van kinderen met CP, en met name op de lange termijn.

Spasticiteit was verdwenen bij de meerderheid, maar niet bij alle kinderen, en er werd geen terugkeer van spasticiteit gevonden op de lange termijn. Ongeveer éénderde van de kinderen, voornamelijk kinderen in GMFCS-niveau III, onderging orthopedische chirurgie na SDR, met name operaties om de voet te stabiliseren. Ongeveer 40% van de kinderen, vooral kinderen in GMFCS-niveau III, werd behandeld met Botuline toxine-A injecties na SDR.

Wij concludeerden dat SDR resulteert in kleine korte termijnverbeteringen, in het bijzonder bij kinderen met GMFCS-niveau I-II. Op de lange termijn toont ongeveer 40% van de kinderen verbeteringen in het grof-motorisch functioneren die beschouwd kunnen worden als boven de verwachting gebaseerd op de percentielscores van hun individuele motorische groeicurve.

Ongeveer 50% van de kinderen werd behandeld door middel van chirurgie of Botuline toxine-A. Dit suggereert dat de uiteindelijke conclusies over de effectiviteit van SDR pas getrokken kunnen worden als het kind volwassen is.

In **hoofdstuk 7** werden de belangrijkste bevindingen van dit proefschrift bediscussieerd, werden suggesties gedaan voor toekomstig onderzoek, en implicaties voor de klinische praktijk geformuleerd.

Aanbevolen wordt om in toekomstig onderzoek meer kennis te verwerven over de eigenschappen van motorische testen, vooral over hun prognostische waarde, en om adequate normen te ontwikkelen. Een langere follow-up van kinderen met een verhoogd risico op ontwikkelingsproblemen is nodig, niet alleen voor wetenschappelijke doeleinden, maar ook om eventuele hulpverlening tijdig te kunnen starten. Een langere follow-up van kinderen die een SDR hebben ondergaan is noodzakelijk, vooral omdat de lange termijneffecten van deze operatie nog grotendeels onbekend zijn. Cohortonderzoeken naar de lange termijneffecten zouden ook moeten focussen op het identificeren van de meest geschikte kandidaten voor SDR.

Aanbevelingen voor de klinische praktijk betreffen de lange termijn follow-up van kinderen met een verhoogd risico op ontwikkelingsproblemen en na SDR, met bij voorkeur een vaststaande combinatie van meetinstrumenten waarover consensus in Nederland bestaat. Het gebruik van de GMFM-66 en GMFCS, inclusief motorische groeicurves en percentielscores, wordt aanbevolen aan alle clinici die werken met kinderen met CP in multidisciplinaire teams. Kinderfysiotherapeuten kunnen met hun kennis en vaardigheden een belangrijke rol spelen in de (mede-) diagnostiek en behandeling van kinderen met CP in multidisciplinaire revalidatieteams.

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Curriculum vitae

Na het behalen van het Atheneum B-diploma aan het Fioretti-college in Lisse, studeerde Petra van Schie Fysiotherapie aan de (toenmalige) Academie voor Fysiotherapie 'Jan van Essen' in Amsterdam. Sinds haar diplomering in 1985 werkt zij bij de afdeling Fysiotherapie van het VUmc. Na ervaring te hebben opgedaan op vele verschillende klinische afdelingen en bij vele poliklinische specialismen, besloot ze zich te specialiseren in de behandeling van kinderen. In 1992 startte ze met een studie Orthopedagogiek aan de Universiteit van Amsterdam, waar zij in 1997 haar bul behaalde met als specialisatie 'Lichamelijk en geestelijk gehandicapte en langdurig zieke kinderen'. Haar afstudeerproject betrof een onderzoek naar de effecten van Conductieve Opvoeding volgens Petö bij kinderen met cerebrale parese in Revalidatiecentrum Heliomare, Wijk aan Zee.

Na afronding van deze studie werd zij door (inmiddels professor) dr. J.G. Becher aangesteld als parttime junior-onderzoeker bij de afdeling Revalidatiegeneeskunde van het VUmc op achtereenvolgens een onderzoek naar de effecten van Selectieve Dorsale Rhizotomie, en de effecten van Intrathecale Baclofen bij gegeneraliseerde dystonie. Na afronding van deze projecten werkte zij van maart 2001 tot 2003 onder leiding van Prof. Dr. A. Vermeer parttime als orthopedagoog-onderzoeker bij de Faculteit Sociale Wetenschappen, Capaciteitsgroep Algemene Pedagogiek en Orthopedagogiek van de Universiteit Utrecht. Hier voerde zij het valideringsonderzoek uit van de Nederlandse vertaling van de vragenlijst 'Measure of Processes of Care'(MPOC). Intussen was zij ook gestart met de postacademiale opleiding Kinderfysiotherapie aan de Hogeschool Utrecht, welke zij in 2004 afrondde met een literatuurscriptie over de effecten van Botulinetoxine A-behandeling op de handvaardigheid van kinderen met een unilaterale spastische cerebrale parese.

In 2005 werd een door haar geschreven subsidieaanvraag voor een onderzoek naar de lange termijneffecten van Selectieve Dorsale Rhizotomie gehonoreerd. Zij was zeer nauw betrokken bij de opzet en uitvoering van deze studie, die inmiddels is afgerond. Sinds september 2005 is zij parttime als onderzoeker betrokken bij het PERRIN CP 5-9 project, een prospectief onderzoek naar determinanten van de ontwikkeling van kinderen met cerebrale parese in de leeftijd van 5 tot 9 jaar. Zij combineert deze functie met die van praktiserend kinderfysiotherapeut in zowel de polikliniek als de kliniek van het VUmc, waarbij zij tevens betrokken is bij onderzoek naar de ontwikkeling van prematuur geboren kinderen, kinderen na perinatale asfyxie en kinderen met het syndroom van Down. Daarnaast is zij enthousiast Gross Motor Function Measure (GMFM)-trainer.

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