Asymmetry and infants born preterm

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Photographs Elise Althoff, Mike Valkenhoff
'Balancing stones' by Kent Avery, Vancouver CA
Cover design Joëlle Zeggelaar, goboef.nl
Layout Renate Siebes, Proefschrift.nu
Printed by Ridderprint, Ridderkerk
ISBN 9789 03935 8320

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Asymmetrie en prematuur geboren kinderen

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht op gezag van de rector magnificus,
prof.dr. G.J. van der Zwaan, ingevolge het besluit van het
college voor promoties in het openbaar te verdedigen
op donderdag 11 oktober 2012 des middags te 12.45 uur

door

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geboren op 18 augustus 1953
te 's-Gravenhage

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Dit proefschrift werd financieel ondersteund door de Stichting Steunfonds Faculteit Gezondheidszorg van Hogeschool Utrecht, het Stimuleringsfonds van het Koninklijk Nederlands Genootschap voor Fysiotherapie (KNGF) en de Nederlandse Vereniging Fysiotherapie bij Kinderen (NVFK).

CONTENTS

LIST OF ABBREVIATIONS

AIMS	Alberta Infant Motor Scale
aOR	Adjusted odds ratio
BW	Birth weight
CA	Corrected age
CDC	Clinical diagnostic criteria
CI	Confidence interval
CMT	Congenital muscular torticollis
CP	Cerebral palsy
DP	Deformational plagiocephaly
GA	Gestational age
GMs	General movements
IA	Idiopathic asymmetry
ICD-10	International classification of diseases - 10th version
MS	Medical specialists
NICU	Neonatal intensive care unit
OR	Odds ratio
PPT	Pediatric physical therapists
RFL	Red flags
SA	Symptomatic asymmetry
SD	Standard deviation
TEA	Term-equivalent age
TIMP	Test of Infant Motor Performance

Chapter 1

General introduction

Relevance of asymmetry in infancy

Asymmetry in infancy refers to a health condition with a high prevalence rate in the first months of life.[1-6] Such an asymmetry has a wide variation in appearances, like an asymmetric shape of the head, positional preference of the head and trunk, right versus left differences in postural control of head or trunk, and in motor performance. Two features are characteristic at the younger ages: a positional preference of the head and a deformational plagiocephaly (DP). A 'positional preference' is defined as a condition in which the infant's head is turned toward one side most of the time and active movement to the other side is restricted.[2, 4] DP refers to a condition in which the head becomes asymmetrically deformed as the result of external molding forces being applied to the malleable cranium. A positional preference of the head and DP are phenomena with mutual influence.[7-10]

Cot death due to Sudden Infant Death Syndrome decreased in The Netherlands considerably following the initiation of the "Safe Sleeping" campaigns from 1987 onward.[11] The prevalence of asymmetry in infancy increased exponentially during this period. The same impact has been reported in many Western countries following the initiation of programs to decrease prone sleeping.[1,5,12,13] Before the "Safe Sleeping" campaign, the prevalence of DP was not a subject to epidemiological studies. In recent literature the prevalence of DP in The Netherlands varies between 13% and 20%.[4,14] Boere-Boonekamp estimated in her study in 2001 that 25% of the infants with a positional preference and/or DP (approximately 5000 a year in The Netherlands) were referred to pediatric physical therapists.[2] According to the multi-professional guideline 'Prevention, signaling and intervention of positional preference and deformational plagiocephaly', published by the Dutch Center of Youth Healthcare in 2012 (www.ncj.nl), the referral to pediatric physical therapists increased to about 18,000 a year.

Prevention appears a plausible solution to reduce the high prevalence, but there is only a limited body of evidence for the effect of prevention strategies.[14,15] In a single study, the effect of pediatric physical therapy intervention in an early phase on the decrease of DP has clearly been proven.[16] In the long term, the effect is still subject of debate. In general, a DP decreases over time, but in a minority of children a degree of flattening remains. Studying the natural course of asymmetry has not been done very often.[2,17,18] This kind of research is needed to prevent unnecessary treatment and to identify those infants that will benefit from intervention.

Etiology of asymmetry

Several theories are described about the etiology of this highly prevalent asymmetry in healthy infants, like intra-uterine constraint[7,19], child-rearing practices[4,13,17,20] and delayed motor development.[4,17,21-23] Hence, this asymmetry can be classified as idiopathic. However, there are infants with asymmetry caused by an underlying disorder, disease or dysfunction, such as a visual dysfunction[24], malformation of the spine[25], craniosynostosis[26-28], or Grisel syndrome.[29] In case of a symptomatic asymmetry, diagnostic and intervention strategies as well as prognosis might be quite different from an idiopathic asymmetry. In Dutch clinical practice, well baby clinic physicians or general practitioners often refer young infants to pediatric physical therapists for diagnostic reasons. Besides, parents have direct access to physical therapists since 2006, without consulting a physician. The diagnostic skills of pediatric physical therapists have to be substantiated and transparent. They have to distinguish symptomatic asymmetry from idiopathic asymmetry. Timely recognition of signs and symptoms, might avoid missing serious pathology. Although a few algorithms about differential diagnostics are described in the current literature, diagnostic criteria were not determined.[30-34] The first part of this thesis aims at a screening instrument, applicable in the differential diagnostic process.

Risk factors for asymmetry

Next to etiologic aspects, some groups are particularly at risk for developing a positional preference and/or DP. Identified groups are boys[8,20,35], first-born[2,4,17], and multiple born infants.[19,36] Mild prematurity has also been described as a risk factor in some studies[2,20], but not consistently.[17] In the neonatal follow-up clinic of the Wilhelmina Children's Hospital in Utrecht, The Netherlands, a positional preference and/or DP is observed frequently at term-equivalent age in infants born preterm. If these infants develop an asymmetry more often, questions raised about causality and outcome. Infants born preterm are at risk for a number of medical complications associated with motor performance, like intraventricular haemorrhage and periventricular leukomalacia[37-39], chronic lung disease[40-42], and necrotising enterocolitis.[43] Moreover, a different course of motor development in the early months of life[44,45], and an elongated, laterally flattened head shape[46] are known infant factors accompanying preterm birth. Besides, the neonatal intensive care (NICU) environment, and a long duration of mechanical ventilation might play a role in limiting the motor behaviour of these young infants. In

the second part of this thesis, the prevalence, natural course, and prognostic factors for idiopathic asymmetry in infants born preterm are explored in order to determine which infants will benefit early intervention.

Prematurity and intra-uterine growth retardation

Birth weight (BW) and gestational age (GA) are the first characteristics to define when studying a population of infants born preterm (Table 1.1).

Advantages in neonatal intensive care have improved the survival rate of infants born at younger gestational ages.[47] In 2008, 7.7% of all births (n=177,713) in the Netherlands was preterm (≥22 and <37 weeks GA) and 1.5% (n=2637) <32 weeks of gestation, according to the Netherlands Perinatal Registry (www.perinatreg.nl). About 1700 of them were born <32 weeks GA and survived the neonatal period. Classified according to BW, 1513 infants survived with a BW <1500 grams, and 424 with a BW <1000 grams. Only infants <32 weeks GA and/or with a BW <1500 grams, or with an intensive care indication are admitted to one of the 10 NICUs in The Netherlands.

Interpretation of BW according to GA identifies infants who are dysmature or small for GA. In this thesis the clinical cut-off point for small for GA is used, being <10th percentile.

Table 1.1 Classification of birth weight, gestational age, and birth weight for gestational age

Birth weight (grams)	**Classification**	
≥2500	Normal birth weight	
≥1500 and <2500	Low Birth Weight	
≥1000 and <1500	Very Low Birth Weight	
<1000	Extremely Low Birth Weight	
Gestational age (weeks)	**Classification**	
≥38	Full-term	
≥37 and <38	Nearly preterm	
≥30 and <37	Preterm	
≥26 and <30	Very preterm	
<26	Extremely preterm	
Weight for gestational age	**Clinical**	**Research**
Small	<P10	<-2 SD
Appropriate	≥P10 and <P90	≥-2SD and <+2SD
Large	≥P90	≥+2SD

Motor performance in infants born preterm

Very preterm born infants appear to have their own motor developmental profile, especially in the first year of life. Several factors are involved. Biological factors, like insufficient postnatal growth or disproportion of head circumference compared to body mass play at least a biomechanical role in anti-gravity activities.[48-51] A different maturation process of the neurological system, particularly the cerebellum is presumed to influence the quality of movement patterns, and the inter-muscular coordination, muscle power regulation and postural control.[48,50,52,53] At last, infants born preterm are exposed to gravity too early with an immature motor system. Moreover, the younger the GA or the BW, the more risk factors there are for delayed or impaired motor development.[54-56] As mentioned before, delayed motor performance has been described in full-term born infants as one of the possible causes of the emergence of positional preference and in developing DP. The intention to study the natural course of asymmetry in infants born very preterm opened up the opportunity to observe the role of motor performance, in particular the development of postural control at a very young age.

Within the prospective studies of this thesis we used three instruments designed to apply early in life. These instruments objectify the quality and variability of movement patterns, postural and selective control, and gross motor maturation.

General Movement Assessment

The General Movements (GMs) assessment is used to assess the integrity of the central nervous system by observing the quality of endogenously generated whole-body movements while in a supine position. They can be observed from the preterm period until 4-5 months of age. Before term-age GMs are referred to as preterm. From term age onward until approximately 6 to 9 weeks post-term age, GMs have a so-called writhing character, gradually disappearing whereas fidgety GMs emerge up to six months of life, more and more suppressed by intentional movements.[57-59] The GMs are classified being normal, subnormal, mildly abnormal or definitely abnormal. GMs observed around 3 months of age (stage: fidgety movements) are the best predictors of abnormal or mildly abnormal motor development.[58] Normal GMs of full-term born infants at term age are described as slow-to-moderate, writhing-type movements of the whole body, with a fluent character, a small-to-moderate amplitude and variability in repertoire. GMs at term age of infants born preterm occasionally have a larger amplitude and a faster speed. The inter-tester reliability is high (0.87-0.93). The specificity of the GMs

assessment is best at the age of three months (>0.82), but lower during the writhing movement period.[60]

Test of Infant Motor Performance

The Test of Infant Motor Performance (TIMP) version 5.1 is commonly used to examine postural and selective motor control needed for functional performance in daily life in infants from the preterm period until 17 weeks post-term.[53] The test consists of 13 observed items and 42 elicited items and is based on age standards of a sample of 990 United States infants.[61] Discriminating infants at risk for poor motor outcome is the most important goal of the TIMP. Excellent test-retest and rater reliability are reported among trained observers.[62] The TIMP Screening Instrument (TIMPSI) is a shortened alternative that can be used for very young and vulnerable infants.[63]

Alberta Infant Motor Scale

The Alberta Infant Motor Scale (AIMS) is a norm-referenced instrument based on a sample of 2202 infants born in Alberta, Canada.[64] It is observational in nature and is validated as a measure of gross motor maturity of typical developing infants <19 months of age. For infants born preterm (GA <37 weeks) correction for prematurity has to be used. The scale has 58 items on a developmental continuum, divided in four positions: prone, supine, sitting and standing position. For each item, qualitative criteria regarding posture, weight bearing and anti-gravity movements are described. A raw score is obtained by summarising all observed items plus the preceding items. Raw scores can be converted into a Z-score or a percentile-score. The objectives are to identify infants with delayed or aberrant gross motor performance, and to evaluate motor development of infants at risk for developmental delay or with a condition that present with immature motor development, like NICU-graduates. The AIMS has excellent intra- and interrater reliability coefficients and a good predictive validity in at-risk infants with typically cut-off points for various ages.[64,65] In 2006 van Haastert et al. published adjusted norm values for infants born preterm, based on a sample of 800 infants born with a GA <32 weeks, who had been admitted to the NICU of the Wilhelmina Children's Hospital.[44]

Predicting motor development

The paradigm on theoretical approaches of infant motor development shifted in the last decades from a more maturational (Gesell, 1946 and McGraw, 1940) and a cognitive (Piaget, 1953) theory towards an ecological perspective (Gibson, 1979), in which motor

development is seen as a dynamic system interacting with the environment. The maturational approach, with its linear prediction of motor development dependent on the maturation of the central nervous system, led to the creation of many tests that are still used today. The cognitive approach emphasised the importance of motor development to later cognitive development. Theories about motor learning (Bernstein, 1967; Schmidt, 1975) evolved into the concept of motor control by authors like Shumway-Cook & Woollacott. They stated that postural control is a prerequisite to acquire adequate motor skills. The ecological approach underlines also the role of biological, environmental and task related factors acting as constraints (Newell, 1986) that determine developmental transitions (Thelen, 1986; Ulrich, 1993) instead of predictable ages and stages. Edelman (1987) combined a maturational and a dynamic system perspective in his neural group selection theory, stating that variability and plasticity of brain connections are determined by both experience and development.[66] This variety of theories accentuates how precarious prediction of motor development can be.

The motor development of infants born preterm is often monitored in a neonatal follow-up clinic. One of the objectives of a neonatal follow-up program is to predict gross motor outcome and target the appropriate infants for early intervention. An important milestone for parents is if, and when they can expect their child to walk independently.

Motor skill acquisition is influenced by infant, culture and context factors. Compared to their full-term born counterparts, infants born preterm are delayed in the onset of walking.[67-69] Not all factors that influence motor development can be investigated, but infant factors, like neuromaturation, postural control and muscle strength play an important role in the development of walking skills.[67-69] The AIMS measures early gross motor maturation, while the TIMP focuses on postural control.[67-69] Considering the different constructs of both tests, the question arised, which instrument has the best clinical value in neonatal follow-up. In the last part of the thesis we analysed the predictability of gross motor maturation and independent walking in a birth cohort of infants born very preterm, comparing the two tests.

AIMS OF THE THESIS

The studies presented in this thesis focus on three different, but mutually connected themes all about young infants: firstly the differential diagnostics to distinguish symptomatic from idiopathic asymmetry in all infants under six months of age; subsequently the prevalence and predictors of idiopathic asymmetry in infants born very preterm during the same period of time; and last, the predictability of gross motor development and walking skills up to 15 months corrected age in infants born very preterm.

The aims were:

- To synthesize current information in the literature on diagnoses, incidence rates, and signs and symptoms that are thought to cause a symptomatic asymmetrical posture or movement pattern in infants during their first six months of life.
- To develop a screening instrument for pediatric physical therapists to distinguish a symptomatic asymmetry in the clinical evaluation of infants in the first six months of life.
- To determine the prevalence and natural course of idiopathic asymmetry in infants born preterm.
- To explore differences in gross motor maturation at six months corrected age (CA) for prematurity between infants born preterm, with and without positional preference at term-equivalent age (TEA), and infants with and without DP.
- To determine predictive factors for the persistence of asymmetry in motor performance and/or DP.
- To examine the ability of TIMP and AIMS to predict the level of gross motor maturation and independent walking at 15 months CA.
- To explore risk factors associated with delayed onset of independent walking.

OUTLINE OF THE THESIS

Chapter 1 presents a general introduction on the topics, and aims and outline of the thesis.

Part I: Symptomatic asymmetry

Chapter 2 presents an overview of the most prevalent disorders possibly leading to symptomatic asymmetry and reflects the findings in current literature on incidence and signs and symptoms of these disorders.

Chapter 3 describes the development of a differential diagnostic screening instrument, containing a classification scheme, clinical diagnostic criteria for differential diagnostics, and a list of 'red flags' on the basis of a literature search and expert validation.

Part II Idiopathic asymmetry in infants born very preterm

Chapter 4 explores the prevalence of DP, the persistence of DP at six months CA, and the level of gross motor maturity derived from medical records of a birth cohort of infants born at <32 weeks of gestation.

In **Chapter 5**, a prognostic study is described in which the prevalence, natural course, and prediction factors of asymmetry in motor performance or DP are identified in a cohort of infants born with a GA <30 weeks and/or a BW <1000 grams.

Part III: Prediction of gross motor development and walking skills in infants born very preterm

In **Chapter 6**, the concurrent validity is established of two instruments designed to apply early in life, the TIMP and AIMS, as well as their ability to predict gross motor development around 15 months CA and the age of walking independently in infants born very preterm.

Chapter 7, summarizes the results of the studies presented in this thesis, discusses implications for clinical practice and gives recommendations for future research.

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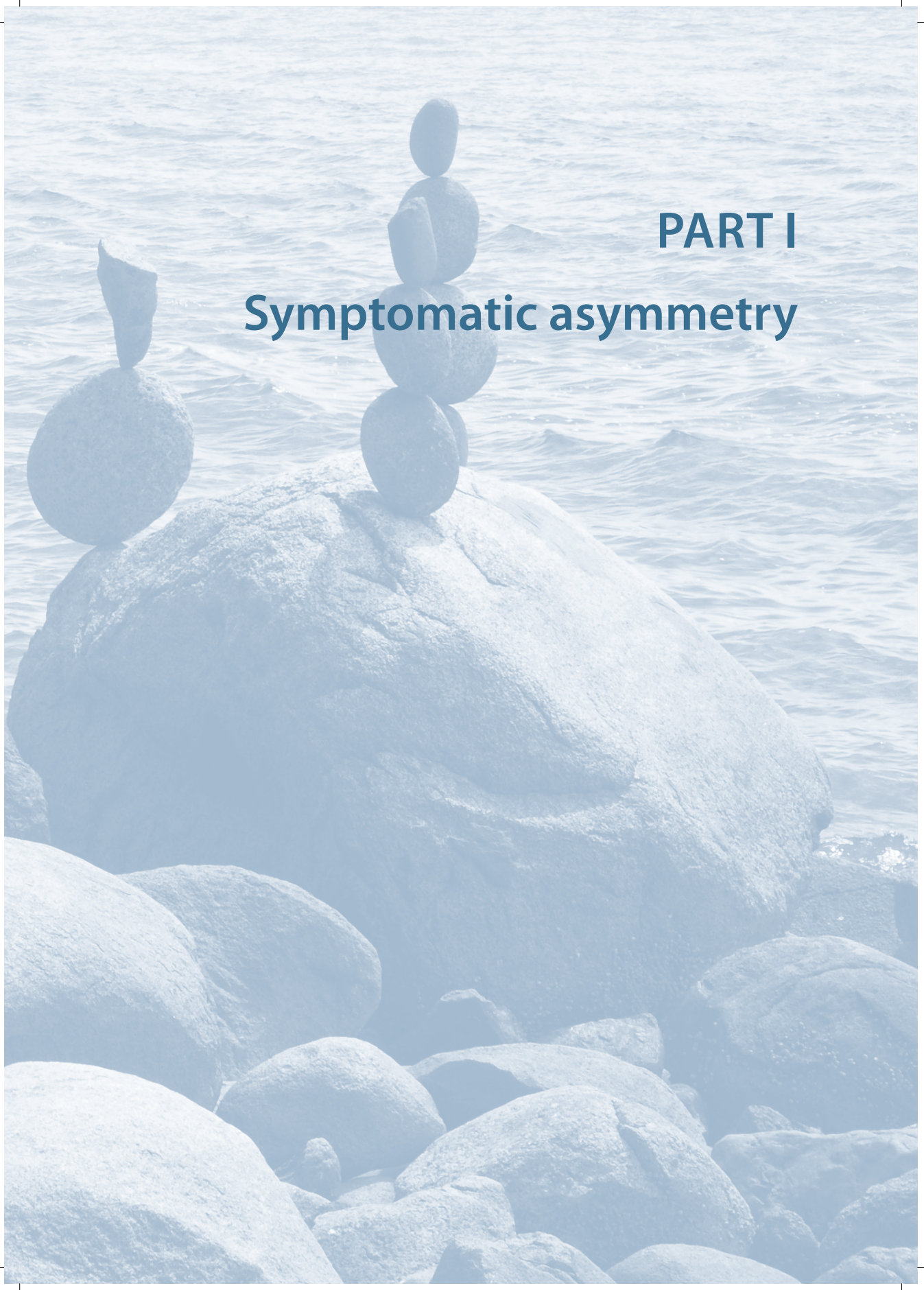

PART I

Symptomatic asymmetry

Chapter 2

Symptomatic asymmetry in the first six months of life: differential diagnosis

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Eur J Pediatr 2008;167(6):613-9.
Epub 2008 Mar 4.

ABSTRACT

Asymmetry in infancy is a clinical condition with a wide variation in appearances (shape, posture, and movement), etiology, localization, and severity. The prevalence of an asymmetric positional preference is 12% of all newborns during the first six months of life. The asymmetry is either idiopathic or symptomatic. Pediatricians and physiotherapists have to distinguish symptomatic asymmetry (SA) from idiopathic asymmetry (IA) when examining young infants with a positional preference to determine the prognosis and the intervention strategy. The majority of cases will be idiopathic, but the initial presentation of a positional preference might be a symptom of a more serious underlying disorder. The purpose of this review is to synthesize the current information on the incidence of SA, as well as the possible causes and the accompanying signs that differentiate SA from IA. This review presents an overview of the nine most prevalent disorders in infants in their first six months of life leading to SA. We have discovered that the literature does not provide a comprehensive analysis of the incidence, characteristics, signs and symptoms of SA. Knowledge of the presented clues is important in the clinical decision making with regard to young infants with asymmetry. We recommend designing a valid and useful screening instrument.

INTRODUCTION

The objective of this descriptive review is to determine and classify the possible causes of asymmetry seen in young infants who have an asymmetric head and/or body posture, as well as to present an overview of the nine most prevalent disorders in infants in the first six months of life leading to the diagnosis of symptomatic asymmetry (SA). Asymmetric infants form an increasing and complicated group of children seen by professionals from various clinical specialties, such as well baby clinic physicians, pediatricians, pediatric physiotherapists, orthopedic surgeons, and plastic surgeons.[1-6] Asymmetry in infancy is a mostly benign symptom, but in this early phase of life, the differential diagnostics are extensive. The background of the professional influences the way in which associated clinical problems are evaluated. A screening instrument would be helpful. The first step in this process is to synthesize the current information in the literature about differential diagnostics.

Twelve percent of all Dutch newborns develop a positional preference in the first few months of life, different from the physiological asymmetry.[2] A "positional preference" is defined as a condition in which the infant's head is turned toward one side most of the time and active movement to the other side is restricted.[2,5] About 25% of these infants (approximately 5000 a year in the Netherlands) are referred to pediatric physical therapists.[2] Asymmetry in infancy is a clinical condition with a wide variation in appearances (shape, posture, and movement), etiology, localization, and severity. From the referred infants, the asymmetry is either idiopathic or symptomatic, and originates ante- and/or postpartum.[1,3,7-9] In case of an idiopathic asymmetry (IA), the etiology is uncertain; environmental factors play a major role in the development of the asymmetry.[2,8-11] In SA, an underlying disorder, disease, or dysfunction causes the asymmetry. The majority of cases will be idiopathic, but an initial presentation of positional preference might be a symptom of a serious underlying problem. In the last decade, many studies on the appearances of IA have been published. If the focus in diagnostics and pattern recognition is on IA, there is a chance that an SA will be missed.[12,13] When examining young infants with a positional preference, differentiating SA from IA is necessary to determine the prognosis and to choose appropriate intervention strategies.

This review will address the following question: which diagnoses, incidence rates, signs, and symptoms are described in the literature and are thought to cause a symptomatic asymmetrical posture or movement pattern in infants during their first six months of life?

METHODS

Search strategy

This review is based on a comprehensive literature search on SA. The following strategy is used: peer-reviewed literature on this topic in journals with a science citation index was searched, as well as clinical textbooks from the various clinical specialties. Computerized bibliographic databases were searched (PubMed, Pedro, Cinahl, and Cochrane Controlled Trials Register), and related papers and their references. General keywords used were: asymmetry, plagiocephaly, torticollis, posture, scoliosis, (differential) diagnosis, and screening. The search then focused on specific diagnoses that might cause asymmetry in infancy condition with the keywords: etiology, tumors, disorders (related to) vision, hearing, central nervous, or musculoskeletal system, obstetric complications, brachial plexus palsy/lesion, clinical syndromes (Grisel, Sandifer), congenital anomalies and syndromes, gastroesophageal reflux, (birth) trauma, and clavicle fracture. Finally, we focused on the incidence and prevalence. The search was limited to citations that included: "all infants, birth–23 months," had an abstract, were written in English, and the search terms were in the title or abstract. The year of publication was not restricted. When more papers on the same subject were found, the most current studies were chosen. Only diagnoses that could be observed in infants in the first six months of life were included. Unique case reports and innocuous abnormalities that require no specific treatment were not included.

RESULTS

The prevalence and/or incidence of the various medical diagnoses leading to SA was not always documented. Some disorders had no consistency in their reported incidence rates. The majority of children with a positional preference or asymmetry during the first six months of life are diagnosed with an IA.[1-3,5,7,8,10,11] Table 2.1 shows a selection of the most frequently detected disorders causing an SA.

In the last decade, discussion on positional preference leading to deformational plagiocephaly (DP) has increased substantially. A relatively high number of hits found during a search in January 2008 within PubMed resulted in the following: asymmetry (811), plagiocephaly (206), torticollis (225), posture (405), and scoliosis (623). However, when combined with "differential diagnosis" or "screening," the result decreased to less than 20 each. Differential diagnosis from craniosynostosis was often described.[7,14-16]

Table 2.1 Disorders related to symptomatic asymmetry (SA) from the literature search

Disorders with known incidence	Incidence /1000
1. Developmental dysplasia of the hip (DDH)	40
2. Perinatal fracture of the clavicle	35
3. Congenital muscular torticollis (CMT)	20
4. Obstetric brachial plexus palsy	4
5. Central nervous system disorders	2
6. Craniosynostosis/lambdoid suture	0.03
Remaining groups of disorders	
7. Congenital abnormalities or malformations	
Musculoskeletal	
Chromosomal	
8. Sensory systems:	
Ocular disorders	
Hearing disorders	
9. Acquired asymmetry postpartum in one of the remaining systems (non-musculoskeletal)	

The main designs were retrospective or prospective descriptive studies and reviews. In diagnoses with a low incidence, the studies were predominantly case reports.

All diagnoses were classified according to the International Classification of Diseases.[17] The results of the literature search are presented below, starting with the diagnosis with the highest incidence rate.

Developmental dysplasia of the hip

Developmental dysplasia of the hip (DDH) has a high rate of co-morbidity with congenital muscular torticollis (8–20%)[18] and, to a lesser extent, with postural torticollis or scoliosis.[3] The reported incidence rate in the Netherlands ranged from 3 to 4% of all newborns[5,8,18], with 80% being unilateral.[19,20] The clinical signs which are described include asymmetry in hip abduction and leg length and/or asymmetrical skin folds in the inguinal and upper thigh region. The strong association with other asymmetries warrants a thorough screening on the signs of developmental dysplasia of the hip in infants with an asymmetry.

Perinatal fracture of the clavicle

A fracture of the clavicle during birth may induce a positional preference in the first weeks of life and, as such, may cause an asymmetry. A perinatal fracture can be an option

in the differential diagnostics of asymmetry during the first weeks of life. A co-incidence with other perinatal injuries (like brachial plexus injury) was described by Perlow et al.[21] The obstetric brachial plexus lesion is described separately. The incidence varies between 0.1 and 3.5%[21-24], and these fractures usually consolidate within 3 weeks without complications. The clinical presentation can be asymptomatic. When symptomatic, signs include: decreased or absent movement and pain, or tenderness on movement of the arm on the affected side and palpable irregularity along the clavicle.[22]

Congenital muscular torticollis

Congenital muscular torticollis (CMT) is frequently described in the literature. Unilateral fibrosis or thickening of and tightness in the sternocleidomastoid muscle can cause a characteristic posture of the head and restricted neck movements. The etiology of the pseudo-tumor or mass is unclear.[6,18,25,26] A compartment syndrome due to intra-uterine malposition is the most frequently mentioned etiological hypothesis.[6,25,27,28] An association with birth trauma and breech presentation is mentioned, but the evidence is weak, since CMT is also seen in infants born via a cesarean section.[18,29] A pseudo-tumor can be palpated in the second or third week after birth. Incidence rates of CMT vary between 0.3 and 2%.[6,18,25-27] Ultrasound screening soon after birth has indicated that the incidence rate could be 3.9%. This screening method tends to be especially sensitive in detecting occult cases of fibrosis.[25]

Fibroids of the uterus and other intrauterine tumors are described as a possible etiology to an atrophy of the sternocleidomastoid muscle of the child.[30] This phenomenon can cause a unilateral muscular dysfunction and a strong imbalance between both muscles. The distinction between CMT and postural torticollis is not always clear.[31] A CMT is primarily a condition with a structural fibroid shortening of the sternocleidomastoid muscle, visible and palpable in the first weeks of life, as opposed to a postural torticollis that occurs secondary to a positional preference and a DP.[1,2,4,7,8]

Obstetric brachial plexus palsy

Palsy of the brachial plexus during delivery is caused by traction or compression of the plexus during labor. In most cases, the upper brachial plexus is affected; in 15% of the patients, hand function is also impaired. The described incidence is 0.1–0.4%.[21,32,33] The extent of the neural damage becomes evident during the first six months of life[33], although in severe cases, the inactivity of the extremity is observed from birth onwards.

Timely recognition of severe cases is important, since neurosurgical intervention can enhance future capacities. Between 20 and 25% of the infants experience persistent functional impairments.[32]

Central nervous system disorders

Cerebral palsy (CP) syndromes, in particular, spastic unilateral CP, are neurological disorders that can cause asymmetry.[12,34] Serious disorders of the central nervous system are generally easy to recognize, but a CP may also be discrete with subtle features. Early diagnosis, before the age of six months, might be difficult.[35,36] The neurodevelopmental (motor) behavior is an important issue in early recognition: persistent infantile reflexes and abnormal muscle tone, motor delay, abnormal spontaneous movement patterns (especially "general movements"), and poor postural control are more or less predictors of CP.[35,37,38] In a review on the epidemiology of CP, the world-wide prevalence of all types of CP is estimated at 0.2%.[39]

Hypotonia and developmental delay were also mentioned as causes for developing positional preference and DP. A neurological disorder might be the underlying problem, but it is not always diagnosed at this young age.[7,12,34]

Craniosynostosis

Craniosynostosis, the premature fusion of one or more cranial sutures, is most frequently described in relation to asymmetry and plagiocephaly, possibly as a result of the over-referral of infants with deformational non-synostotic DP to craniofacial or plastic surgery clinics. Primary craniosynostosis is either simple or compound and part of a genetic syndrome.[16] Premature closing of one lambdoid suture is the most frequently mentioned differential diagnosis of DP.[14-16] The incidence of this single suture craniosynostosis is rare (1–3 cases to 100,000 newborns)[1,40] and can be clinically differentiated from DP by four major signs: from the vertex view, a trapezoid head shape can be observed, a palpable unilateral ridge, bulging of the unilateral mastoid, and an asymmetric skull base with tilt to the ipsilateral side.[14,15,40] The impact of the premature closure of cranial sutures in complex craniosynostosis is impressive: strong progressive deformation of the skull, risk of increasing intracranial pressure, and developmental problems. When evident, timely surgical intervention is warranted.[3,7,14-16]

The following three categories are groups of disorders. Clear incidence rates could not be found.

Congenital abnormalities or malformations

Musculoskeletal congenital malformations must be considered when an asymmetry is present immediately after birth.[12,34] Well-known malformations are those of the spine, such as a Klippel-Feil syndrome, hemi-vertebrae, and a hemi-atlas.[41-43] Exceptional phenomena are hypoplasia or aplasia of the face, neck, or trunk muscles.[44] Patients may show defects in other systems as well, such as syndactyly, deafness, or a congenital heart disease. The co-incidence of defects may be an important sign of a syndrome. An asymmetric development or posture can be an associated finding in a variety of syndromes and abnormalities. These features are often present immediately after birth, but will not always be discovered until a second stage.[42] Local abnormalities, such as a vascular ring (around the trachea) or tracheomalacia, are occasionally an indirect cause of an asymmetric posture.[45]

Disorders in sensory systems

In the screening of infants with asymmetry, eye movement and/or vision and hearing disorders must be considered. Infants with congenital nystagmus and restrictive or paralytic strabismus may use anomalous head positions to maximize visual function.[46-48] No clear incidence rates were found. A predictive factor for an ocular origin of torticollis is the family history of ocular problems, in particular, congenital nystagmus. The ocular pathology may be subtle. In case of doubt, infants must be referred to an ophthalmologist.[46]

Theoretically, a unilateral hearing disorder can induce a positional preference in young infants. In the literature search, no match was found for hearing loss and torticollis, except in syndromes such as Klippel-Feil or Moebius. A connection between ear malformation and hearing loss is mentioned.[49]

Acquired asymmetry, non-musculoskeletal

A number of disorders in systems other than the musculoskeletal system can cause a postpartum asymmetry, but the asymmetry is not the only symptom. The disorders have in common that their symptoms are not stable and occur some time after birth. The signs and symptoms can be seen as so-called "red flags" and require immediate medical evaluation. It may be secondary to a trauma[50] or to inflammatory conditions, such as pharyngitis.[51-54] Grisel syndrome (a non-traumatic atlanto-axial rotatory subluxation following infections of the upper respiratory tract) is often described, but never under the age of six months.[6,34,54] Another cause can be related to the cardio-respiratory or

Table 2.2 Disorders related to symptomatic asymmetry (SA) from the literature search

Signs & symptoms	Hints for disorders
General history	
Heavy pain	Retro-pharyngeal abscess[53]
Vomiting/drowsiness	Increased intracranial pressure[58]
Lethargy / irritability	Tumor[27,58]; Intracranial injury[50]
Trauma	Intracranial injury[50]
Seizures/convulsions	Epilepsy; Increased intracranial pressure; Sandifer syndrome[17]
Acute onset	Infection, Abscess[53]; Grisel syndrome (> 6 months)[29,55]
Stridor, Dyspnoea	Vascular ring[45]
Reflux	Sandifer syndrome; Pathological gastroesophageal reflux[17]
Fever	Infection, Abscess[53]
Specific examination	
Sunset phenomenon	Increased intracranial pressure
Bulging anterior fontanel	Increased intracranial pressure, Intracranial injury[50]
Abnormal course	
Increasing head tilt	Infection[53]; tumour[27,58]
Recurrent episodes	Benign paroxysmal torticollis[56,57]

the digestive system, such as Sandifer syndrome (fluctuating asymmetry with abnormal body movements and contortions of the neck, associated with gastroesophageal reflux).[55-57] The most alarming causes of asymmetry are related to neurological syndromes, such as syringomyelia, epilepsy, high intracranial pressure, postencephalitic syndromes, or life-threatening tumors of the central nervous system.[6,12,13,27,34,58] These disorders are mainly described in case studies, without proven incidence rates. The signs and symptoms of these non-musculoskeletal causes are described in Table 2.2.

DISCUSSION

Asymmetry in infancy is a condition with a high prevalence in infants in the first six months of life. In the majority of cases, the origin is idiopathic and is often related to environmental factors.[1,2,9-11,31] This review addresses the possible causes, incidence rates, and symptoms of symptomatic asymmetries due to an underlying disorder, dysfunction, or disease.

Not all of the incidence rates could be found, while some inconsistencies were observed in the current literature. The disorders with a high prevalence are well described in epidemiologic studies. The rarer diseases were, most of the time, documented in case reports without incidence rates. The incidence rates mentioned in the studies are inconsistent because of different opinions regarding the operationalization and assessment of the SA. Frequently, psychometric properties of instruments and concepts have not been described or evaluated. Variations in incidence rates (e.g. CMT) are inevitable, considering the variety in inclusion criteria and diagnostic tests used in the studies. The sequence in estimated incidence rates, as proposed in Table 2.1, is open to debate.

A clear description of signs and symptoms was not always presented in the literature. The variety in the etiology of asymmetry is considerable. The level of evidence of the included studies varies. Literature of more than 10 years ago mainly described underlying causes of SA, in particular, non-muscular torticollis.[12,34] They still turned out to be useful in establishing criteria for differential diagnostic screening and are widely cited in current studies. However, an update regarding new developments in studies on infant asymmetry is needed. The exponential increase of plagiocephaly in the last decade, related to the recommendations to put babies on their back to sleep, is reflected in the objectives of recent studies.[1,2,5,59] They mainly focused on IA and its predispositions, with little attention to SA. A number of recent papers described features to distinguish craniosynostosis from DP. Although craniosynostosis has a very low incidence, craniofacial clinics are deluged with infants with DP.[1,31,60] One of the positive effects of this situation is that authors from this background described useful clinical diagnostic criteria for craniosynostosis.

Van Vlimmeren et al.[9] stated in their review on diagnostic strategies, that asymmetry in infancy is a diagnosis with a large spectrum of features and a multifactorial etiology without consensus on definition, nomenclature, or classification. In the present review, a classification by virtue of etiology is proposed. The dichotomy, symptomatic versus idiopathic, is often used in medicine[61-64] and fits well with this health problem, since a large number of children have unexplained asymmetry.

Although flow diagrams for diagnostic strategies are presented in some reviews[4,6,12,34,31], clear clinical diagnostic criteria that could be used were not mentioned. The criteria found in the present review might be considered in a future study. An expert validation, such as a Delphi study with clinical experts, could be a next step towards establishing clinical diagnostic criteria as warning flags in young infants with IA or SA.

This review presents an overview of the most common disorders underlying SA in infants less than six months of age. We have discovered that the literature does not provide a comprehensive analysis of the incidence, characteristics, signs, and symptoms of SA. Knowledge of the presented clues is important in the clinical decision making with regard to young infants with asymmetry. The endpoint of this review may be a starting document for the creation of a protocol, but it needs additional studies in order for it to become a valid and useful screening instrument.

Acknowledgements

We like to thank Raoul H. H. Engelbert, PhD, PCS, PT, Associate Professor, Amsterdam School for Health Professions, Amsterdam, the Netherlands, for his substantive comments.

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Chapter 3

Symptomatic asymmetry in very young infants: A Delphi study on the development of a screening instrument

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Physiother Theory Pract 2011;27(3):194-212.
Epub 2010 Sep 8.

ABSTRACT

The objective of this study was to develop a screening instrument for pediatric physiotherapists to distinguish a symptomatic asymmetry in the clinical evaluation of young infants (age <6 months) with an asymmetric head posture. We chose two consensus methods, a Two-Round Delphi-design and an expert meeting using nominal group technique, for reaching agreement about classification of diagnoses and clinical diagnostic criteria (CDC). Seventeen diagnoses with an expression of asymmetry with 69 matching CDC were assessed. In two Delphi rounds, six medical specialists and seven pediatric physiotherapists were polled anonymously on the classification, completeness, and relevance of the diagnoses and the CDC. Panel consistency in Round 2, expressed as Cronbach's-α, was 0.89. In Round 3, a face-to-face meeting with eight therapists, the previously selected diagnoses and CDC were prioritised, reduced to ten diagnoses and 21 CDC, and completed with eight hard clinical signs (red flags). Finally, a differential diagnostic screening instrument, containing a classification scheme, the CDC for differential diagnostics, and a list of 'red flags' was established, on the basis of literature search and expert consensus. Cross-validity and reliability of the instrument will be investigated in future research.

INTRODUCTION

A non-physiologic idiopathic asymmetry in shape and/or posture of the head in young infants is an increasingly prevalent clinical condition that warrants careful examination in pediatric physiotherapy practice.[1-4] Physiologically, young infants may have an asymmetric posture due to the influence of the 'asymmetric tonic neck reaction' and an instable posture in the supine position in the first months of life. This asymmetry is bilaterally and non obligatory.[5] In contrast to physiological asymmetry, 12–17% of all newborns develop a positional preference during the first six months of life.[1,4,6] In the prevalence studies, a "positional preference" is defined as a condition in which the infant's head is turned toward one side most of the time and active movement to the other side is restricted. About a quarter of them are treated by pediatric physiotherapists.[1] A distinct positional preference of the head in the first weeks of life or a frequently seen distinct plagiocephaly at birth may secondarily cause any asymmetry in shape and/or function of the entire body. In this way, healthy and neurologically normal infants may develop a deformational plagiocephaly, a postural torticollis, or a postural scoliosis.[1,4,7-10] The high prevalence rate is related to the medical advice to put babies on their back to sleep to diminish the risk on 'cot death'.[11-14] The etiology of this idiopathic asymmetry (IA) is unknown, but risk factors to develop a plagiocephaly in the first months of life are: male gender; first born; positional preference when sleeping; one-sided handling during diaper changing and bottle feeding; tummy time when awake less than three times per day; and slow achievement of motor milestones.[1,4,8,9,11,15]

Generally, this idiopathic asymmetry is a condition with a benign prognosis. On the other hand, an asymmetric head posture can sometimes be one of the symptoms of an underlying disorder, disease or dysfunction, such as a malformation of the spine, a visual dysfunction, or a tumor at the posterior fossa. Besides, abnormalities like developmental dysplasia of the hip are more often seen in infants with an asymmetric (head) posture. Timely recognition of such a symptomatic asymmetry (SA) is important with a view to treatment and/or prognosis.[3,16,17] In the Dutch situation, well baby clinic physicians or general practitioners often refer young infants to pediatric physiotherapists for diagnostic reasons. Besides, parents have direct access to physiotherapists since 2006. In the current literature, a few algorithms about differential diagnostics of symptomatic asymmetry exist.[3,7,16-18] These studies however, have concentrated on the diagnostic process, rather than on a description of diagnostic criteria. In pediatric physiotherapy practice, the available diagnostic instruments regard asymmetry as a symptom of a central neurological disorder, and are not comprehensive to all causes of symptomatic asymmetry.

A formalised screening process, based on the notion of pattern recognition, should precede the routine diagnostic process. Pattern recognition is defined in terms of an inductive reasoning process, particularly used in diagnostic reasoning by recognizing a set of signs and symptoms.[19] The concept of so-called 'red flags' is important.[20] Red flags are "historical and clinical clues that may indicate the presence of a serious underlying disorder".[21] Recognition of red flags in the diagnostic reasoning process avoids missing serious pathology. Given that a positional preference occurs in the first months of life, we chose to study differential diagnostic screening in infants under six months of age. An instrument for differential diagnostic screening will improve clinical decision making and increase the transparency of the diagnostic process. Such an instrument, originating from a biomedical view, contains diagnostic criteria, consisting of signs and symptoms in the domain of impairments in structure or function.[22]

The objective of the present study was to develop a screening instrument for pediatric physiotherapists to distinguish a symptomatic asymmetry in the clinical evaluation of young infants (<6 months of age) with an asymmetric head posture, based on literature search and expert validity.

METHODS

Design

This study, intended to develop a screening instrument with expert validity, had a qualitative design. Two consensus methods were chosen, which are useful in identifying and measuring matters of uncertainty in medical and health care: 1) a Two-Round Delphi design; and 2) an expert meeting in Round 3, using nominal group technique (Figure 3.1).[23] The Delphi method and the nominal group technique are both considered suitable methods for reaching agreement among colleagues in a bottom-up process in issues like treatment or clinical reasoning protocols.[24] A combination of more than one method, called 'method triangulation', strengthens the validation process, just as the inclusion of expert groups from a different professional background (source triangulation).[25]

The Delphi method enables the participation of experts without the need to physically bring them together.[24] In this method, experts perform a survey independent of one another, but have the opportunity to revise their opinion during the process. They receive questionnaires in a first round and are invited to quantify their opinion and to give qualitative comments whenever they feel the need to. In the second round, they

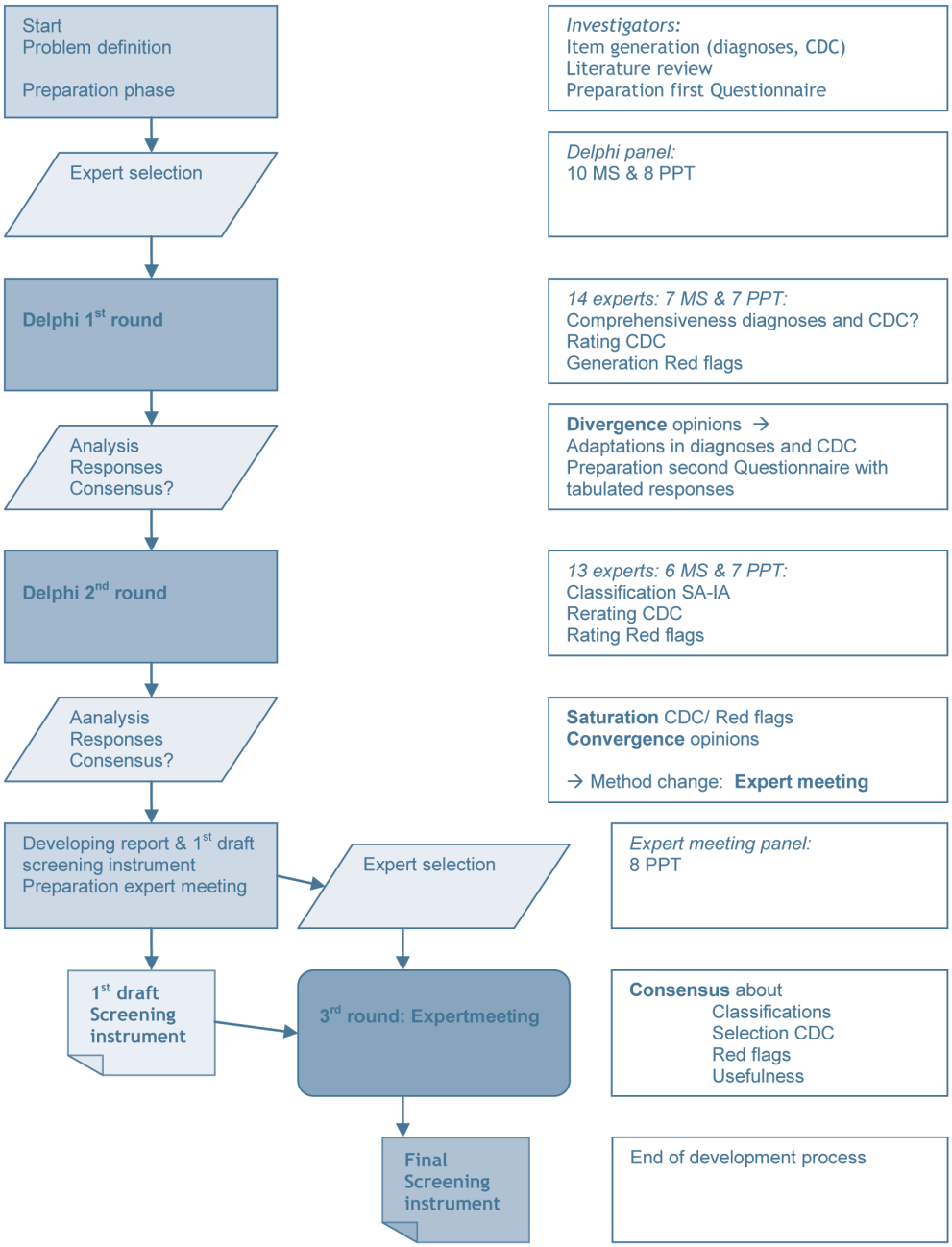

Figure 3.1 Flowchart of the consensus process of a differential diagnostic screening instrument to recognise symptomatic asymmetry. SA = symptomatic asymmetry; IA = idiopathic asymmetry; CDC = clinical diagnostic criteria; MS = medical specialists; PPT = pediatric physiotherapists.

are provided with a summary of the results and are asked to reconsider their initial judgement regarding the results. The process can be continued until an acceptable degree of consensus is reached. The advantages of this method are low costs, controlled interaction, and easy access.[26]

The purpose of a nominal group technique in an expert meeting is to give panelists the opportunity to discuss issues face-to-face, in the view of previous results and their own knowledge on the topic. A meeting is characterised by structured interaction, like separated rounds of idea generation and/or clarification, argumentation, and voting.[23,24]

Preparation phase

Classification

Many possible diagnoses were first classified by two investigators as idiopathic or symptomatic asymmetry, subsequently as localised or generalised, and 'body parts involved'. The investigators have a more than 20 years' experience with this health problem in primary care (JN) and in an academic hospital (IvH). Both are involved in the postgraduate master curriculum of pediatric physiotherapists. The disorders and diseases had been derived from four sources: 1) differential diagnostic schemes used in specialist education[3,27,28]; 2) key informant interviews with two researchers in 'neonatology' and 'asymmetry in infants' respectively; 3) textbooks from the clinical specialties; and 4) peer-reviewed literature on the topic.[22]

Clinical diagnostic criteria (CDC)

The list of preliminary CDC contained observations and manoeuvres (provocations, palpations and measurements) performed during the first examination of the infant. These were clustered around possible diagnoses. To prepare this list, the same sources were used as for the classification proposal. This list enclosed 12 sets of diagnoses with 69 matching CDC regarding symptomatic asymmetry within the musculoskeletal, neurological, and sensory domain. Five diagnoses in systems other than the musculoskeletal were appended in order to generate red flags. Five sets of CDC covering idiopathic asymmetry 'diagnoses' completed the list.

In addition to the list of preliminary CDC, a list of red flags was composed after Round 1, analogous to the CDC list[22], including information derived from Round 1.

Four research questions were formulated to investigate the experts' opinion on the following topics:

1. Can both expert panels, medical specialists and pediatric physiotherapists, assent to the taxonomy and nomenclature of SA and IA?
2. Are the selected CDC correctly formulated, complete, and relevant?
3. Which clues are 'hard' signs (so called 'red flags')?
4. Is the established screening instrument a useful and efficient instrument for the evaluation of symptomatic asymmetry in infants up to six months of age by pediatric physiotherapists?

Delphi method, Round 1 and 2

The Delphi expert panel consisted of two groups: 1) ten medical specialists; and 2) eight pediatric physiotherapists. The medical specialists were recruited from the clinical disciplines that are usually involved in the screening, diagnosis, and/or treatment of infants with different kinds of asymmetries. This panel included two well baby clinic physicians, two pediatricians and specialists from pediatric surgery, orofacial plastic surgery, child-neurology, orthopaedic surgery, otorhinolaryngology, and child-ophthalmology. They were selected on a convenience sample for pragmatic reasons.[29] Eight of ten had an academic affiliation and all were familiar with young infants with an asymmetric condition. An inclusion criterion was that candidate panelists were known to the investigators as interested in physiotherapy procedures regarding this health problem, or were coauthors of scientific publications about the subject. The pediatric physiotherapist panelists were considered experts for different reasons: they were experienced clinical specialists working in a hospital or a private practice. In addition, they were lecturer in the clinical specialist master-education for pediatric physiotherapy or researcher and known as opinion leader in the professional field in the Netherlands.[30] All physiotherapy experts had more than 20 years experience. They were selected on a purposive sample for strategic reasons.[29] Both groups were recruited from all over the country.

The aim of Round 1 was to classify a list of diagnoses and to refine and evaluate the CDC with regard to research question 1 and 2. The experts were invited to recommend additional diagnoses or CDC and to comment upon the definitions of the CDC. Panellists were then asked to value the signs, to establish the degree of relevance of each item as

a clinical diagnostic criterion relating to the diagnosis (research question 2). A five-point scale with the anchors "completely irrelevant" (=1) and "extremely relevant" (=5) was used to record the responses. On this so called 'semantic differential' scale, only the extremes were labelled to give the respondents the opportunity to express their own thoughts about the criteria.[31] With regard to research question 3, the panellists were asked to name signs or symptoms they considered to be a 'red flag'.

Round 2 was intended to obtain convergence in the ratings of Round 1, supported by feedback of the group on the same questions. Panelists were asked to reconsider their own rating of the CDC. Research question 3 was adapted to determine the importance of red flags as potential alarming signs. To get more differentiation in the answers, a 10-point scale, with the extremes "completely unimportant" (=1) to "very important, always examine" (=10), was used to indicate the importance of the red flags.

Prospective panelists were provided with an information package by electronic mail, containing a synopsis of the study plan and the Delphi procedure, an a priori classification scheme, and a matching list of CDC. Questionnaires were used in both rounds, which were sent by e-mail. The panelists were blinded for the other co-panelists.

Expert meeting

In Round 3, a different method and perspective were chosen. The reason for this change was to strengthen the consensus process, because argumentation in a face-to-face meeting is considered a valuable addition to the anonymous Delphi process.[24] The shift to the pediatric physiotherapy perspective had two objectives: 1) to refine the outcome of the Delphi rounds by the professionals who have to use the instrument in practice; and 2) to judge, and answer to research question 4 in Round 3: 'Is the established instrument a useful and efficient instrument for the evaluation of symptomatic asymmetry by pediatric physiotherapists?'

The panel in Round 3 consisted of eight pediatric physiotherapists. Three experts from the previous Delphi rounds were willing to participate in a face-to-face panel. For different reasons, four experts were not able to participate any more: two because of the long travel distance to the meeting; and two due to shortage of time. All four assumed that they had given all the input they wanted. Five new experts with comparable experience and knowledge about the subject were recruited. The mean number of years of experience in the panel was 26.8 years (standard deviation (SD) 3.85).

Prior to the meeting, each panel member was provided with the questions of Round 3, a summary of the results of Round 2 regarding CDC and red flags, and the draft version of the instrument. One of the experts was panel chairman. The procedure of the nominal group technique during the meeting was as follows: first, the project leader (JN) introduced every question with a short presentation; subsequently, the panellists could ask clarifying questions followed by an argumentation round. Finally, they expressed agreement by voting. The basic assumption of consensus during the expert meeting in Round 3 was an agreement of six of eight on all (dichotomised) questions. In case of 5/8, a second argumentation round should be followed by a weighted voting on a 1-9 scale.[32]

In Round 3, the participants were asked to confirm the interpretation of the results from the first two Delphi-rounds to obtain consensus with regard to research question 1–3. In a face-to-face meeting, they discussed definitions and prioritisation. The expert meeting in Round 3 was digitally recorded, and minutes were taken by one of the panelists and the project leader. All panelists had to give their consent to the report afterwards. Finally, all panel members were asked to respond individually by e-mail to research question 4 presented as an open-ended question, about the usefulness of the screening instrument for pediatric physiotherapists. In Figure 3.1 the process and content of the rounds are shown.

Data analysis

The CDC list and the red flags list were recorded in an MS Excel (Microsoft BV, Amsterdam, The Netherlands) spreadsheet. Descriptive analysis was performed for research questions 2 and 3, within and between the expert groups. The panelists were informed with regard to the mean, the median, range and SD scores as feedback for Round 2. Decrease of the variance was interpreted as an increasing convergence. A mean and median score of ≥4 (SD<0.7) on the 5-point scale was considered as a relevant CDC, a score between 3 and 4 as doubtful, and a mean/median score ≤3 (SD>1) as irrelevant. With a mean score of ≥8.5 (SD<1.3) on the 10-point scale, a red flag was considered to be a hard clinical sign. The importance of the signs and symptoms with a lower score were considered as 'dependent on context variables'.

For this study, consensus within the Delphi-group was defined as the homogeneity of the panel, as expressed in the consistency of opinion among the panelists. Cronbach's-α was used to quantify the reliability of the panellists' scores on the CDC list. For a scale to be useful in clinical practice when screening individual patients, Cronbach's-α should

approach 0.90.[31,33] The consistency within the panel was analysed, including the changes between Round 1 and 2.

RESULTS

Round 1 and Revisions

Seven out of ten medical specialists and seven out of eight pediatric physiotherapists returned the questionnaire in the initial round. Reminder e-mails or telephone calls were sent to the non-responders or to panelists who did not complete the questionnaire. One physiotherapist withdrew her cooperation, due to a lack of time. Eventually, three medical specialists, an orthopaedic surgeon, an otorhinolaryngologist, and a pediatric neurologist, did not respond to the several reminders. So, we do not have information about the reasons for their nonparticipation.

In general, classification as either SA or IA was thought to be appropriate and applicable for the health problem 'asymmetry in infancy'. Some rare SA diagnoses were mentioned. The description of some IA diagnoses (e.g., postural torticollis), was not as clear for the medical specialists as it was for the pediatric physiotherapists. IA diagnoses turned out to be a more or less description of symptoms, instead of clear medical diagnoses. Moreover, synonyms were used to describe the same feature, like 'Moulded baby' and 'Turned-Adduction-Curvature syndrome'. A few extra SA diagnoses (e.g., vascular ring), all with a very low incidence, were added to the scheme under the following collective terms: infections, intern causes and anomalies (Table 3.1); two IA diagnoses were merged and the terminology was slightly adapted. The classification in 'localised/generalised' and 'body parts involved' was not considered to be appropriate. Instead, the use of the International Classification of Diseases (ICD), 10th version[34], was recommended to get a systemic taxonomy. Another suggestion was to list SA diagnoses in a declining order of incidence, so to streamline the differential diagnostic process. We decided to use the declining order for the screening instrument only, and to list all possible SA causes in a separate classification scheme (Appendix 3.2). All diagnoses were classified according to the ICD-10. The diagnoses were stratified by the time of the onset of asymmetry in ante-, peri-, or postpartum. Incidence data of diagnoses were derived from the literature.[22]

The panelists rated the CDC on the 5-point scale. Not all the items involved were filled in by all participants. Especially the medical specialists from pediatric surgery, orofacial plastic surgery, and child-ophthalmology restricted their ratings to their own specialty.

Table 3.1 Additions to and modifications of symptomatic asymmetry diagnoses and clinical diagnostic criteria

	Diagnoses	Start ΔR1	Start ΔR2	Start expert meeting	
		Preliminary CDC	Changes CDC /RFL	Order of rank selected SA diagnoses	Final order of rank most prevalent SA diagnoses
	Symptomatic asymmetry				
1	Developmental dysplasia of the hip	5 CDC		1	1
2	Facial palsy	7 CDC	-1 +1	8	X
3	Ocular disorder	9 CDC	3 adapted	4	5
4	Hearing disorder	4 CDC	+1 1 adapted	11	9
5	Malformation cervical spine	4 CDC		6	7 (merged)
6	Malformation thoracic/lumbar spine	5 CDC		7	
7	Craniosynostosis	4 CDC	-1 +2 2 adapted	9	8
8	Syndrome	-	+1	10	10
9	Perinatal fracture clavicle	4 CDC		2	2
10	Congenital muscular torticollis	9 CDC	X→IA	-	4 Added from IA
11	Obstetric brachial plexus palsy	10 CDC		3	3
12	Central nervous system disorder	8 CDC		5	6
				RFL	RFL
13	Infections	-			
14	Osteomelitis, Juvenile Idiopathic Arthritis	-			
15	Intern causes	-	15 pot RFL	6 abs RFL 9 rel RFL	8 abs RFL 7 rel RFL
16	Tumor	-			
17	Trauma	-			
	Anomalies non-musculoskeletal (added Round 2)	-			
	Idiopathic asymmetry				
	Plagiocephaly only				
	Postural torticollis				
	Postural scoliosis				
	Turning-adduction-curvature syndrome		Merged		
	Moulded baby				
	Cervical spine impairment e.c.i	-	Added		
	Congenital muscular torticollis	-	Added from SA		→SA

CDC = Clinical diagnostic criteria; RFL = Red flags; ΔR = Delphi Round; SA = Symptomatic asymmetry; IA = Idiopathic asymmetry; - = Absent; x = Discarded; → = Shifted from group; pot = Potential; abs = Absolutely important; rel = Relatively important; e.c.i. = E causa ignota.

Medical specialists working in a general health care domain (Infant Healthcare Centre or pediatrics) and pediatric physiotherapists completed the document, but they occasionally skipped a single item they did not recognise. The median score of all CDC was 4 (range 1–5). The mean scale score of the CDC was 3.8 (SD ± 0.58); by medical specialists 3.65 (SD ± 0.68), by PPTs 3.98 (SD ± 0.66). On the diagnostic level, generally one or two CDC were rated 4 or more, but often with an SD >1.0. On the CDC level, a mean difference of more than 1 point was occasionally seen between the two panels, with a range from 1 to 5. The respondents used the opportunity to make remarks and corrections and to suggest additional criteria. They missed an age specification on some criteria and criteria derived from the intake. Some experts commented upon the meaning of relevancy (research question 2). Two physicians preferred the terms 'sensitivity' and/or 'specificity'.

In the second round the same format was used, but the CDC were slightly revised. One revision was the age appropriateness of some criteria. Four new CDC were added and two skipped, as suggested by the orofacial plastic surgeon and the child-ophthalmologist. The survey included the frequency distribution on each item of the Round 1 response (mean, SD, median, range) for the total group of experts as well as for both panels separately. The CDC with a mean score of ≥4 were highlighted, being the most relevant signs. To get a maximum response on the most relevant CDC, experts were encouraged to rate at least the highlighted items, if they had not enough time to complete the document.

The revised survey, containing 16 SA diagnoses (with 64 CDC and 15 red flags) and 6 IA diagnoses (with 41 CDC), was sent by e-mail to all 14 respondents together with a report of the results and conclusions. The aim for the next round was to realise enough convergence on the ratings to enable data reduction (Figure 3.1). The results are presented in Table 3.1.

Round 2 and Revisions

Thirteen participants (6 medical specialists and 7 pediatric physiotherapists) completed Round 2. For unknown reasons, the pediatric surgeon did not respond. The panelists agreed with the revised classification scheme, but a few new suggestions for the nomenclature were given (e.g., to use the term 'developmental dysplasia of the hip' instead of 'congenital dysplasia of the hip'). Based on these recommendations, minor changes were made in the classification scheme. A selection of the 10 most frequent occurring SA diagnoses could be established for a draft version of the instrument.

The rating of relevance of the CDC showed less divergence between the panelists than in Round 1. These CDC were mainly the same as those identified in Round 1, yet with a mean SD of 0.72. Many CDC got a score of ≤3 (SD>1) and as such were considered irrelevant. In four SA diagnoses, two CDC could be distinguished, according to the a priori criterion for item reduction (≥4; SD<0.7). In another four diagnoses only one CDC could be included. A second CDC was selected with an SD>0.7 and <1.0. In Table 3.2, the mean, median, range and SD of the selected CDC, as well as the change between the rounds are presented. In two diagnoses (craniosynostosis and congenital malformations), the choice of CDC was disputable for different reasons. No CDC concerning craniosynostosis met the inclusion criteria. One of the experts, the plastic surgeon who is expert at the topic, advised two new CDC in Round 1, as is mentioned before. In Round 2, one of these criteria, 'downward sloping of the posterior cranial base' was not recognised by all experts, leading to a lack of consensus. The three best rated CDC were chosen. With regard to the diagnosis 'congenital malformations', no consistent CDC were formulated and rated. Some experts suggested that the criterion 'dysmorphic features' would do. The results of the rating of all CDC in Round 2 are presented in Appendix 3.1.

A second draft version of the screening instrument was made, containing the 10 most frequent occurring SA diagnoses with the two most relevant CDC for each diagnosis to examine during the differential diagnostic process. This selection had to be conferred with the experts of Round 3.

The third research question focused on the opinion of the experts about the importance of the presented red flags to detect serious pathology. From a lists of 15 signs and symptoms, six had a score >8.5 (SD<1.3) on the 10-point interval scale. Based on these scores, a differentiation was made between 'absolutely' (≥8.5, SD<1.3) and 'relatively' (<8.5) important red flags. Four symptoms: 1) acute onset; 2) stridor; 3) dyspnoea; and 4) increasing head tilt had a borderline score (Table 3.3).

Consistency

Only the scores of panelists who completed the major part of the survey (11/14) could be included in the consistency analysis, because of too many missing values. In Round 1 of the Delphi process, Cronbach's-α was rather low: 0.67 (4 medical specialists, 7 physiotherapists; 34 CDC). After Round 2, in which some experts choose the possibility of scoring only the highlighted items, the data of 8/13 panellists regarding a larger number of CDC (43 CDC) could be used to calculate Cronbach's-α, which was 0.89 (2 medical specialists, 6 physiotherapists).

Table 3.2 Screening instrument symptomatic asymmetry: rating of clinical diagnostic criteria

Symptomatic asymmetry	Clinical diagnostic criteria	Round 2 (n experts =13)					Round 1 (n experts=14)				
Possible diagnosis (incidence/1000)	Findings	mean	SD	med	range	n	mean	SD	med	range	n
1. Developmental dysplasia of the hip (40)	A. Unilateral pROM hip abduction <70°	4.55	0.52	5	4-5	11	4.55	1.04	5	2-5	11
	B. Leg length difference (Galeazzi)	4.18	0.75	4	3-5	11	4.18	1.33	5	1-5	11
2. Perinatal fracture of the clavicle (35)	A. Unilateral arm less active	4.45	0.52	4	4-5	11	3.75	1.29	4	2-5	12
	B. Pressure pain	4.18	0.98	4	2-5	11	3.83	1.34	4	1-5	12
3. Congenital muscular torticollis (20)	A. Persistent posture of the neck with heterolateral rotation, homolateral head-tilt and possibly hyperextension.	4.58	0.51	5	4-5	12	4.42	0.67	4.5	3-5	12
	B. Pseudotumor in the m.SCM, 1-2 weeks post partum	4.33	0.50	4	4-5	9	4.00	0.95	4	3-5	12
4. Obstetric brachial plexus palsy (4)	A. Unilateral loss of function in the arm	4.80	0.42	5	4-5	10	4.64	0.67	5	3-5	11
	B. Asymmetric response on Moro-reflex	4.36	0.50	4	4-5	11	4.25	1.29	5	1-5	12
5. Ocular disorder	A. Poor fixation and following objects (not age-appropriate)	4.67	0.49	5	4-5	12	4.20	0.92	4.5	3-5	10
	B. Strabismus and/or nystagmus	4.33	0.62	4	3-5	12	4.31	1.03	5	2-5	13
6. Central nervous system disorder (2)	A. Abnormal movement patterns	4.70	0.48	5	4-5	10	4.45	0.69	5	3-5	11
	B1. Increased or decreased passive tone	4.50	0.97	5	2-5	10	4.55	0.69	5	3-5	11
	B2. Persistent ATNR **	4.33	0.82	4.5	3-5	6	3.33	1.58	3	1-5	9

Symptomatic asymmetry	Clinical diagnostic criteria	Round 2 (n experts =13)					Round 1 (n experts=14)				
Possible diagnosis (incidence/1000)	Findings	mean	SD	med	range	n	mean	SD	med	range	n
7. Malformation of the spine	A. Asymmetry persisting in all postures	4.73	0.47	5	4-5	11	4.58	0.67	5	3-5	12
	B. Non-correctable scoliosis (actively nor passively)	4.73	0.47	5	4-5	11	4.60	0.52	5	4-5	10
8. Hearing disorder	A. Reaction on sound not age-appropriate	4.45	0.52	4	4-5	11	4.33	0.78	4.5	3-5	12
	B. No acoustical blink	4.20	0.79	4	3-5	10	4.14	1.46	5	1-5	7
9. Craniosynostosis /Lambdoid suture (.03)	A. Plagiocephaly post partum immediately visible and increasing	4.29	1.25	5	2-5	7	*				
	B1. Trapezoid head shape	3.90	1.10	4	2-5	7	3.77	1.36	4	1-5	13
	B2. Downward sloping of the posterior cranial base **	2.71	1.50	3	1-5	7	*				
10. Congenital abnormalities or malformations musculoskeletal (not spine) and/or chromosomal	A. Dysmorphic features (in general) #										

Confirmation, by the Round 3 Expert panel, and results in Round 1 and 2, of the 10 most frequent occurring SA diagnoses with the two most relevant CDC to examine during the differential diagnostic process. n = Number; med = Median; pRom = Passive range of motion; m.SCM = Sternocleidomastoid muscle; ATNR = Asymmetric Tonic Neck Reflex. *Added in Round 2; **Selected in Round 3; # No consistent CDC formulated and rated.

Table 3.3 Rating of red flags in Delphi Round 2 and expert panel Round 3

Red flags	Hints for disease or disorder	Round 2			Round 3	
		Mean (SD)	Median (range)	n	Consensus rate	Result: Agreement
General history						
Heavy pain	Fractures; Osteomyelitis; Retropharyngeal abscess	**9.30 (1.06)**	**10 (7-10)**	**10**	**8/8**	**yes**
Vomiting/ drowsiness	Increased intracranial pressure	**9.20 (1.32)**	**10 (8-10)**	**11**	**8/8**	**yes**
Trauma	Intracranial injury	**9.10 (1.29)**	**10 (7-10)**	**10**	**8/8**	**yes**
Seizures/ convulsions	Epilepsy; Increased intracranial pressure; Sandifer syndrome	**9.09 (1.04)**	**10 (7-10)**	**10**	**8/8**	**yes**
Acute onset	Infection; Abscess; Grisel syndrome	**8.40 (1.90)**	**9 (3-10)**	**10**	**8/8**	**yes**
Stridor	Vascular ring	8.40 (1.90)	9 (5-10)	10	2/8	no
Dyspnoea	Vascular ring; Cardiac problem	8.40 (2.22)	9 (5-10)	10	2/8	no
Reflux	Sandifer syndrome; Pathological gastroesophageal reflux	7.20 (2.49)	6 (4-10)	10	1/8	no
Fever	Infection; Abscess	6.90 (2.81)	6 (3-10)	10	1/8	no
Specific examination						
Sunset phenomenon	Increased intracranial pressure	**9.60 (0.84)**	**10 (8-10)**	**10**	**8/8**	**yes**
Bulging fontanel	Increased intracranial pressure	**8.91 (1.30)**	**10 (7-10)**	**11**	**8/8**	**yes**
Dysmorphic features	Syndrome (in general)	8.10 (2.13)	8 (4-10)	10	4/8	no
Lymphadenopathy	Infection; Pre-symptoms Juvenile Idiopathic Arthritis	7.30 (2.54)	7 (4-10)	10	0/8	no
Abnormal course						
Increasing head tilt	Infection; Tumor	**8.50 (2.32)**	**9.5 (3-10)**	**10**	**8/8**	**yes**
Recurrent episodes	Benign paroxysmal torticollis	8.00 (2.06)	8 (6-10)	9	0/8	no

n = Number of experts; SD = Standard deviation; Round 2: Likert-scale: 1 = Completely unimportant, 10 = Very important, always examine; Round 3: Red Flags in **bold** are established as **absolutely red flags**.

Round 3, expert meeting

Three newly formulated questions, based on the results of Round 1 and 2, and research question 4 had to be answered in this final round.

1. Does the classification scheme cover all possible diagnoses of the health problem 'asymmetry in infancy'?

After a clarification round, the pediatric physiotherapy experts discussed some bottlenecks. The discussions focussed on the nomenclature of cervical spine impairment and on a few causes that were never seen in infants less than six months of age, such as juvenile idiopathic arthritis. The nomenclature was changed and the mentioned diagnoses were removed from the scheme. The experts adopted the completeness of the classification scheme unanimously. They stated that the scheme was comprehensive for all known causes of symptomatic asymmetry in infants under six months of age. See Appendix 3.2 for the definite classification scheme.

2. Are life-threatening diagnoses sufficiently excluded by using the selected red flags?

To be able to answer this question, the panelists discussed the choice of 8.5 (SD<1.30) as a cut-off point. Four symptoms had a mean score very close to 8.5, with large SD values. The result of this choice was that potentially important red flags could be excluded. The panel decided to vote on two more red flags to possibly include in the list of absolutely red flags ('acute onset' and 'increasing head tilt'). The panel decided that if the selected 'absolutely red flags' are verified, relevant life-threatening diagnoses are sufficiently excluded. They advised, depending on the context, to consider the not selected red flags during the diagnostic process. The results of Round 2 and 3 are both presented in Table 3.3.

3. Is there concordance in the panel regarding the selection of the most frequent occurring SA diagnoses and most relevant CDC based on the results of the Delphi process?

The discussion focused on three points: 1) to add congenital muscular torticollis; 2) to add hearing disorders; and 3) to remove the Facial Palsy as this was seen as an asymmetry in the face itself, not leading to asymmetry in posture or movement patterns. The diagnoses malformations of the cervical, thoracic and lumbar spine were merged (Table 3.1).

The panel then considered carefully the choices that were made concerning the reduction in CDC to two CDC that were rated ≥4 in Round 2. The choices of CDC leading to 8/10 diagnoses were confirmed, with minor changes in terminology. Two extra CDC were selected to compensate a relatively high SD. With regard to craniosynostosis, the two best rated CDC, complemented with the extra CDC the plastic surgeon commented

on, were accepted. In Table 3.2, the selected diagnoses with all final modifications regarding CDC are shown. Within the panel, clear consensus was established concerning selection of the most frequent occurring SA diagnoses and most relevant CDC. For the final version of the screening instrument see Appendix 3.2.

4. Is the established instrument useful and efficient for pediatric physiotherapists?

The fourth research question has been answered in writing by all experts of Round 3 individually, after the panelists had received a written report of the meeting and the adaptations to the draft version of the instrument. All experts concluded the instrument to be clarifying, practical and appropriate for clinical practice. They recommended adding a manual to the instrument, especially for the colleagues with minor experience, which has to be updated on a regular basis (Appendix 3.2).

DISCUSSION

Major findings

This qualitative study describes the development of an instrument for differential diagnostic screening in very young infants with asymmetry. The experts agreed on the terminology and classification into symptomatic and idiopathic asymmetries. The study went through a cycle of item generation and reduction on criteria to be used in the differential diagnostic process. The two Delphi rounds and the expert meeting provided consensus between the experts about a set of 21 CDC covering the 10 most frequent diagnoses of SA, which can easily and efficiently be completed in the first assessment of an infant with asymmetry. Furthermore, the experts reached concordance concerning a list of eight red flags to detect serious pathology. The consensus process was expressed in more than one way. The ranking between Rounds 1 and 2 of the CDC was hardly different, but the convergence between the two rounds was obvious. The decrease of the SD, as an indication of increased consensus in the panel, was significant in almost all CDC. Moreover, consensus within the panel was seen as related to the homogeneity of the opinion of the individual panel members. The increase of Cronbach's-α over the two Delphi-rounds was substantial, from 0.67 to 0.89. The value of 0.89 at the end of Round 2 is close to the minimum value (i.e., 0.90) required for clinical application of a diagnostic instrument in individuals.[31,33]

Results in context

The methodology of item generation and the process of expert validation have resulted in clinical agreement on the item selection.[24] The reduction in items created a practical, no time consuming instrument. Only observations and manoeuvres were included in the CDC list. In clinical decision-making, (family) history plays a role too as well as other factors like experience and skills in pattern recognition.[19,30,35] Evidence like sensitivity or specificity of the CDC was almost nonavailable. The instrument under study represents only the procedural part of the diagnostic process and does not pretend to be imperative. Therapists can add their own tests if they feel the need to. An extra complicating factor in the diagnostic process in young infants is the fact that they have an immature motor system. Infants may show transient features and a rapidly changing motor performance.[36]

Strengths and weaknesses

The method and source triangulation strengthened the design of this study. Both methods have advantages and disadvantages, which could compensate each other. For example, the medical specialists had different subspecialty backgrounds. A disadvantage of consensus methods could be the smaller impact of a minority. In relevant cases, like the choice of CDC in recognising craniosynostosis, strong arguments of the expert in the field were discussed and rewarded in Round 3, despite a smaller rating. One more example is the method of rating anonymously in the Delphi rounds versus voting in the context of group dynamics at the expert meeting. Another characteristic of this study was the iterative process. The four research questions gradually became more explicit over the rounds and fitted well with the phase of development. The choices made during this process, directed the outcome of the study. It is unclear whether the outcome would have changed if other decisions were made.

This study has some weaknesses that may have induced bias. First, a consensus method can be biased when the process starts from a narrow point of view.[37] The items included in the Delphi study were formally collected from literature review[22] and key informant interviews, to have a wide scope on all diagnoses and CDC involved. We are aware of the fact, that the content of the starting list influences the item generation process. To compensate for this a priori structured list, the experts in the Delphi rounds had the possibility to comment on the items and to add new items. The items judged in the expert meeting were explicitly based on the results of the two Delphi rounds. Second,

comparable question marks have to be raised at the point of expert selection. The heterogeneity in panel composition, the experience, and specialty of the experts do have an effect on group judgement.[24,26,32] The experience of the medical specialists in the Delphi panels was not inquired; the pediatric physiotherapy panel had an extensive experience. The choice for two subgroups in the two Delphi rounds, medical specialists and pediatric physiotherapists, made the panel heterogeneous and created the possibility to compare views on a relevant topic for both professions. Despite an a priori promise, not all the initial participants performed the survey. The three panelists who did not participate were from relevant medical specialties in the diagnostic process. The impact of their nonparticipation is unclear. In the pediatric physiotherapy panel in the third round, a minority of the panel members participated in the Delphi rounds too. On the other hand, the five new experts in Round 3 could show a more objective vision towards the scores in the previous rounds. The choice to invite only physiotherapists in the final expert meeting made it possible to focus on their own diagnostic process. Finally, the fact that a number of CDC has not been rated can have caused hidden bias and as such influenced the outcome. We did not expect the medical specialists to skip the items beyond their specialty. A reasonable explanation can be that medical specialists are used to judge only issues regarding their own specialty and consult other specialists for other health questions. Therefore, the combination of general practitioners and specialists was valuable for the purpose of our instrument.

Implications

We advise pediatric physiotherapists to use the 'red flag' list in the first intake to exclude serious pathology. The differential diagnostic instrument can be used to formulate and verify hypotheses during the diagnostic process.[38] In doubt, the infants must be referred to a pediatrician to confirm the diagnosis. The diagnosis idiopathic asymmetry can only be made 'per exclusionem' (Appendix 3.2).

CONCLUSION

A screening instrument was developed to distinguish symptomatic asymmetry in the first six months of life. The instrument contains a classification scheme, a set of clinical diagnostic criteria for differential diagnostics, and a list of 'red flags', and is based on a literature search and expert consensus.

Application of the instrument in new studies can be a starting point toward collecting evidence.[37] More research is needed to confirm the usefulness of the instrument. The next stage is to investigate validity by observations, cross-validation in a sample of infants, who are already diagnosed on a particular symptomatic asymmetry and in determining the predictive validity of the criteria.

Acknowledgments

We gratefully acknowledge all members of the expert panels for their participation in and contribution to this study: M. Boere-Boonekamp MD, PhD, A. Bulk-Bunschoten MD, PhD, H. Crombag PPT, J. Deenen- van Zon PPT, R. Engelbert PPT, PhD, W. Eskes MD, P. van Essen PPT, L. de Groot PPT, PhD, M. Kuijpens PPT, MSc, I. Matthijssen MD, PhD, I. Russell MD; R. Severijnen MD, PhD, N. Schalij-Delfos MD, PhD, P. van Schie PPT, PhD, M. Schoenmakers PPT, PhD, F. Sleijpen PPT, MPT, A. Vermeulen PPT, and L. van Vlimmeren PPT, PhD. We also want to thank N. van Meeteren, PT, PhD and R. van Dolder, MT, MSc, for helpful advice in the designing of the study and J. van der Net, PPT, PhD for commenting on the final version of the manuscript.

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APPENDIX 3.1

Summary Round 2: Results of rating clinical diagnostic criteria

Symptomatic asymmetry	Mean	Median	SD
Developmental dysplasia of the hip			
Unilateral pROM hip abduction <70 (in flexion-abd-exorot)	**4.55**	**5.0**	**0.52**
Leg lenght difference (Galeazzi)	**4.18**	**4.0**	**0.75**
Posture of one leg > adduction/endorotation/extension	**3.89**	**4.0**	**0.78**
Asymmetrical skin folds in inguinal and upper thigh region	**3.00**	**3.0**	**1.32**
Unilateral leg less active	**2.56**	**3.0**	**0.73**
Perinatale fracture of the clavicle			
Unilateral arm less active	**4.45**	**4.0**	**0.52**
Pressure pain (first weeks only)	**4.18**	**4.0**	**0.98**
Homolateral lateroflexion of the head	**3.75**	**3.5**	**0.89**
Palpable thickness in clavicle	**3.63**	**4.0**	**1.41**
Obstetric brachial plexus palsy			
Unilateral loss of function of the arm	**4.80**	**5.0**	**0.42**
Unilateral arm less active	**4.43**	**5.0**	**0.79**
Position unilateral arm more elbow extension and shoulder endorotation (C5-7)	**4.38**	**4.5**	**0.74**
Asymmetric response on Moro-reflex	**4.36**	**4.0**	**0.50**
Asymmetric recoil reaction in arms	**3.63**	**4.0**	**0.92**
Asymmetric palmar grasp reaction	**3.29**	**4.0**	**1.60**
Asymmetric traction response in arms	**3.14**	**3.0**	**1.35**
Asymmetric response in arms in pull-to-sit manoeuvre	**3.14**	**3.0**	**1.35**
Preference heterolateral rotation of the head	**3.13**	**3.0**	**0.99**
Cervical rotation not restricted	**3.00**	**3.0**	**0.93**
Ocular disorders			
Poor fixation and following objects (not age-appropriate)	**4.67**	**5.0**	**0.49**
Difficult to make eye contact	4.58	5.0	0.51
Nystagmus	**4.33**	**4.0**	**0.65**
Wandering eye movements	3.88	4.0	0.64
No optical blink	3.44	4.0	1.13
Strabismus (beyond 3 months)	**3.22**	**3.0**	**0.83**
Startle-like reaction on unexpected matters	2.67	3.0	1.00
Doll's head phenomenon	2.67	3.0	1.22
Horizontal Vestibular Linear Reaction (optokinetic provocation) abnormal	2.44	2.0	1.13

Symptomatic asymmetry	Mean	Median	SD
Central nervous system disorder			
Abnormal movement patterns	**4.70**	**5.0**	**0.48**
Increased or decreased passive tone	**4.50**	**5.0**	**0.97**
(Unilateral) loss of variation and dissociation in movement patterns (e.g. General Movements)	4.43	5.0	0.79
Persistent Asymmetric Tonic Neck Reflex (ATNR)	**4.33**	**4.5**	**0.82**
Asymmetric posture increasing during movement	3.57	4.0	0.98
Abnormal response on postural reactions	3.43	3.0	1.62
Asymmetry in palmar grasp reflex/reaction	3.00	3.0	1.15
Asymmetry in plantar grasp reflex	2.86	3.0	1.35
Malformation of the cervical spine			
Asymmetry persisting in all postures	**4.73**	**5.0**	**0.49**
Cervical scoliosis	4.27	4.0	0.79
Abnormal (asymmetric) appearence of the neck (webbing, l'homme sans cou)	4.13	4.0	0.41
Post partum immediately visible	3.88	4.0	0.82
Malformation of the thoraco/lumbar spine			
Non-correctable scoliosis (passively)	**4.73**	**5.0**	**0.47**
Scoliotic posture	4.00	4.0	0.93
Asymmetric response on Galant reaction	3.80	4.0	0.79
Gibbus (in horizontal suspension)	3.00	3.0	1.07
Persistent skin folds concave side, visible in all positions	2.63	3.0	0.92
Congenital muscular torticollis			
Asymmetric posture of the neck with heterolateral rotation, homolateral head-tilt and possibly persistency or increase of that posture in all positions, hyperextension	**4.58**	**5.0**	**0.51**
Pseudotumor in the m.SCM palpable	**4.33**	**4.0**	**0.50**
The condition appears 1-2 weeks post partum	**4.33**	**4.0**	**0.71**
Restricted aROM and pROM of the neck in opposite direction	4.11	4.0	0.78
Pseudotumor m.SCM visible	3.78	4.0	0.97
pROM in opposite direction >10 degrees restricted	3.78	3.0	0.97
Asymmetric reaction in head at pull-to sit manoeuvre	2.89	3.0	1.36
Skin rash homolateral in neck folds	1.88	2.0	0.83
Craniosynostosis			
Abnormal head shape post partum immediately visible and increasing	**4.29**	**5.0**	**1.25**
Trapezoid head shape (lambdoid suture)	**3.90**	**4.0**	**1.10**
Deviant growth curve for circumference of the skull	3.78	4.0	0.97
Palpable thickening of a cranial suture	2.89	3.0	1.17
Homolateral inferior tilt of the posterior skull base	**2.71**	**3.0**	**1.50**

Appendix 3.1 continues on next page

Appendix 3.1 – *continued*

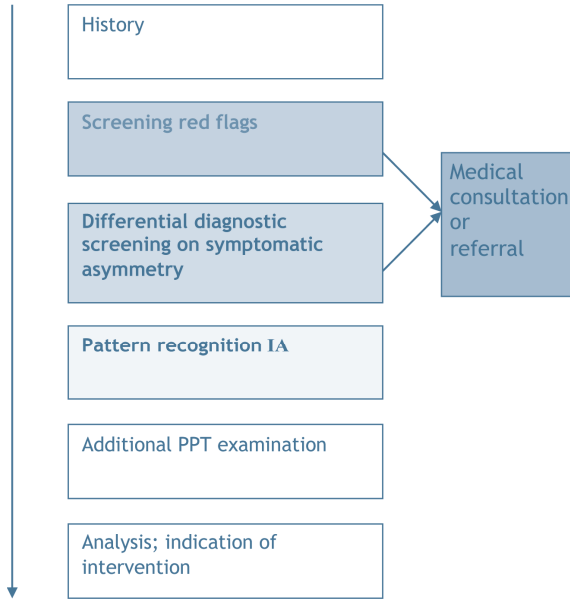
Symptomatic asymmetry	Mean	Median	SD
Hearing disorder			
Reaction on sound not age-appropriate	**4.45**	**5.0**	**0.52**
No acoustical blink	**4.20**	**4.0**	**0.79**
No vocalisation in interaction (beyond 2 months)	3.88	4.0	0.64
Startle-like reaction on unexpected matters	2.63	3.0	0.92
Abnormal shaped auricle	1.75	1.5	0.89

Criteria in **bold face** have been selected in the concept version of the screening instrument after Round 2. pROM = Passive range of motion; C5-7 = 5th to 7th cervical nerves; m.SCM = Sternocleidomastoid muscle; aROM = Active range of motion.

APPENDIX 3.2A

Screening instrument

Diagnostic process in differential diagnostics of symptomatic asymmetry from idiopathic asymmetry



Red flags	Hints for disease or disorder
General history	
Severe pain	Fractures, Osteomyelitis; Retropharangeal abscess
Vomiting, drowsiness	Increased intracranial pressure
Trauma	Intracranial injury
Seizures/convulsions	Epilepsy; Increased intracranial pressure; Peroxismale torticollis
Acute onset	Infection; Abcess; Grisel syndrome
Stridor	Vascular ring
Dyspnoea	Vascular ring; Cardiac problem
Reflux	Sandifer syndrome; Pathological gastroesophageal reflux
Fever	Infection; Abcess
Specific examination	
Sunset phenomenon	Increased intracranial pressure
Bulging fontanel	Increased intracranial pressure
Dysmorphic features	Syndrome (in general)
Lymphadenopathy	Infection; Pre-symptoms JIA
Abnormal course	
Increasing head tilt	Infection; Tumor
Recurrent episodes	Benign paroxysmal torticollis

Appendix 3.2A continues on next page

Appendix 3.2A – *continued*

	Symptomatic asymmetry	Clinical diagnostic criteria	
	Possible diagnosis (incidence/1000)	Most relevant findings	Additional relevant findings
1	Developmental dysplasia of the hip (40)	Unilateral pROM hip abduction <70°	Leg length difference (Galeazzi)
2	Perinatal fracture of the clavicle (35)	Unilateral arm less active	Pressure pain
3	Congenital muscular torticollis (20)	Persistent posture of the neck with heterolateral rotation, homolateral head-tilt, and possibly hyperextension	Pseudotumor in the m.SCM, 1-2 weeks post partum
4	Obstetric brachial plexus palsy (4)	Unilateral loss of function in the arm	Asymmetric response on MORO-reflex
5	Ocular disorder	Poor fixation and following objects (not age-appropriate)	Strabismus and/or nystagmus
6	Central nervous system disorder (2)	Abnormal movement patterns	Increased or decreased passive tone; Persistent ATNR
7	Malformation of the spine	Asymmetry persisting in all postures	Non-correctable scoliosis (actively nor passively)
8	Hearing disorder	Reaction on sound not age-appropriate	No acoustical blink
9	Craniosynostosis (Lambdoid suture) (0.03)	Plagiocephaly post partum immediately visible and increasing	Trapezoid head shape; Downward sloping of the posterior skull base
10	Congenital abnormalities or malformations musculoskeletal (not spine) and/or chromosomal	Dysmorphic features (in general)	

IA = Idiopathic asymmetry; PPT = Pediatric physical therapy; JIA = Juvenile idiopathic arthritis; pROM = Passive range of motion; m.SCM = Sternocleidomastoid muscle; ATNR = Asymmetric tonic neck reflex.

APPENDIX 3.2B

Symptomatic asymmetry classification scheme

Possible differential diagnoses in young infants (<6 months of age)

International Classification of Diseases	Localisation	Diagnosis specification
Prenatal origin		
Diseases of the eye and adnexa		• Congenital nystagmus • Restrictive or paralytic strabismus • Congenital homonymous hemianopia • Monocular blindness
Diseases of the ear and mastoid process		• Unilateral deafness or partial hearing loss
Congenital malformations, deformations musculoskeletal	M.Sternocleidomastoid	• Congenital muscular torticollis
	Spine	• Klippel Feil syndrome • Sprengels deformation • Hemivertebrae • Hemiatlas • Congenital scoliosis
	Other	• Craniosynostosis (frequently part of syndrome) • Aplasia/hypoplasia facies/neck/ trunk muscles
Congenital malformations, deformations and chromosomal abnormalities over all	Localised	• Laryngomalacia • Tracheomalacia • Vascular ring
	Generalised	• Syndromes, e.g. Goldenhar, hemihypertrophia
Perinatal origin		
Disease of the nervous system	Central	• Tone regulation disorder (hemiplegia)
	Peripheral	• Obstetric Brachial Plexus Palsy • Facial Palsy
Childbirth		• Fracture of the clavicle, humerus
Postnatal origin / acquired		
Infectious diseases	Oto-rhino-laryngology	• Grisel syndrome after pharyngitis e.g.(>6 months) • Retropharyngeal abscess • Lymfadenopathy neck region

Appendix 3.2B continues on next page

Appendix 3.2B – *continued*

International Classification of Diseases	Localisation	Diagnosis specification
	Other	• Osteomyelitis cervico-brachial region • Soft tissue infections • Pre-symptoms Juvenile Idiopathic Arthritis (>6 months)
Neoplasms	Head/neck region	• Posterior fossa tumor • Intramedullar tumor (astrocytoma) • Cerebellar tumor
Diseases of the respiratory system		• Compulsive posture due to dyspnoea • Tracheostoma
Diseases of the nervous system		• Epilepsy • Syringomyely • Increased intracranial pressure
Diseases of the digestive system		• Pathologic gastro-esophageal reflux • Peroxysmal torticollis • Sandifer syndrome
Diseases of the musculoskeletal system		• Developmental dysplasia of the hip
Injury		• Trauma • Abuse
External causes (complications)		• Status post surgical intervention • Status post elongated drip-feeding • Ventriculo-Peritoneal drain

APPENDIX 3.2C

Explanation differential diagnostic screening instrument on symptomatic asymmetry in young infants

Objective

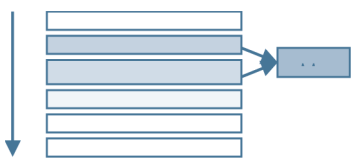
A differential diagnostic screening instrument for pediatric physiotherapists (PPTs) to distinguish a symptomatic asymmetry (SA) in the clinical evaluation of young infants (< six months of age) with an asymmetric head posture, examining red flags and clinical diagnostic criteria (CDC) at the first examination of the infant. The red flags and CDC can be used to formulate and verify hypotheses about the origin of the asymmetry. If no red flags or CDC are found, the diagnosis idiopathic asymmetry (IA) can be stated 'per exclusionem'. Subsequently, additional examination procedures are needed for the continuing PPT clinical reasoning process of both SA and IA and to determine an indication of the need for intervention.

Content

The instrument comprises a chart and a short instruction to examine CDC. The front of the chart consists of a scheme of the differential diagnostic (DD) process, red flags to excluded serious pathology, and clinical diagnostic criteria (CDC) to detect the most frequent SA diagnoses. On the back, a comprehensive classification scheme can be found with all possible diagnoses that may lead to an SA. In this short manual the use of the chart will be explained.

CHART FRONT

The figure at the top left of the sheet illustrates the DD process. If, with the help of this instrument, red flags or CDC are found by the PPT, medical consultation or referral will be needed to confirm the diagnosis in most cases.



Red flags

At the top right of the sheet, the red flags are listed, subdivided in (1) symptoms asked for in the general history interview, (2) signs that were seen during examination, and (3) signs of an abnormal course of the asymmetric posture. The eight (red and in bold printed) red flags are very important and are always an indication for referral. The remaining seven red flags can be considered as relatively important. The PPT has to make a consideration, depending on the context, whether or not consultation is needed.

Red flags
General history
Severe pain
Vomiting, drowsiness
Trauma
Seizures/convulsions

Clinical diagnostic criteria to detect SA

The table with 21 CDC to detect the 10 SA diagnoses with the highest incidence is at the bottom of the sheet. To facilitate the DD process, the table starts with the diagnosis with the highest incidence (between brackets the known incidence of the disease per 1000 infants). The most relevant CDC are in the third column, the CDC in the fourth column are additional.

	Symptomatic asymmetry	Clinical diagnostic criteria	
	Possible diagnosis (incidence/1000)	Most relevant findings	Additional relevant findings
1	Developmental dysplasia of the hip (40)	Unilateral pROM hip abduction <70°	Leg length difference (Galeazzi)

The CDC can easily and efficiently be detected in the first examination of an infant with an asymmetric head posture, order at random, but preferably starting with the hands off examination, followed by the hands on manoeuvres. The set of CDC is not imperative, the PPT can add his own test if he feels the need to.

CHART BACK

On the back of the chart, a comprehensive overview is given of current known disorders and diseases possibly leading to a SA, classified according to the International Classification of Diseases (ICD10) and stratified by time of origin (pre-, peri-, or postnatal).

Instructions to examine CDC

Only specific manoeuvres are described.

Developmental dysplasia of the hip

CDC1: pROM can best be examined symmetrically in supine position, moving the hips to flexion-exorotation-abduction position.

CDC2: Leg length is best examined with the Galeazzi-test, by looking at the symmetry of the height of the knees when the infant is supine with both legs flexed and the feet next to each other on the surface. A positive Galeazzi sign (unequal knee heights) suggests a unilaterally dislocated hip.

Congenital muscular torticollis

CDC2: Palpation of the sternocleidomastoid muscle over the full length. A pseudotumor is usually not palpable in the first two weeks after birth.

Central nervous system disorder

CDC1: Special attention to left/right differences in movement patterns of the arms.

CDC2B: An asymmetric tonic neck reflex (ATNR) that persists beyond the first months is abnormal. A strongly pronounced ATNR is suspect at all ages.

Craniosynostosis

CDC2A: From a cranial view, the trapezoid-shaped head can be seen in infants with a premature closure of one of the lambdoid cranial sutures. The DD from (non-synostotic) deformational plagiocephaly (DP), with a more parallelogram-shaped head is important. The position of the ear is different too. If one of the other sutures is involved, another shape has to be expected, quite different from the DP.

CDC2B: From a posterior view an inferior tilt of skull base can be seen, resulting in inferior displacement of the homolateral ear.

Symptomatic asymmetry

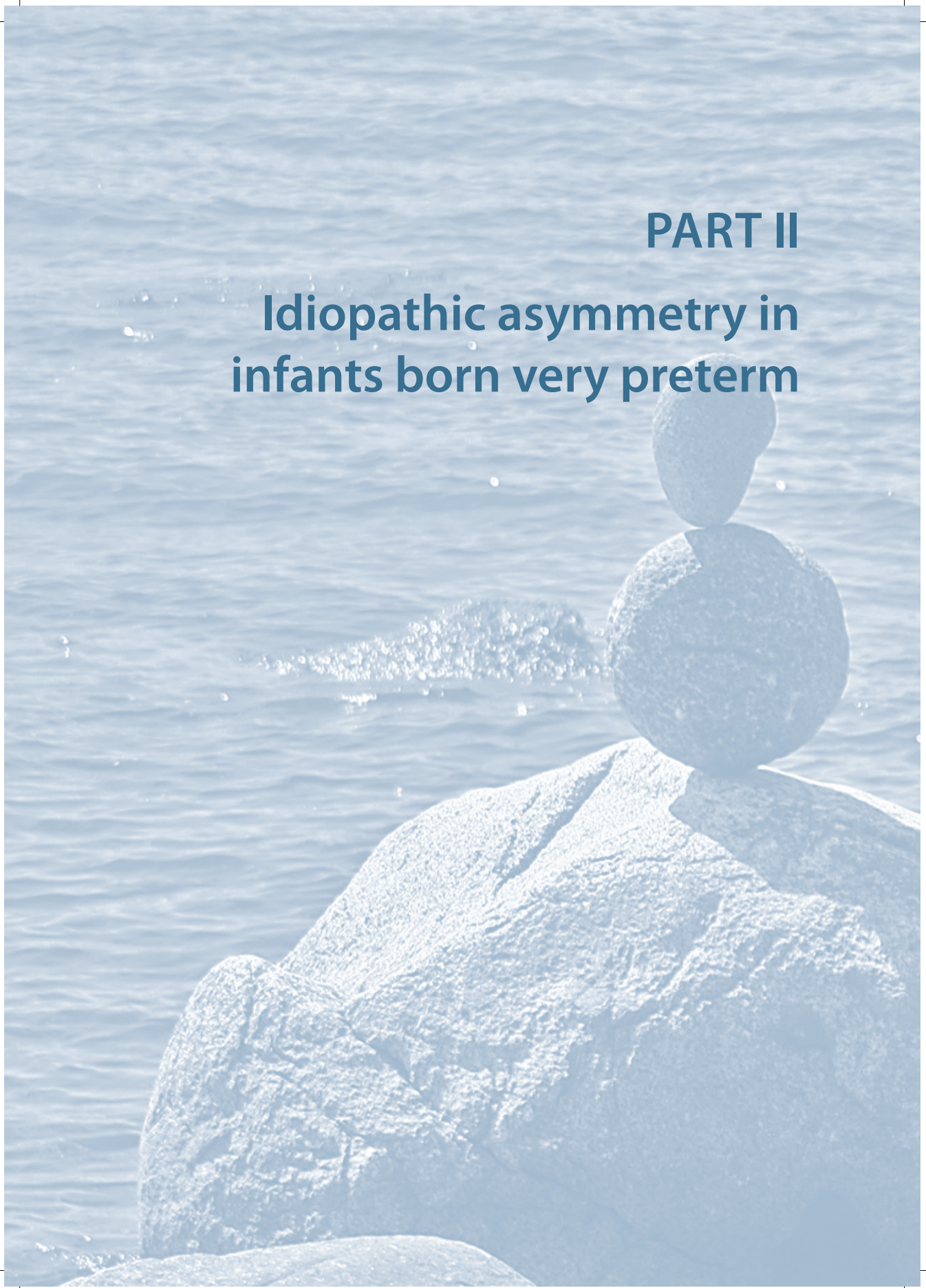
In case the PPT examination of the CDC or the presences of a red flag indicates that an SA diagnosis must be considered, the infant has to be referred for medical diagnostics. In some cases consultation of a physician will suffice, for example in diagnosis 2 and 3: A *Fracture of the clavicle* might have been the origin of the head preference, but only in the first weeks. *Congenital muscular torticollis* can first be treated by a PPT, but the strategies may differ from the intervention to normalise an IA like postural torticollis. Only if treatment is not effective enough, referral to a medical specialist is needed to consider surgical intervention.

In case of an *Obstetrical brachial plexus palsy* or a *Central nervous system disorder*, the infants usually need to be treated by a PPT, but firstly the diagnosis has to be confirmed by a medical specialist.

Idiopathic asymmetry

If no indication for SA has been found, the asymmetry can be classified as idiopathic. IA is the most prevalent condition in young infants. Several localisations of IA can be distinguished, like deformational plagiocephaly, postural torticollis, and postural scoliosis. This DD instrument does not cover that aspect.

The DD instrument for SA in young infants has been developed by Dutch medical specialists and pediatric physiotherapists, based on review of the literature and a Delphi-study on expert (content) validity. In future research, (predictive) validity and reliability will be investigated.



PART II

Idiopathic asymmetry in infants born very preterm

Chapter 4

Prevalence and predictors of idiopathic asymmetry in infants born preterm

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Early Hum Dev 2012;88(6):387-92.
Epub 2011 Nov 1.

ABSTRACT

Objective: An idiopathic asymmetry in posture of the head is recognized as a risk factor to develop a deformational plagiocephaly (DP). In our neonatal follow-up clinic, an idiopathic asymmetry is often observed in infants born preterm at term-equivalent age (TEA).

Aims: To explore (1) the prevalence of an idiopathic asymmetry in 192 infants (gestational age ≤32.0 weeks) at TEA and 6 months corrected age (CA), (2) whether demographical, perinatal, and medical factors were predictors of the asymmetry, and (3) differences in motor maturation between infants with and without asymmetry.

Methods: In a retrospective study, frequencies of idiopathic asymmetry and DP, putative predictors, and Alberta Infant Motor Scale scores at 6 months CA were abstracted and analyzed with Chi^2, Mann-Whitney, logistic regression and T-test.

Results: The prevalence rate of a positional preference of the head at TEA was 44.8% (n=86), 10.4% (20/192) had a DP at TEA and 13% (25/192) at 6 months CA. Positional preference, multiple birth and male gender predicted the presence of DP ($p<.05$, odds ratio 3.0, 3.2, and 3.1 respectively). Gross motor maturity at 6 months CA was less developed in infants with a positional preference at TEA compared to preterm norms ($p=0.01$).

Conclusions: The high prevalence of a positional preference in infants born preterm at TEA requires extra alertness to prevent the development of a DP, especially in boys and twins. Although, considering the lower prevalence of plagiocephaly at 6 months CA, therapists should be aware of over treating these infants.

INTRODUCTION

The increasing prevalence of an asymmetry in posture and/or shape of the head in young infants has been attributed to the successful initiation of the "Safe Sleeping" Campaign to prevent Sudden Infant Death Syndrome.[1-6] If the asymmetry is not a symptom of an underlying pathology, it can be defined as an idiopathic asymmetry. Features of an idiopathic asymmetry are a so called 'positional preference', defined as a condition in which the infant's head is turned toward one side most of the time, with restricted active movement to the other side[1,7] and/or a deformational plagiocephaly (DP). A too strong positional preference of the head in the first weeks of life or a frequently seen distinct plagiocephaly at birth, probably associated with a constrained intra-uterine position, may secondarily cause any asymmetry in shape and/or function of the entire body.[8-10] In recent literature, the prevalence of asymmetry varies between 13 and 22%.[9,11] A prospective study showed that 17.9% of a cohort of healthy full-term newborns (n=380) had a positional preference at the age of 7 weeks, whereas 22.1% was found to have a DP.[8] In many studies, environmental factors like positioning and parental care practices are described as risk factors regarding this phenomenon[8,11,12]; mild prematurity has been described as a risk factor too.[12]

Developmental specialists in our neonatal follow-up clinic observe quite often a positional preference at term-equivalent age (TEA) in infants born preterm. In order to determine which infants need early intervention, this phenomenon needs further exploration. The neonatal intensive care unit environment, an elongated, laterally flattened head shape, and a different course of gross motor maturation in the early months of life are likely to play a role in the motor behavior and postural control of premature infants.[13] The main objectives of the present study were to explore the magnitude of this asymmetrical appearance and to examine if any predictors of this asymmetry could be detected in a cohort of infants born preterm. The objectives were:

1. To determine the prevalence of a positional preference and DP in a cohort of infants born preterm with a gestational age (GA) ≤32.0 weeks, around TEA and at six months corrected age (CA). We hypothesized that the prevalence of both positional preference and DP would be higher than in full-term born infants.
2. To examine predictors (in demographical, perinatal and medical factors and in motor behavior at TEA) of a positional preference and DP at TEA and the presence of these at six months CA. Besides known factors from the literature in full-term born infants, we expected the duration of need for mechanical ventilation during

admission to be a factor that influences variation in positioning, as well as suspect cranial ultra-sound findings.

3. To explore differences in gross motor maturation at six months CA between infants with and without positional preference at TEA, and in infants with and without DP at six months CA.

METHODS

Design and subjects

In a retrospective, longitudinal design, infants born preterm (GA≤32.0 weeks) in 2006 were included. They were survivors of a level three neonatal intensive care unit and visited the neonatal follow-up clinic. The first visit was at TEA, the second at six months CA. Data were abstracted from individual electronic patient files, medical correspondence and pediatric physical therapy charts, and checked for completeness with the Netherlands Perinatal Registry (www.perinatorg.nl). The Institutional Review Board and Ethics Committee approved the present study.

According to the neonatal registration of the hospital, 495/559 (88.6%) infants survived the neonatal intensive care period. Of these, the proportion of infants born preterm with a GA≤32.0 weeks was 48.9% (n=242). Eighty six percent of them (n=208) visited the neonatal follow-up clinic at TEA as well as at six months CA. The parents of 34 infants choose not to participate in the follow-up program, or were only seen at TEA. The reasons of non-participation were not always documented, but for most parents the travelling distance was the main reason to prefer follow-up in a district general hospital, close to their home. Sixteen infants were excluded due to a diagnosis of a symptomatic asymmetry[14,15]: four with a central nervous system disorder (afterwards diagnosed as two infants with spastic bilateral cerebral palsy, and two with severe psychomotor retardation), four with a congenital malformation, four with a sensory system disorder (auditory or visual), three with developmental dysplasia of the hip and one with an obstetric brachial plexus lesion. The remaining 192 infants made up our study population (see Figure 4.1).

Demographical data (gender, ethnicity), perinatal data (GA, birth weight [BW], mode of delivery, multiple birth, Apgar score at 5 minutes), and medical data (duration of the neonatal intensive care/high care unit stay, duration of need for mechanical ventilation, chronic lung disease, necrotizing enterocolitis, and cranial ultrasound findings during admission like intraventricular haemorrhage [grades II-IV][16] and periventricular

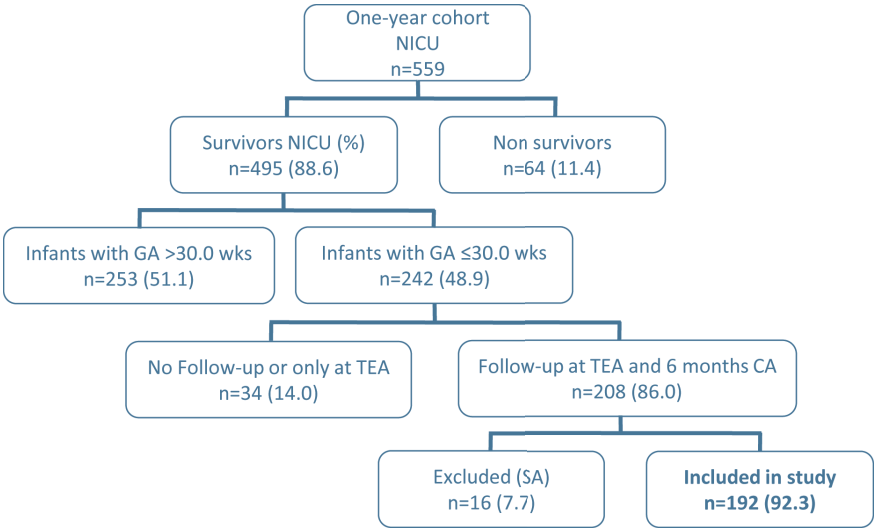

Figure 4.1 Flowchart of the cohort of infants admitted to the neonatal intensive care unit (NICU) in one year. GA = Gestational age; wks = Weeks; TEA = Term equivalent age; CA = Corrected age; SA = Symptomatic asymmetry.

leukomalacia [grades I-III])[16,17] were recorded. All infants had weekly cranial ultrasound examinations during admission and again at TEA. Chronic lung disease was defined as the need for oxygen at 36 weeks post menstrual age.[18] These medical factors were considered relevant for their influence on the variability of positioning and movement patterns.[19,20] Ethnicity was defined based on the background of the parents according to Statistics Netherlands (www.cbs.nl): Western (including Dutch) or non-Western (one or both parent(s) being born abroad). We compared BW to the reference curves for BW by GA, gender and parity of the Netherlands Perinatal Registry.[21]

Neonatal follow-up clinic

In our hospital, one of the largest level three neonatal intensive care units of the country, the neonatal follow-up clinic is organized in such a way that two experienced developmental specialists (a neonatologist and a pediatric physical therapist), examine the infants simultaneously during a 20-minutes-session. The neonatologist performs the medical examination and the physical therapist the motor assessment. There are two teams who cooperate in this way for more than 15 years. The teams consult each other in case of doubt. The starting point is that the infants are examined by the same team at both visits.

An asymmetry in posture and/or movement of the head was registered if, during the examination, the infants' head was turned in the supine position toward one side most of the time and active movement to the other side was restricted, or the rotated position of the head could not be maintained. In prone position the positional preference had to be consistent. A DP was defined as a unilateral occipital flattening of the skull and/or ear deviation (the homolateral ear is typically displaced anteriorly with respect to the other ear). Other cranial deformations like scaphocephaly or brachycephaly were not defined as DP. The DP was observed from a cranial and posterior view. No objective measurements were applied.

The intrinsic motor behavior at TEA was qualified by using the GMs observation technique.[22-24] Because the GMs are an indicator of variation in motor behavior, we expected that infants with (mildly) abnormal GMs are more likely to have a positional preference or DP. Normal GMs of full-term born infants at term age are described as slow-to-moderate, writhing-type movements of the whole body, with a fluent character, a small-to-moderate amplitude and variability in repertoire.[23-25] GMs of infants born preterm occasionally have a larger amplitude and a faster speed.[23] The inter-tester reliability is high (0.87-0.93). The specificity of the GMs assessment is best at the age of three months (>0.82), but lower during the writhing movement period.[23] The examiners classified the GMs as normal, mildly abnormal (lack of fluency, poor repertoire) or definitely abnormal (cramped-synchronized). All examiners were trained, certified and experienced in this observation method.

Gross motor maturation was examined with the Alberta Infant Motor Scale (AIMS) at six months CA. The AIMS is an observation instrument, norm-referenced and performance based. Reliability and validity are high (>0.90).[26] In 2006, van Haastert et al. published adjusted norms for Dutch infants born preterm.[27]

Data analysis

Statistical analysis was conducted using SPSS software (version 17.0; SPSS, Inc, Chicago, Illinois). Descriptive data were generated for frequencies, proportions, means, standard deviations (SD), or medians and interquartile ranges, if appropriate, on all demographical, perinatal and medical data of the cohort, and on the GMs classification at TEA. GA and BW are seen as influential factors on the development and health condition of preterm born infants. To see whether these factors were effect modifiers on putative predictors, we analyzed differences in characteristics between infants born

with a GA<30.0 weeks or ≥30.0 weeks, and infants with a BW <1000 grams or ≥1000 grams using a Chi²-test or a Mann Whitney U-test.

To explore predictors in demographic, perinatal and medical factors predicting the presence of an idiopathic asymmetry at TEA or a DP at six months CA, univariate analysis was performed on variables with a frequency >10 using cross tabs, Chi²-tests and logistic regression analysis. Variables with a *p*-value <.20 were included in a multivariate logistic regression model. Variables with a cell count in the cross tabs <5 were not included. The significance level for removal out of the model was set at *p*>.10.

Z-scores of the raw scores on the AIMS were computed both in accordance with the norm (full-term born) population[26] and with a preterm population.[27] A T-test for independent samples was conducted to compare the scores on the AIMS for infants with and without idiopathic asymmetry at TEA, as well as for infants with or without DP at six months CA. A *p*-value of <.05 was considered significant.

RESULTS

In the neonatal follow-up clinic, 192 infants with a mean (SD, range) GA of 29.9 weeks (± 1.67, 24.9-32.0) and a mean (SD, range) BW of 1282 grams (± 347, 590-2390) were seen at least twice during the first year of life. Of those infants, 56% were born by Caesarean section, 60% were male and 34% were part of a multiple birth (mostly twins, one triplet). The proportion of very preterm born infants (GA<30.0 weeks) was 38.5% (74/192) of which four were extremely preterm (GA<26.0 weeks). The proportion of extremely low BW (<1000 grams) infants was 19.8% (38/192) and very low BW (<1500 grams) 54.7% (105/192). Only 2 infants had a birth weight <-2SD, classified as small for GA. From the group with a GA<30 weeks, 47.3% (35/74) had a BW<1000 grams. Both the duration of the neonatal intensive care/high care stay, and the duration of need for mechanical ventilation showed a large range and had a skewed distribution (median 16 days (range 2-137) and 0 days (range 0-40) respectively), but was significantly longer in infants with a GA<30 weeks or a BW<1000 grams. Subependymal haemorrhage, intraventricular haemorrhage grade II, periventricular leukomalacia grade I, and chronic lung disease, were recorded in >10 infants. All other medical factors had a lower frequency (see Table 4.1). Infants with a GA<30 weeks had significantly more often an intraventricular haemorrhage grade II, while infants with a BW<1000 grams had more often a periventricular leukomalacia grade I. In both groups, chronic lung disease was more present compared to infants with a higher GA and BW.

Table 4.1 Characteristics of 192 infants born ≤32.0 weeks of gestation

Idiopathic asymmetry 86 (44.8) No idiopathiac asymmetry 106 (55.2)	All infants	Infants with GA <30 wks	Infants with GA 30—≤ 32.0 wks	*p*-value	Infants with BW <1000 grs	Infants with BW ≥1000 grs	*p*-value
Numbers (%)	192 (100)	74 (38.5)	118 (61.5)		38 (19.8)	154 (80.2)	
Gender (%)				.16			.41
Male	115 (59.9)	49 (66.2)	66 (55.9)		25 (65.8)	90 (58.4)	
Female	77 (40.1)	25 (33.8)	52 (44.1)		13 (34.2)	64 (41.6)	
Mode of Delivery (%)				.43			.04*
Vaginal	84 (43.7)	35 (47.3)	49 (41.5)		11 (28.9)	73 (47.4)	
Cesarean section	108 (56.3)	39 (52.7)	69 (58.5)		**27 (71.1)**	81 (52.6)	
Ethnicity (%)				.41			.88
Western	173 (90.1)	65 (87.8)	108 (91.5)		34 (89.5)	139 (90.3)	
Non-Western	19 (9.9)	9 (12.2)	10 (8.5)		4 (10.5)	15 (9.7)	
Multiple births (%)				.52			.41
Single	127 (66.1)	51 (68.9)	76 (64.4)		23 (60.5)	104 (67.5)	
Multiple	65 (33.9)	23 (31.1)	42 (35.6)		15 (39.5)	50 (32.5)	
Cranial US findings (%)							
SEH	12 (6.3)	4 (5.4)	8 (6.8)	-	1 (2.6)	11 (5.7)	-
IVH grade II	19 (9.9)	**12 (16.2)**	7 (5.9)	.03*	5 (13.2)	14 (9.1)	.54
IVH grades III,IV	10 (5.2)	3 (4.1)	7 (5.9)	-	2 (5.3)	8 (5.2)	-
PHVD	4 (2.1)	1 (1.4)	3 (2.5)	-	1 (2.6)	3 (1.9)	-
PVL grade I	23 (12.0)	11 (14.9)	12 (10.3)	.37	**9 (23.7)**	14 (9.2)	.02*
cPVL grades II, III	9 (4.7)	5 (6.8)	4 (3.4)	-	3 (7.9)	6 (3.9)	.38
Other medical factors (%)							
Chronic lung disease	36 (18.8)	**31 (41.9)**	5 (4.2)	.00*	**23 (60.5)**	13 (8.4)	.00*
NEC	6 (3.1)	4 (5.4)	2 (1.7)	-	4 (10.5)	2 (1.3)	-
V-P shunt insertion or Rickham reservoir	3 (1.6)	3 (4.1)	0 (	-	3 (7.9)	0 (	-
Median duration of NICU/HC stay in days (IQR)	16 (20)	**32 (39.5)**	11.5 (10.3)	.00**	**58.5 (38.5)**	14 (13)	.00**
Median duration of need for mechanical ventilation in days (IQR)	0 (4)	**4 (12)**	0 (2)	.00**	**9.5 (21)**	0 (3)	.00**

GA = Gestational age; BW = Birth weight; wks= Weeks; grs = Grams; US = Ultrasonography; SEH = Subependymal haemorrhage; IVH = Intraventricular haemorrhage; PHVD = Post-haemorrhagic ventricular dilatation; (c)PVL = (Cystic) periventricular leukomalacia; NEC = Necrotizing enterocolitis; VP = Ventriculo-peritoneal; NICU = Neonatal intensive care unit; HC = High care; IQR = Inter quartile range. */** and in bold difference significant on $p<.05$ level tested with Chi square-test /Mann Whitney-U-test.

Prevalence of positional preference and deformational plagiocephaly

At TEA, the prevalence rate of a positional preference of the head was 44.8% (86/192 and 91% to the right side); 10.4% (20/192) of the infants had an, often minimal, DP. At six months CA, none infant with a positional preference was reported but in 13% (25/192) a DP was observed. In ten infants, the DP reported at TEA was resolved, while in eight infants no asymmetry was reported at TEA (see Figure 4.2). Four infants, two twins, had a corrective helmet at the second follow-up visit.

Predictors for idiopathic asymmetry

In the univariate analysis, with a positional preference at TEA as dependent variable (n=86), only periventricular leukomalacia grade I and intraventricular haemorrhage grade II met the inclusion criteria of the multivariate regression model. Both variables stayed in the model, but were not a significant factor for the presence of a positional preference (p<.05). If positional preference with DP at TEA was chosen as dependent

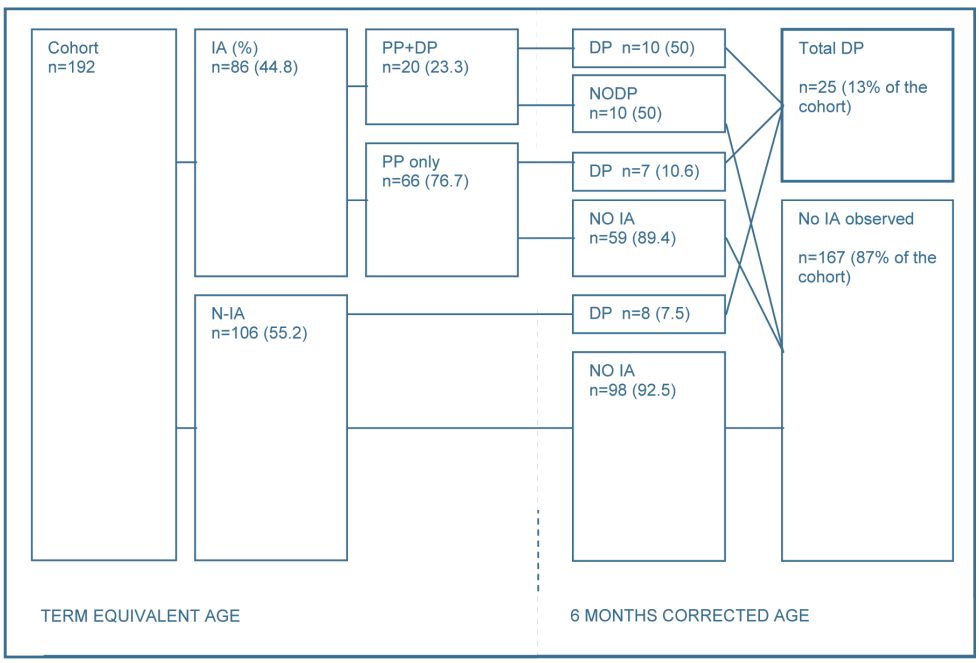

Figure 4.2 Prevalence of idiopathic asymmetry (IA), positional preference (PP) and/or deformational plagiocephaly (DP) in the cohort very preterm born infants at term-equivalent age and 6 months corrected age. n = Number.

variable (n=20), only chronic lung disease, was significantly associated (*p*=.003; odds ratio (OR) 4.4 (95% confidence interval (CI) 1.66-11.61).

GMs were described in 145/192 (75.5%) infants. Only one infant had abnormal GMs at TEA. Mildly abnormal observed GMs at TEA were seen in 27/145 (19%) infants. No significant association was found with a positional preference at TEA. The number of infants with mildly abnormal GMs and a DP was too small for the Chi^2 test (<5).

Univariate analysis showed that the only significant factors predicting the presence of a DP (n=25) at six months CA were male gender (*p*=.03) and multiple birth (*p*=.02). In a multivariate model, both variables were significant predictors with an adjusted OR of 3.2 (95% CI 1.14-9.15) and 3.1 (95% CI 1.28-7.31), respectively (see Table 4.2).

Because the association between positional preference and DP is obvious, this was separately tested as a predictor for the presence of DP at six months CA, with an OR of 3.0 (95% CI 1.23-7.39; *p*=.02).

Gross motor maturation

At six months CA, 13.5% (n=26) of the infants were not able to perform the total AIMS test, due to being irritable or tired. Using the adapted norms for (Dutch) infants born preterm[27], the mean Z-score of the remaining 166 infants who completed the AIMS was 0.51 and showed a significant difference between infants with and without idiopathic asymmetry at TEA (*p*=.01; Z=0.26, SD=1.10 versus Z=0.71, SD=1.21). Compared to the original AIMS-norm references, the mean Z-score was -1.17.[26] Between infants with and without DP at six months CA, no differences were found in gross motor maturation. See Table 4.3.

Table 4.2 Predictors of deformational plagiocephaly at 6 months corrected age

Included	Regression coefficient (SE)	Wald statistic	*p*-value	aOR	95% CI for aOR
Gender	1.17 (0.53)	4.84	.03	3.22	1.14-9.15
Multiple birth	1.12 (0.45)	6.33	.01	3.06	1.28-7.31
Constant	-3.19 (0.53)	35.57	.00		
Included	**Regression coefficient (SE)**	**Wald statistic**	***p*-value**	**OR**	**95% CI for OR**
Preferential posture at TEA	1.11 (0.46)	5.85	.02	3.02	1.23-7.39
Constant	-3.61 (0.78)	21.22	.00		

SE = Standard error; (a)OR = (Adjusted) odds ratio; CI = Confidence interval; TEA = Term-equivalent age.

Table 4.3 AIMS Z-scores at 6 months corrected age

	All infants (n=192)	IA at TEA (n=86)	No IA at TEA (n=106)	*p*-value	DP at 6mo CA (n=25)	No DP at 6 mo CA (n=167)	*p*-value
Mean CA in m (SD)	6.3 (1.1)	6.4 (1.1)	6.2 (1.2)		6.2 (1.0)	6.3 (1.5)	
Tested infants n (%)	166 (86.5)	75 (87.2)	91 (85.8)		21 (84)	145 (86.8)	
Z-score PT norm: mean (SD)	0.51 (1.18)	**0.26 (1.10)**	**0.71 (1.21)**	**.01***	0.39 (1.43)	0.52 (1.14)	.64
Z-score FT norm: mean (SD)	-1.17 (0.96)	-1.27 (0.98)	-1.05 (0.95)	.08	-1.20 (1.16)	-1.17 (0.93)	.89

AIMS = Alberta Infant Motor Scale; n = Number; IA = Idiopathic asymmetry; TEA = Term-equivalent age; mo = Months; CA = Corrected age; SD = Standard deviation; PT = Preterm; FT = Full-term. * and in bold difference significant on $p<.05$ level.

DISCUSSION

This retrospective cohort study of 192 infants born preterm, with a GA between 24.9 and 32.0 weeks, revealed a high proportion of infants with a positional preference at TEA (44.8%) compared to the 13-20% reported in full-term born infants[7,8,11], whereas in only 10.4% a DP was observed. At 6 months CA, DP is observed in 13% of the infants. In 5.2% the early DP was resolved. From the included demographical, perinatal, and other medical factors, only chronic lung disease increased the odds of having a DP at TEA, but not at 6 months CA. At six months CA, a DP was more often observed in males and multiplets. Infants with a positional preference at TEA are three times more likely to have a plagiocephaly at 6 months than infants without positional preference. No association was found between idiopathic asymmetry and the quality of GMs at TEA. A small difference was found in gross motor maturity at six months CA between infants with and without an idiopathic asymmetry at TEA, when compared to the Dutch preterm norms. Other putative early predictors in infant factors, like postural control and motor maturity at TEA, could not be investigated in this study.

The etiology of the high prevalence of a positional preference in infants born preterm is still unclear, but could theoretically be attributed to both environmental (intra- and extra-uterine) and infant factors.[13,28,29] The fact, that infants born preterm are subjected to extra–uterine gravity in an earlier stage of their neuromaturation than full-term born

infants, can be regarded as an environmental risk factor for developing a positional preference. Moreover, the infants might be approached merely from the right side during their hospital stay due to the position of satellite equipment at the right-hand side of the incubators in the neonatal intensive care unit. Right handedness of nurses and parents will increase the infants' orientation toward the right side, although a positioning scheme is used. Besides, there are a number of infant factors that theoretically could increase the risk of asymmetry. The neuromotor system plays a role in the postural control and variability of the intrinsic movements of all infants. In infants born preterm, immaturity of the system may lead to an asymmetrical performance and posture even when these infants are healthy.[13,29-32] A strong preference to turn the head to the right side and subtle asymmetries in fetal movements in infants born preterm have been described previously.[28,33-35] At TEA, infants born preterm have some variable differences in tone patterns compared to full-term newborns.[32] Biomechanical factors, like the ratio between a relatively large head compared to body weight and height, which we observe often in preterm born infants, may attribute to a high prevalence of positional preference in the first months of life.

In full-term born infants, the development of a DP is strongly associated with a positional preference of the head when awake or sleeping.[8] We did not find equally strong associations in our cohort of infants born preterm, who had proportionately a lower prevalence of DP at TEA and at 6 months CA. The prevalence of positional preference and DP are age-dependant. Hence, a part of the difference can be explained by a different age of the infants under study. The full-term born infants examined in the study of Boere-Boonekamp were between one and six months of age[7], in the van Vlimmeren cohort, they were examined shortly after birth and at seven weeks of age.[8] With the latter study, there was also a difference in the way DP was determined: Van Vlimmeren et al. quantified the asymmetry of the skull by means of plagiocephalometry[8,36], where we used visual observation only. This may explain another part of the difference. An environmental protective factor for the development of DP might be that during their stay in the neonatal intensive care unit, all infants are monitored and also placed in other positions than supine. Another difference with full-term born infants is that preterm born infants are more frequently monitored by health care professionals from birth onwards and their parents are made aware of the risk of DP at an early stage. Infant factors can be mentioned too: very young infants are not able to keep their head in the midline position and their head is turned sideways over the full range.[13] Finally, infants born very preterm are at risk for developing a scaphocephaly with flattening of the

skull on both sides, due to poor mineralization of the skull.[37,38] This head shape might hamper the infant to turn the head from one side to the other.

The duration of the need for mechanical ventilation was not a predictor for positional preference or DP, but in the infants with chronic lung disease the odds of having DP at TEA was more than four times higher. It is conceivable that these infants were sicker and were less moving during their extended hospital stay. However, for the presence of DP at six months CA, chronic lung disease was no longer a significant predictor, nor was a suspect cranial ultra-sound finding. Only two determinants were included in the prediction model for the presence of DP, multiple birth and male gender. Both have been described as a risk factor for DP in full-term infants too.[5,39] The frequency of multiple births is considerably higher in infants born preterm.

A priori, we hypothesized that less variability in the intrinsic motor repertoire would be associated with the presence of an idiopathic asymmetry at TEA. However, we found no difference in the quality of GMs between infants with and without a positional preference at TEA. The observation of the GMs at TEA was not a predictor for idiopathic asymmetry.

The finding that gross motor maturity at 6 months CA was significantly less well developed in infants who showed a positional preference at TEA was based on a well established preterm norm-population as published by van Haastert et al.[27], and not on the original AIMS norm-referenced values, because very preterm born infants show a different gross motor profile compared with term infants. Anyway, we did not find a significant difference in the mean level of gross motor maturity between infants with and without a DP at six months CA, which has been reported in studies with full-term born infants as well.[40,41] It is conceivable that a positional preference in preterm born infants diagnosed at TEA is a transient phenomenon according to the level of the neuromaturation, supported by the finding that these infants had a lower score on gross motor maturation at six months CA. Motor maturation however is a complex process, with inter- and intra-individual fluctuations over time in scoring patterns[42,43], which requires more than one measurement. We only had data of a single point assessment in this time frame of six months.

Other limitations in this study were: the retrospective design, which may have induced missing data and a less objective and standardized way of determination of the asymmetry, a lack of information about the stay in the community hospitals after discharge from the neonatal intensive care unit, the unknown reasons for non-

participation in the follow-up program of a minor part of the infants, and the advices and involvement of a pediatric physical therapist during that period. The criteria for determination of idiopathic asymmetry and/or DP were not graded to severity.

A more comprehensive assessment tool is needed, which is responsive for small changes in postural control and selective movement in very young infants. A prospective study, with a standardized examination and recording of prognostic factors of asymmetry, is currently going on to gain insight in the natural course and predictive infant factors with respect to posture and movement related to the development of an idiopathic asymmetry in infants born preterm.

CONCLUSION

In nearly half of the studied cohort of infants born at a GA ≤32.0 weeks, a positional preference was observed at TEA, which is substantially higher than the prevalence in full-term born infants. At six months CA, only a minor proportion of the infants had a DP.

The high prevalence of a positional preference in infants born preterm at TEA requires extra alertness and timely advice of parents and caregivers to prevent the development of a plagiocephaly, especially in boys and twins. Although, considering the lower prevalence of plagiocephaly at 6 months CA, therapists should be aware of over treating these infants.

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Chapter 5

Natural course of asymmetric motor performance and deformational plagiocephaly in very preterm born infants

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Submitted for publication.

ABSTRACT

Objectives: To describe the natural course of a positional preference and deformational plagiocephaly (DP) up to 6 months corrected age (CA) in infants born with a gestational age <30 weeks or birth weight <1000 grams, and to explore predictive factors for the persistence of these phenomena.

Patients and methods: A prospective cohort of 120 infants was examined three times. The presence of DP and a score of 1-6 on an asymmetry performance scale were used as outcome measures at 6 months CA. Predictive factors were determined after regression analysis of socio-demographic, perinatal and medical factors.

Results: The prevalence of a positional preference of the head at term-equivalent age was 65.8% (79/120) and 36.7% (44/120) at 3 months CA. DP was observed in 30% (36/120) and 50% (60/120), respectively. At 6 months CA, 15.8% (19/120) scored ≥2/6 on the asymmetry scale and a DP was found in 23.3% (28/120). The presence of a DP at 3 months CA predicted an asymmetric motor performance at 6 months CA. Chronic lung disease and/or slow gross motor maturation at 3 months CA predicted the persistence of DP.

Conclusion: A positional preference of the head at term-equivalent age seems to be a normal aspect of the motor repertoire of very preterm born infants, with limited ability to predict persistence of asymmetric motor performance. The high prevalence of DP at 3 months CA had more than halved by 6 months CA, except in infants with a history of chronic lung disease and/or slow gross motor maturation.

INTRODUCTION

The high prevalence (13-22%) of asymmetric posture and/or shape of the head is widely described in term born infants.[1-3] A positional preference of the head and a deformational plagiocephaly (DP) are phenomena with mutual influence.[4,5] In many studies, environmental factors like positioning and parental care practices are regarded as risk factors for the development of DP. Mild prematurity has also been described as a risk factor.[6] In our preliminary retrospective study of 192 infants born with a gestational age (GA) ≤32 weeks, a much higher prevalence of positional preference of the head (n=86, 44.8%) at term-equivalent age (TEA) was reported during neonatal follow-up. DP was observed in 10.4% (20/192) at TEA, and in 13% (25/192) of the infants at six months corrected age (CA). Positional preference, multiple birth and male gender were found to predict the persistence of DP.[7]

These findings were inconclusive regarding the role of motor performance, in particular the development of postural control. In fact, the infant factors contributing to the persistence of asymmetric motor performance beyond the age of 3 months remain unknown. Very preterm born infants present with a high risk for developmental sequelae. Among the factors that seem to play a role in the motor behaviour of these young infants are the neonatal intensive care environment, a relatively immature stage of development, a different course of motor development in the early months of life[8-10] and an elongated, laterally flattened head shape.[11] As a precaution, many prematurely born infants are referred to a pediatric physical therapist. At present, it is unknown whether asymmetry in posture and performance in these infants can be regarded as a benign transient phenomenon in their developmental trajectory.

Objectives

1. To describe the natural course of a positional preference and DP in very preterm born infants up to six months CA.
2. To explore predictive factors for the persistence of these phenomena.

PATIENTS AND METHODS

To determine the prevalence, predictors and natural course of idiopathic asymmetry in very preterm born infants (GA <30 weeks), all participants underwent three assessments within a six-month period beginning in April 2009. The infants were examined in the

neonatal follow-up clinic around TEA (T1) and six months CA (T3) by two pediatric physical therapists (MJCE and ICvH). At three months CA (T2) all infants were examined at home by the first author (JN). All therapists had extensive experience with the assessment of preterm infants. All parents provided informed consent prior to enrolment in this study, which was approved by the Institutional Review Board.

Participants

The eligible infants were born in, or referred to the level-three neonatal intensive care unit within one week of birth, from January 2009 through to October 2010. Inclusion criteria were: infants born with a GA <30 weeks or a birth weight (BW) <1000 grams, who visited the neonatal follow-up clinic at TEA. Exclusion criteria included those infants diagnosed with any disease or dysfunction leading to symptomatic asymmetry.[12,13]

Neonatal follow-up

In the first year of life, a neonatologist [LSdV or CK-E] and a pediatric physical therapist simultaneously examined the infants during a 20-minute session in the neonatal follow-up clinic. The same team examined these infants at all visits. At three months CA, a 30-minute assessment was performed for all infants in the home setting. The examiners were blinded to the findings of the previous assessments.

Asymmetry

Positional preference of the head was defined as the infant's head being turned to one side for about 75% of the assessment time while they were in a supine position. Active movement to the other side was restricted, and passive rotation of the head could not be maintained. A DP was defined as a unilateral occipital flattening of the skull and/or homolateral anterior ear displacement. The skull was observed from both the cranial and posterior view. The degree of deformity was evaluated using the clinical classification according to Argenta, where Argenta degree I is the mildest form with one-sided posterior flattening only; degree II also demonstrates forward ear displacement; and Argenta III and IV indicate involvement of the frontal skull and the face.[14]

The positional preference, which can be observed at a younger age, has usually resolved by six months.[7,15] Older infants might show asymmetric motor performance in postural control of the head or trunk in more vertical position, or in rolling. We compiled an

asymmetry clinical scale (Appendix 5.1) to define the persistence of an asymmetric motor performance measured at T3, consisting of head and trunk control, arm movements (e.g. reaching and grasping), leg movements (e.g. kicking), asymmetry in range of motion (>10°) of the cervical spine or hips, and in bi-directional skills (e.g. rolling and pivoting). A score of ≥2 (out of six) on the scale was defined as asymmetric motor performance. The items of the composite score and cut-off point for asymmetry were discussed with three experts in the field. The items described in this scale were chosen because asymmetry in one of these items is often indicative of a need for continued physical therapy.

Predictive factors

Demographic data (gender, ethnicity), perinatal data (GA, BW, mode of delivery, multiple birth, Apgar score at five minutes), and medical history (duration of admission, duration for mechanical ventilation and continuous positive airway pressure, diagnosis of chronic lung disease, necrotizing enterocolitis, sepsis, and cranial ultrasonography findings during admission including intraventricular hemorrhage [grades I-IV][16] and periventricular leukomalacia [grade I–III][16,17]) were recorded. Chronic lung disease grade I was defined as the need for oxygen for >1 month after birth, while grade II was defined as the need for oxygen at 36 weeks post-menstrual age.[18,19] These medical factors were believed to impact the variability of positioning and movement patterns.[20,21] The social environment (age and educational level of the parents, family composition, use of day-care), child rearing practices and receiving pediatric physical therapy were examined via a digital questionnaire, which was sent by e-mail to parents 1 week prior to the 3-month assessment (Appendix 5.2).

Motor performance tests

The General Movements (GMs) assessment is used to assess the integrity of the central nervous system by observing endogenously generated whole-body movements while in a supine position.[22,23] GMs observed around 3 months of age (stage: fidgety movements) are the best predictors of abnormal or mildly abnormal motor development.[24] The GMs were observed at T1 and T2 and classified being normal, subnormal, mildly abnormal or definitely abnormal.

The Test of Infant Motor Performance (TIMP) is commonly used to examine postural and selective motor control needed for functional performance in daily life in infants from 34 weeks post-menstrual age to 17 weeks post-term. The test consists of 13 observed

items and 42 elicited items.[25] The TIMP Screening Instrument (TIMPSI) is a shortened alternative that can be used for very young and vulnerable infants.[26] The TIMPSI was performed at T1 and the TIMP at T2.

The Alberta Infant Motor Scale (AIMS) is a norm-based assessment for the motor repertoire of infants between 0 and 19 months. It consists of observations in four postures reflecting the maturation level.[27] Preterm norm values are available, thereby facilitating the AIMS' application in this special population.[10] The AIMS was used twice, at T2 and T3.

Data analysis

Statistical analyses were performed in SPSS (version 17.0; SPSS Inc, Chicago, Illinois, USA). Frequencies, means, standard deviations (SDs), medians (interquartile range) and proportions were calculated where appropriate. The TIMP and AIMS scores were converted into Z-scores. Norm-values of both term and preterm born infants were acting as reference for the AIMS.

The relationship between potential predictive factors and idiopathic asymmetry were analysed by means of cross tabulation, univariate logistic regression and odds ratios. Putative predictive factors with a $p<.05$ were included in a multivariate model, after analysis of potential confounding relationships.

In the multivariate logistic regression analyses, the independent effects of selected predictive factors on the dependent factor (persistence of asymmetric motor performance and DP at six months CA) were assessed. Adjusted odds ratios with 95% confidence intervals were calculated. Backward logistic regression analyses and likelihood ratio tests ($p<.05$) determined whether or not a variable would be retained in the model.

RESULTS

In total, 162 infants visited the neonatal follow-up clinic at TEA. Sixteen of them were excluded due to diagnosed symptomatic asymmetry.[13] Two infants presented with a sensory system disorder (one auditory, one visual), five with a congenital malformation or syndrome, one with a developmental dysplasia of the hip, and two with an obstetric brachial plexus lesion. Six infants were excluded due to a suspected central nervous system disorder based on abnormalities on the term-equivalent MRI and in movement patterns or tone: three were subsequently diagnosed with a spastic unilateral cerebral

palsy, one with severe psychomotor retardation, while in two infants the dystonia turned out to be transient. Of the remaining 146 eligible infants, written consent was obtained from the parents of 122 (83.6%), see Figure 5.1. No significant differences were seen in the characteristics of infants enrolled in the study compared with those whose parents declined participation. Two infants did not attend the second or third assessment and were subsequently excluded from all analyses.

The final study cohort consisted of 120/146 (82.2%) infants with a mean GA of 28 ± 1.6 weeks (range 24.7-32.0), and a mean BW of 1053 ± 249 grams (range 570-1680). Six infants (5%) had a BW<1000 grams, while their GA was ≥30 weeks. Thirteen (10.8%) were small for gestational age, which was defined as a BW<P10 according to the references curves for BW by GA, gender and parity of the Netherlands Perinatal Registry.[28] The mean ± SD CA at each assessment was 10.2 ± 7.65 days (T1), 3.1 ± 0.14 months (T2), and 6.5 ± 0.73 months (T3). Characteristics of the cohort are presented in Table 5.1.

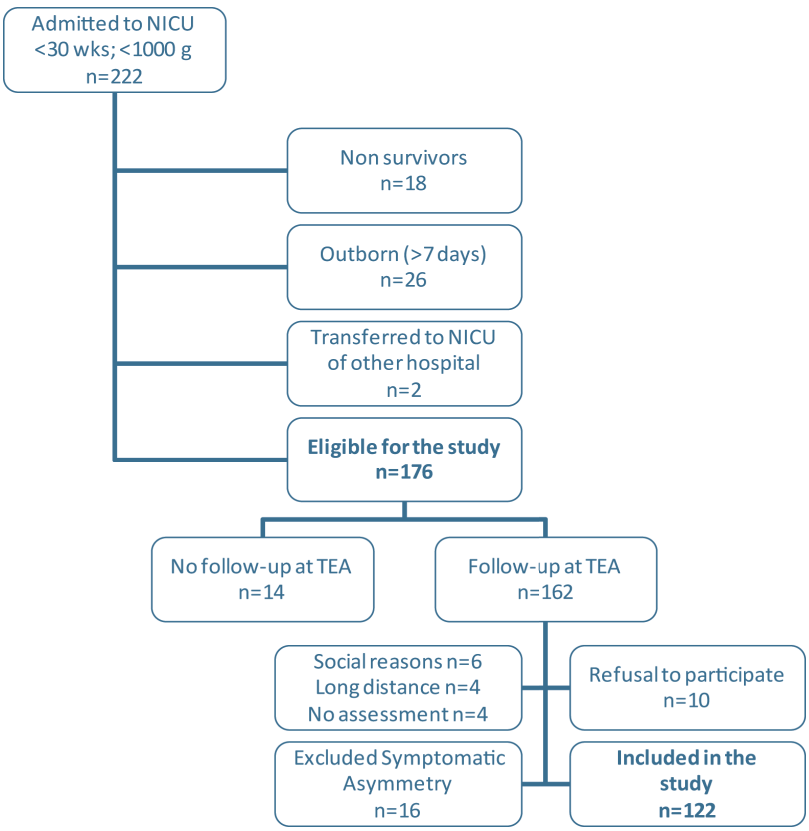

Figure 5.1 Flowchart of the cohort of infants (gestational age <30 w; birth weight <1000g) admitted to the neonatal intensive care unit (NICU) between January 2009 and October 2010.

Table 5.1 Characteristics of 120 infants born at <30.0 weeks GA or with a BW <1000 grams

Characteristics	Number (%)
Included infants	120 (100)
Gestational age	
Mean (SD), in weeks	28 (1.57)
Birth weight (%)	
Mean (SD), g	1053 (249)
Mode of delivery (%)	
Vaginal	51 (42.5)
Caesarean section	69 (57.5)
Gender (%)	
Male	65 (54.2)
Female	55 (45.8)
Ethnicity (%)	
Western	99 (82.5)
Non-Western	21 (17.5)
Multiple births (%)	
Single	77 (64.5)
Multiple (1 triplet)	43 (35.5)
Apgar score at 5 minutes, median (IQRange)	8 (1.75)
n = Apgar5 <7 (%)	15 (12.5)
n = Apgar5 ≥7 (%)	105 (87.5)
Median duration of NICU/HC stay in days (IQR)	39 (29.75)
Median duration of need for mechanical ventilation in days (IQR)	3 (7)
Median duration of need for CPAP in days (IQR)	27.5 (30)
Cranial ultrasound findings (%)	
IVH grade I	12 (10.0)
IVH grade II	25 (20.8)
IVH grade III	10 (8.3)
IVH grade IV	0 (
PVL grade I	43 (35.8)
c-PVL	0 (
PHVD	12 (10.0)
PHVD with VP-shunt insertion	2 (1.7)
Sepsis (%)	
Early onset	7 (5.8)
Late onset (>7 days)	25 (20.8)
Other medical conditions (%)	
CLD grade I: >30 days O_2	47 (39.2)
CLD grade II: O_2 >36 weeks GA	17 (14.2)
NEC	2 (1.7)

IQRange = Inter-quartile range; NICU = Neonatal intensive care unit; HC = High-care; CPAP = Continuous positive airway pressure; IVH = Intraventricular haemorrhage; (c)PVL = (Cystic) periventricular leukomalacia; PHVD = Post-haemorrhagic ventricular dilatation; VP = Ventricular-peritoneal; CLD = Chronic lung disease; NEC = Necrotising enterocolitis.

Prevalence and natural course

Asymmetry in motor performance

The prevalence of a positional preference of the head was 65.8% (79/120) at T1 and 36.7% (44/120, 75% to the right side) at T2. At T3, 15.8% (19/120) scored ≥2 on the asymmetry clinical scale, predominantly on asymmetry in postural control in the trunk and rolling form supine to prone. Of these 19 infants, 10 showed a positional preference at T2, whereas no positional preference or DP was previously observed in three infants.

Deformational plagiocephaly

A DP was observed in 30% (36/120) of the infants at T1 and in 50% at T2. At T1 the DP scores were as follows: Argenta I: n=24; Argenta II: n=8; Argenta III and IV: n=2 each. At T2 the DP scores were: Argenta I: n=11; Argenta II: n=22; Argenta III: n=13 and Argenta IV: n=14. At T3, 28/120 (23.3%) infants were judged to have a DP with ear deviation (Argenta ≥II). More specifically, the distribution in degree of deformity was: Argenta I: n=16; Argenta II: n=14; Argenta III: n=10; Argenta IV: n=4. In two infants, the DP was first seen at T3.

A minority of infants, 22/120 (18.3%), did not show asymmetry at any of the three assessments. In 50% of the study cohort, previously reported positional preference or DP had resolved at T3. The prevalence of asymmetry at each of the assessments, as well as the cumulative incidence up to T3 are reported in Table 5.2.

Predictive factors

The factors examined in univariate analyses are presented in Tables 5.3A and 5.3B ($p<0.05$ only).

Univariate analyses of predictors of asymmetry in motor performance

Male gender was associated with a positional preference at T1, and chronic lung disease with a positional preference at T2. All other demographic, perinatal and medical variables did not show a significant association with a positional preference at T1 or T2, nor with asymmetric motor performance at T3.

Mildly abnormal GMs at T1, observed in 21/120 (17.5%) infants, were associated with a positional preference at the same time. However, this relationship was not maintained in later assessments. A lower Z-score on the TIMP and the AIMS test at T2 were

Table 5.2 Natural course of positional preference (PP) and deformational plagiocephaly (DP) in 120 very preterm born infants through to 6 months corrected age

	PP T1[a]	DP T1 Arg ≥1[b]	PP T2	DP T2 Arg ≥1[b]	ACS T3 ≥2	DP T3 Arg ≥2[b]	n infants	n cumulative
Infants with ACS ≥2[c]	+	+	+	+	+	+	4	4
	+	-	+	+	+	+	2	6
	+	-	-	+	+	+	1	7
	-	-	+	+	+	+	2	9
	+	+	+	-	+	-	1	10
	+	-	+	+	+	-	1	11
	+	+	-	-	+	-	1	12
	+	+	-	+	+	-	1	13
	+	-	-	+	+	-	3	16
	-	-	-	-	+	-	3	19
Subtotal (%)	14 (11.7)	7 (5.8)	10 (8.3)	14 (11.7)	19 (15.8)	9 (7.5)	19 (15.8)	19
Infants with DP at T3; with ACS 0 or 1	+	+	+	+	-	+	10	29
	+	+	-	+	-	+	1	30
	+	-	+	+	-	+	1	31
	+	+	-	-	-	+	1	32
	-	-	+	+	-	+	4	36
	-	-	+	-	-	+	1	37
	-	-	-	-	-	+	1	38
Subtotal (%)	13 (10.8)	12 (10.0)	16 (13.3)	16 (13.3)	0	19 (15.8)	19 (15.8)	38
Infants with absence of asymmetry at T3	+	+	+	+	-	-	5	43
	+	-	+	+	-	-	7	50
	+	+	-	+	-	-	7	57
	+	-	-	+	-	-	7	64
	+	-	+	-	-	-	1	65
	-	-	+	+	-	-	2	67
	-	-	+	-	-	-	3	70
	-	-	-	+	-	-	2	72
	+	+	-	-	-	-	4	76
	-	+	-	-	-	-	1	77
	+	-	-	-	-	-	21	98
	-	-	-	-	-	-	22	120
Subtotal (%)	52 (43.3)	17 (14.2)	18 (15.0)	30 (25.0)	0	0	82 (68.3)	120
Total (%)	79 (65.8)	36 (30.0)	44 (36.7)	60 (50.0)	19 (15.8)	28 (23.3)		

Columns show point prevalence (cross-sectional); rows show cumulative incidence (longitudinal). n = Number.
[a] T1 = term-equivalent age; T2 = 3 months corrected age; T3 = 6 months corrected age.
[b] The observation of a plagiocephaly was dichotomized in this table: Argenta (Arg) degree I[14] or more at T1 and T2 was classified as +; at T3 a degree II or more was classified +.
[c] At T3 the score on the asymmetry clinical scale (ACS) was dichotomized using a score of ≥ 2 out of 6 as cut-off point.

Table 5.3A Univariate analyses of asymmetric motor performance (cross-sectional)

		PP, T1 = TEA, n=79		PP, T2 = 3 mo CA, n=44		ACS ≥2, T3 = 6 mo CA, n=19	
Factors	n (%)	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Demographical / perinatal factors							
Gender							
Boys	65 (54.2)	**2.2 (1.01-4.75)**	**.046**[e]	1.2 (0.56-2.50)	.657	2.7 (0.92-8.19)	.070
Medical factors							
CLD							
Grade II	17 (14.2)	1.3 (0.42-3.95)	.656	**2.9 (1.02-8.28)**	**.047**[e]	1.2 (0.30-4.52)	.825
Asymmetry factors							
DP							
at T1 Arg≥1	36 (30.0)	**31.8 (4.17-243.08)**	**.001**[e]	**3.1 (1.39-7.03)**	**.006**[e]	1.4 (0.52-4.05)	.480
at T2 Arg≥1	60 (50.0)	NA		**15.5 (5.76-41.98)**	**.000**[e]	**3.3 (1.12-9.99)**	**.030**[e]
at T3 Arg≥2	28 (23.3)	NA		NA		**3.9 (1.39-10.88)**	**.010**[e]
Motor performance factors							
General movements at T1							
Subnormal	10 (8.3)	1.5 (0.37-6.36)	.550	1.9 (0.52-7.21)	.326	0.5 (0.06-4.59)	.573
Mildly abnormal	21 (17.5)	**4.0 (1.09-14.46)**	**.037**[e]	1.2 (0.44-3.19)	.730	0.8 (0.21-3.11)	.760
Postural control Z-scores							
TIMPSI at T1[a]		1.0 (0.65-1.55)	.981	0.8 (0.50-1.14)	.184	0.8 (0.48-1.37)	.430
TIMP at T2[b]		NA		**0.3 (0.17-0.64)**	**.001**[e]	0.5 (0.24-1.02)	.055
AIMS Z-scores at T2		NA					
Full term norms[c]				**0.4 (0.19-0.71)**	**.003**[e]	0.6 (0.28-1.29)	.192
Preterm norms[d]				**0.5 (0.34-0.81)**	**.004**[e]	0.7 (0.44-1.23)	.236

PP = Positional preference; OR = Odds ratio; CI = Confidence interval; ACS = Asymmetry clinical score; Arg = Argenta; TEA = Term-equivalent age; DP = Deformational plagiocephaly; CLD = Chronic Lung Disease; NA = Not applicable; mo = Months; n = Number; CA = Corrected age.

[a] Corrected age standardized postural and selective motor control from TIMP screening version.[26]

[b] Corrected age standardized postural and selective motor control from TIMP.[25]

[c] Corrected age standardized neuromaturation test scores from AIMS.[27]

[d] Corrected age standardized neuromaturation test scores adapted for infants born preterm.[10]

[e] Statistically significant factor at univariate level with $p<.05$.

Table 5.3B Univariate analyses of deformational plagiocephaly (DP) (cross-sectional)

		DP Arg≥1, T1 = TEA, n=36		DP T2 Arg≥1, T2= 3 mo CA, n=60		DP Arg ≥2, T3 = 6 mo CA, n=28	
Factors	n (%)	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Demographical / perinatal factors							
Gender							
Boys	65 (54.2)	1.8 (0.79-3.95)	.164	**2.8 (1.33-5.88)**	**.008** [d]	1.7 (0.72-4.13)	.222
Gestational age in weeks		**0.8 (0.59-0.97)**	**.030**[d]	1.0 (0.81-1.27)	.922	0.9 (0.66-1.13)	.299
Birth weight in grams/100		0.9 (0.80-1.10)	.415	1.0 (0.83-1.11)	.609	**0.8 (0.66-0.96)**	**.020** [d]
Small for gestational age	13 (10.8)	1.0 (0.30-3.63)	.949	1.7 (0.52-5.51)	.382	**3.3 (1.01-10.85)**	**.048** [d]
Medical factors							
Admission in days		1.0 (0.99-1.03)	.293	1.0 (0.99-1.02)	.378	**1.0 (1.00-1.04)**	**.019** [d]
Intubation in days		1.0 (0.96-1.09)	.460	1.0 (0.97-1.09)	.335	**1.1 (1.00-1.14)**	**.037** [d]
CLD							
Grade I	47 (39.2)	1.4 (0.62-3.02)	.439	1.6 (0.78-3.43)	.192	**2.6 (1.11-6.23)**	**.029** [d]
Grade II	17 (14.2)	2.4 (0.84-6.78)	.104	2.0 (0.70-5.87)	.196	**5.0 (1.70-14.57)**	**.003** [d]
Asymmetry factors							
Positional preference							
At T1	79 (65.8)	**31.8 (4.17-243.08)**	**.001**[d]	**5.3 (2.29-12.47)**	**.000** [d]	1.4 (0.56-3.52)	.477
At T2	44 (36.7)	NA		**15.5 (5.76-41.98)**	**.000** [d]	**21.6 (6.71-69.50)**	**.000** [d]
ACS ≥2 at T3	19 (15.8)	NA		NA		**3.9 (1.39-10.88)**	**.010** [d]
DP arg≥1							
At T1	36 (30.0)	NA		**5.7 (2.31-14.00)**	**.000** [d]	**4.8 (1.96-11.78)**	**.001**[d]
At T2	60 (50.0)	NA		NA		**13.6 (3.81-48.30)**	**.000** [d]

Factors	n (%)	DP Arg≥1, T1 = TEA, n=36		DP T2 Arg≥1, T2= 3 mo CA, n=60		DP Arg ≥2, T3 = 6 mo CA, n=28	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Motor performance factors							
General movements at T2							
Subnormal	14 (11.7)	NA		1.0 (0.33-3.15)	.969	**2.6 (0.80-8.81)**	**.124**
Mildly abnormal	14 (11.7)	NA		1.4 (0.44-4.24)	.593	**4.7 (1.44-15.23)**	**.010**[d]
TIMP Z-scores at T2[a]		NA		0.7 (0.40-1.25)	.238	**0.5 (0.24-0.89)**	**.021**[d]
AIMS Z-scores at T2							
Full term norms[b]		NA		0.8 (0.44-1.34)	.346	**0.4 (0.19-0.78)**	**.008**[d]
Preterm norms[c]		NA		0.8 (0.57-1.21)	.339	**0.5 (0.32-0.85)**	**.009**[d]

OR = Odds ratio; CI = Confidence interval; Arg = Argenta; TEA = Term-equivalent age; DP = Deformational plagiocephaly; CLD = Chronic Lung Disease; NA = Not applicable; mo = Months; n = Number; CA = Corrected age.

[a] Corrected-age standardized postural and selective motor control from TIMP.[25]

[b] Corrected-age standardized neuromaturation test scores from AIMS.[27]

[c] Corrected-age standardized neuromaturation test scores adapted for infants born preterm.[10]

[d] Statistically significant factor at univariate level with $p<.05$.

both significantly associated with a concurrent positional preference, but not with asymmetric motor performance at T3.

Univariate analyses of predictors of deformational plagiocephaly

GA was associated with the presence of DP at T1, while male gender was linked with DP at T2. The univariate analyses revealed a significant association of persistence of DP at T3 with BW, small for gestational age, days of admission, days on mechanical ventilation, and diagnosis of chronic lung disease grade I and II.

Infants with mildly abnormal GMs or a low Z-score on the TIMP or AIMS at T2 were more likely to demonstrate persistent DP at T3 (see Table 5.3A and B). After accounting for potential confounding factors, we selected chronic lung disease grade II, BW, and the AIMS Z-score at T2 for inclusion in the multivariate analysis.

With the exception of physical therapy intervention at T2 (42/120; 35%), neither the social environment, child-rearing practices nor physical therapy involvement at other times were significantly associated with any of the outcome variables at T3. Infants with asymmetric motor performance or DP at T3 were more likely to have received physical therapy at T2. Indications for pediatric physical therapy according to the parents varied from issues relating to motor development (13), positional preference and/or DP (12), to high excitability (8). The parents of 9/42 infants did not report any problems in the questionnaire.

Association of asymmetry in motor performance with deformational plagiocephaly

A positional preference at T1 was strongly associated with the presence of DP at T1 and T2, but not at T3. Infants with a positional preference at T2 or a score ≥2 on the asymmetry clinical scale at T3 were significantly more likely to show a DP at T3.

Multivariate analysis

The only factor predicting asymmetric performance at T3 was the presence of a DP (Argenta ≥1) at T2 (OR 3.3, 95% CI 1.12-9.99; *p*=.030). A diagnosis of a chronic lung disease grade II in the neonatal period (aOR 4.5, 95% CI 1.46-13.58; *p*=.009) predicted the odds of persistent DP at T3, while an AIMS score of +1 SD from the mean at T2 decreased these odds by 40% (aOR 0.4, 95% CI 0.20-0.86; *p*=.018).

DISCUSSION

In very preterm born infants, we found remarkably high prevalence rates of positional preference and DP at TEA and at three months CA, when compared to studies on term born infants.[1-3,29,30] Interestingly, these rates are even higher than those reported in our retrospective study in infants born ≤32 weeks GA.[7] This difference in prevalence of positional preference may be partly explained by the lower GA of the infants, as well as the more standardized observation criteria utilized to detect features of asymmetry in the current study. Our findings suggest that a positional preference at TEA might be considered normal in very preterm born infants. With respect to DP, the decreased stiffness of the cranium has been cited as a potential source for increased prevalence of DP in preterm born infants[31]; however, we assume that this is unlikely in our cohort since the increase in DP was observed at an older age (i.e., between TEA and three months CA). Moreover, considerable decreases in DP and degree of DP were observed between three and six months CA; both of which were larger than those described in full-term born infants.[15] This indicates that a small degree of DP seems inevitable in this population, but its evolution is positive in most preterm born infants. The cumulative incidence of asymmetry in motor performance with concomitant DP, as presented in Table 5.2, revealed an unpredictable distribution across the time frame, making it difficult to predict the change in these outcomes from TEA onwards.

We analysed a number of factors hypothesized to predict the persistence of DP based on previous studies[3,6,32,33] including plausible medical factors, and clinical observations. Relatively few significant associations were observed between these potential predictors and persistent DP. More specifically, infants with a history of chronic lung disease, either independently or in combination with a slow gross motor maturation at three months CA, compared to a norm population were more likely to show DP at six months CA. Infants who are oxygen-dependent for a longer period tend to show an increased active extension of trunk and neck muscles with subsequent motor asymmetries, and might be less active in exploring their full motor repertoire.[34-36] Slow gross motor development has also been reported in studies on term infants with DP.[3,37-40] Unlike studies in term born infants, child rearing practices and socio-demographic variables were not predictive of persistent DP.[3,5,6,41] This may be attributable to the fact that all parents in our neonatal follow-up clinic receive the same information to prevent progression of DP whenever a positional preference is observed in an infant. Therefore, the awareness of parents about the risk of DP may have influenced specific child rearing practices.

The strength of the present study lies in its longitudinal design. Such a design provides an insight into the development of the various phenomena of asymmetry and its associations. Further, the age- related homogeneity of this cohort and the optimal environment for the second assessment (i.e., examination performed in the home setting) likely strengthened our findings. Despite these strengths, a number of limitations must also be acknowledged like the use of a self-created asymmetry clinical scale to assess asymmetry in motor performance due to the lack of a well-established assessment tool. However, asymmetry in motor performance appears to play a minor role in the persistence of DP. Another limitation is the unknown influence of pediatric physical therapy on the outcome variables. The fair degree of association between the persistence of DP and pediatric physical therapy intervention at three months CA does not provide any insight into the effect of the intervention. The indication for therapy was often non-specific. Moreover, any effect has to be studied in a different design.

In future studies, we suggest research to reinforce the predictive factors reported in the present study, as well as to explore and investigate the effects of early prevention of asymmetry and intervention, particularly in those infants that are at higher risk for persistence of asymmetry.

CONCLUSION

In very preterm born infants, a positional preference of the head at TEA seems to be a normal aspect of their motor repertoire, with limited ability to predict persistence of asymmetric motor performance. The high prevalence of DP, as seen at three months CA, had more than halved by six months CA, except in infants with a history of chronic lung disease grade II and/or slow gross motor maturation at three months CA.

Acknowledgements

We appreciate the assistance of Maaike Sprong, PT, MSc (data collection), Eric Stutterheim, PT, MSc (designing the digital questionnaire), Carla Tims (data management), Cas Kruitwagen, MSc (statistical advice), and Joyce Obeid (editing the manuscript). We are grateful to the parents and their children for participation in this study.

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APPENDIX 5.1

Asymmetry clinical scale used at 6 months corrected age

Item	Dimensions	Score
Postural control: head not in midline	Supine and/or prone, sit, standing, pull to sit, lateral righting, ventral suspension	0 or 1
Postural control: trunk asymmetry	Supine and/or prone, sit, vertical suspension, ventral suspension, lateral righting	0 or 1
Arm movements left ≠ right	Reaching and/or support, grasping	0 or 1
Leg posture / movements left ≠ right	Hip posture unilateral more adduction Kicking and/or support	0 or 1
Range of Motion (ROM) difference between left/right >10°	Cervical spine: active ROM rotation and/or lateroflexion passive ROM if necessary	0 or 1
	Hips: passive ROM flexion/abduction/exorotation-manoeuvre	
Change in position towards left ≠ right	Rolling and/or pivoting in prone	0 or 1
Total score and interpretation (0-6)	**0-1 = no (clinically relevant) asymmetry;** **≥2 = Asymmetric motor performance**	**… points**
Conclusion	**Idiopathic asymmetry** **Direction** **Symptomatic asymmetry, namely …**	**Yes/No** **R/L** **Yes/No**

APPENDIX 5.2

Digital questionnaire [in Dutch]

ENQUÊTE API ONDERZOEK PREMATUREN

Geachte ouder,

Wij zijn verheugd, dat u hebt ingestemd met deelname aan de API-studie, een wetenschappelijk onderzoek naar de ontwikkeling van een houdingsasymmetrie bij zeer vroeg geboren kinderen. Uw kind is nu ongeveer drie maanden oud is, rekening houdend met de vroeggeboorte. Wij komen bij u thuis een kinderfysiotherapeutisch onderzoek doen, waarin wij samen met u gaan kijken naar hoe het kind beweegt. Deze gegevens vergelijken wij straks met de gegevens van de controles op de neonatologie polikliniek.

Wij vragen u ook deze vragenlijst in te vullen. Hiermee willen wij wat achtergrondgegevens over de kinderen verzamelen. Wij hopen zo beter inzicht te krijgen in de posities waarin de kinderen liggen en over eventuele adviezen en therapieën wanneer een kind een asymmetrie heeft.

Wanneer u zelf nog vragen heeft over zaken, die betrekking hebben op het onderzoek, stelt u deze dan gerust aan de onderzoeker die bij u thuis komt.

Wij moeten en zullen ons houden aan strenge onderzoekseisen, die vooraf door de Medisch Ethische Toetsingscommissie van het Universitair Medisch Centrum Utrecht. Wij zullen zorgvuldig met alle gegevens omgaan en niet aan derden verstrekken.

De vragenlijst

Het invullen van de vragenlijst kan op de computer en vraagt ongeveer 10 minuten tijd. U kunt de lijst ook eerst rustig doorlezen om te weten wat er allemaal gevraagd wordt. Wanneer u dat prettig vindt, kan de lijst ook samen met de onderzoeker ingevuld worden als zij bij u thuis komt. U kunt hem tussentijds bewaren door de knop BEWAREN aan te klikken. Als de lijst klaar is kan hij digitaal verstuurd worden via de knop VERZENDEN. U krijgt een kopie van de lijst op uw eigen e-mailadres.

Nogmaals hartelijk dank voor uw medewerking.

Met vriendelijke groet,

Drs. Jacqueline Nuysink
Kinderfysiotherapeut-onderzoeker
Wilhelmina Kinderziekenhuis
Universitair Medisch Centrum Utrecht

ALGEMENE INFORMATIE

Code kind _____

Code onderzoeker _____

Door wie wordt de vragenlijst ingevuld?
- O Moeder
- O Vader
- O Verzorgende

Wat is de geboortedatum van de moeder? _____ dd-mm-jjjj

Wat is de geboortedatum van de vader? _____ dd-mm-jjjj

Wat is de geboortedatum van uw baby? _____ dd-mm-jjjj

Wat is uw woonsituatie?
- O Samenwonend
- O Alleenwonend
- O Anders, nl _____

Wie zorgt/zorgen thuis voor het kind?
- O Moeder
- O Vader
- O Vader en moeder samen
- O Anders, nl _____

Hoeveel kinderen heeft u? _____

Hoeveel andere kinderen heeft u (nog) thuis wonen? _____

Hoeveel jaar is uw thuiswonend kind (1)? _____

Is uw baby deel van een meerling?
- O Nee
- O Ja

Gebruikt u of gaat u gebruik maken van kinderopvang?
- O Nee
- O Ja
- O KDV
- O Gastoudergezin
- O Familie
- O Oppas thuis
- O Anders, nl _____

Hoeveel dagdelen per week heeft u kinderopvang?	_____
Wat is de hoogst afgemaakte opleiding van de moeder?	O Geen school afgemaakt O Basisschool O VMBO / MAVO / LBO O Gymnasium / VWO / HAVO / MBO O Universiteit / HBO O Anders, nl _____
Wat is het huidige beroep van de moeder? Indien huisvrouw, dan graag dit als beroep invullen.	_____
Indien moeder buitenshuis werkt, hoeveel uur werkt de moeder dan gemiddeld per week?	_____
Wat is de hoogst afgemaakte opleiding van de vader?	O Geen school afgemaakt O Basisschool O VMBO / MAVO / LBO O Gymnasium / VWO / HAVO / MBO O Universiteit / HBO O Anders, nl _____
Wat is het huidige beroep van de vader? Indien huisman, dan graag dit als beroep invullen.	_____
Indien vader buitenshuis werkt, hoeveel uur werkt de vader dan gemiddeld per week?	_____
Heeft uw kind kinderfysiotherapie?	O Nee O Ja O Andere therapie, nl _____
Hoe vaak?	O Eenmalig O 1 x per maand O 2 x per maand O 1 x per week O Anders, nl _____

Wat was uw hulpvraag aan de kinderfysiotherapeut?

Totaal aantal behandelingen tot nu toe? _____

Is de asymmetrie al verbeterd na de start van de behandeling?
- O NVT
- O Verergerd
- O Hetzelfde
- O Verbeterd
- O Opgelost

STATUS KIND

Wat vind u van de lichaamshouding van uw kind?

Helemaal niet tevreden O 1 O 2 O 3 O 4 O 5 Helemaal tevreden

Wat vind u van de vorm van het hoofdje van uw kind?

Helemaal niet tevreden O 1 O 2 O 3 O 4 O 5 Helemaal tevreden

Is bij uw kind een voorkeurshouding opgevallen?
- O Nee
- O Ja

Indien vorige vraag met ja beantwoord:
- O Naar rechts (uitgaande van het kind)
- O Naar links
- O Anders, nl _____

Is bij uw kind een afplatting of vervorming van het hoofd opgevallen?
- O Nee
- O Ja

Indien vorige vraag met ja beantwoord:
- O RE - achter (uitgaande van het kind)
- O LI - achter
- O RE - voor
- O LI - voor
- O Achterzijde

Zijn de adviezen duidelijk, die u gekregen hebt om een voorkeurshouding bij uw kind te voorkomen?

○ NVT

Heel erg onduidelijk ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 Heel erg duidelijk

Indien er toch sprake is van asymmetrie, waar is dit voor het eerst gesignaleerd?

- ○ NVT
- ○ WKZ
- ○ Perifeer ziekenhuis
- ○ Follow-up kliniek WKZ
- ○ Consultatiebureau
- ○ Thuis (ouders)
- ○ Elders, nl _____

Zijn adviezen duidelijk, die u gekregen hebt om de voorkeurshouding bij uw kind te verbeteren?

○ NVT

Heel erg onduidelijk ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 Heel erg duidelijk

Van wie heeft u adviezen gekregen?

VERZORGING VAN HET KIND

Waaruit bestaat de voeding van uw kind sinds hij/zij thuis is?

- ○ Sondevoeding
- ○ Borstvoeding
- ○ Flesvoeding
- ○ Combinatie fles/borstvoeding

Indien uw kind flesvoeding krijgt, dan wordt de fles daarbij hoofdzakelijk:

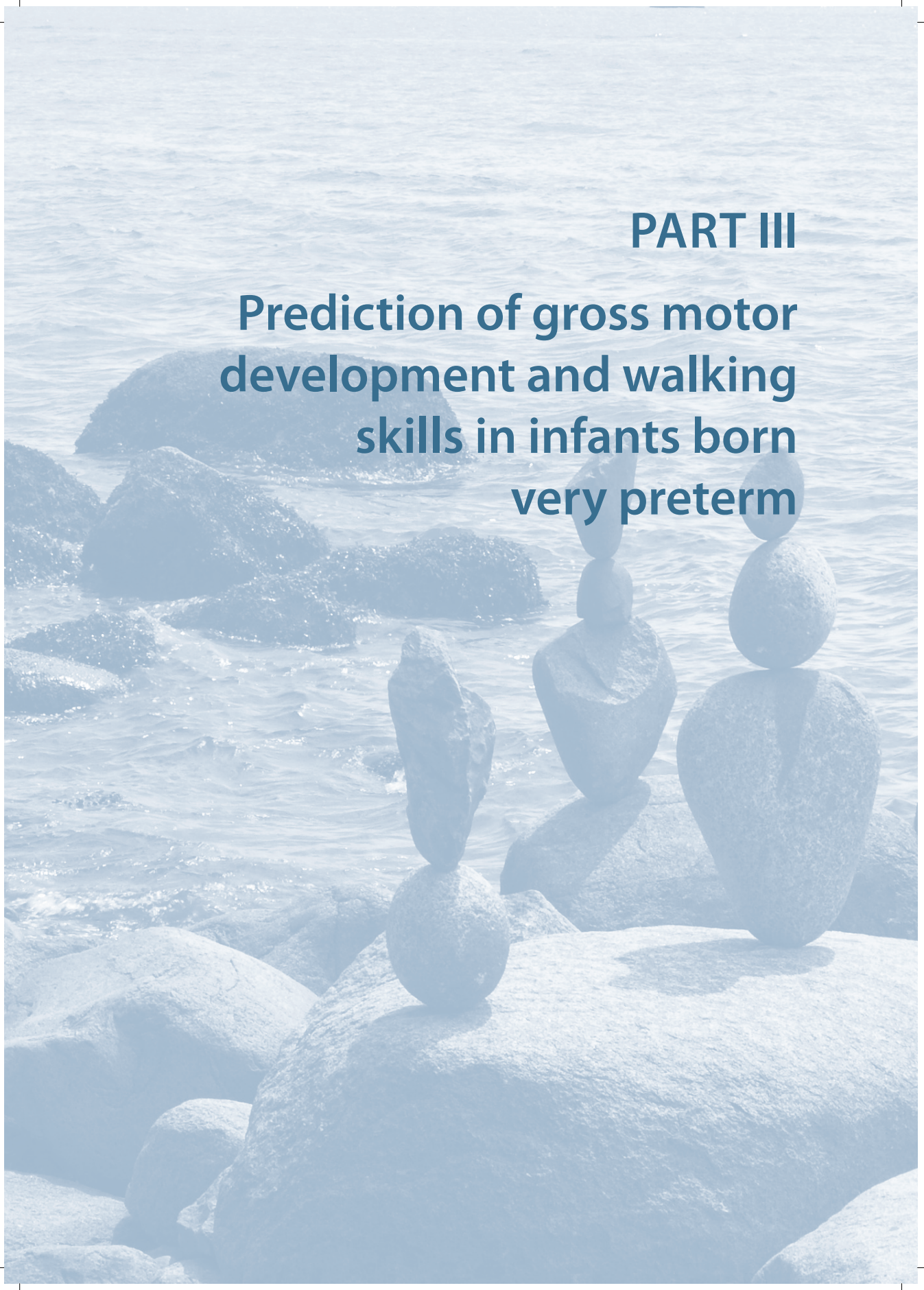
- ○ NVT
- ○ Op de linkerarm aangebonden (uitgaande vanuit de verzorger)
- ○ Op de rechterarm aangebonden
- ○ Afwisselend op de linker- en rechterarm aangeboden
- ○ Recht vooruit aangeboden (bijv. op schoot of in stoeltje)

De meest voorkomende slaaphouding van uw kind gedurende de afgelopen 3 maanden was:	○ Uitsluitend rugligging ○ Zijligging op rechts (uitgaande van het kind) ○ Zijligging op links ○ Buikligging ○ Variabel
Hoe ligt uw kind op de rug?	○ Het hoofd vrijwel altijd in de middenlijn ○ Het hoofd afwisselend naar links en rechts gedraaid ○ Het hoofd altijd naar dezelfde kant gedraaid
Op welke leeftijd hebt u het kind voor het eerst op de buik gelegd (niet om te slapen)?	○ Nog niet gedaan ○ In de derde maand ○ In de tweede maand ○ In de eerste maand ○ Direct vanaf het begin
Hoe vaak per dag legt u het kind op de buik (niet om te slapen)?	○ Nooit ○ Soms maar niet dagelijks ○ 1 à 2 keer per dag ○ 3 à 5 keer per dag ○ Meer dan 5 keer per dag
Hoe lang ligt uw kind gemiddeld per keer op de zij (niet om te slapen)?	○ Nooit ○ Max. 5 minuten ○ Tussen 5 en 15 minuten ○ Tussen 15 en 30 minuten ○ Meer dan 30 minuten
Hoe lang verblijft uw kind dagelijks in de maxi-cosi of wipstoel (alle tijden bij elkaar opgeteld?)	○ Nooit ○ Minder dan half uur ○ Tussen 30 en 60 minuten ○ Tussen 1 en 2 uur ○ Meer dan 2 uur
Tijdens de verzorging wordt uw kind neergelegd:	○ Recht vooruit ○ Met het hoofd links op de commode uitgaande van de verzorger) ○ Met het hoofd rechts op de commode ○ Afwisselend

Hartelijk dank voor het invullen van de vragenlijst. Wanneer u het invullen wilt onderbreken, of als u nog twijfels heeft over een of meer antwoorden kunt u de knop BEWAREN aanklikken en de lijst afronden samen met de fysiotherapeut die bij u komt voor het onderzoek van uw kind.

Wanneer alle vragen ingevuld zijn, kunt u de knop VERZENDEN aanklikken. De lijst wordt dan via een beveiligde lijn verzonden naar de onderzoeker in het UMC.

U ontvangt op uw e-mail adres een kopie van de door u ingevulde vragenlijst.



PART III

Prediction of gross motor development and walking skills in infants born very preterm

Chapter 6

Prediction of independent walking in infants born preterm using the Test of Infant Motor Performance and Alberta Infant Motor Scale

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Submitted for publication.

ABSTRACT

Aim: To assess concurrent and predictive validity of the Test of Infant Motor Performance (TIMP) and the Alberta Infant Motor Scale (AIMS) for motor development and independent walking of infants born preterm (gestational age <30 weeks).

Method: 113 infants were examined at 3 months corrected age (CA) with both tests and around 6 and 15 months CA with the AIMS. At 3 months CA, correlations of raw-scores, Z-scores, and a cut-off score of the TIMP for diagnostic agreement were determined. Regression was used to determine predictive validity, and survival analysis to predict age of independent walking.

Results: The correlation between TIMP and AIMS raw-scores was 0.82, and between Z-scores 0.71. A cut-off Z-score of -1.0 on the TIMP had a diagnostic agreement of 92% (κ=0.67) with an AIMS-score <P10. The AIMS-scores at 6 months CA predicted the AIMS-scores at 15 months CA, 'early stepping' (OR 2.6; 95% CI 1.55–4.47), and 'walks alone' (OR 3.2; 95% CI 1.86-5.65). The median age of independent walking was 15.7 (95% CI 15.21-16.26) months CA. No significant medical prediction factors were found.

Interpretation: A prediction on gross motor development at 15 months CA and independent walking could be given at the earliest age of 6 months CA using the AIMS.

INTRODUCTION

Advantages in neonatal intensive care have improved the survival rate of infants born at younger gestational ages.[1] The incidence of infants with very premature birth (<32 weeks gestation) who survived the neonatal period was 9.6/1000 in 2008, and of infants <30 weeks 3.3/1000 according to the Netherlands Perinatal Registration (www.perinatreg.nl). The younger the gestational age (GA) or the birth weight (BW), the more risk factors there are for delayed or impaired development.[2-4] Infants with a gestational age <30 weeks are at high risk and their development is often monitored in a neonatal follow-up clinic. One of the objectives of a neonatal follow-up program is to predict gross motor outcome and target the appropriate infants for early intervention. For parents it is important if and when their child might start to walk independently.[5,6]

Motor skill acquisition is influenced by infant, culture and context factors.[7,8] Compared to their full-term born counterparts, infants born preterm are delayed in the onset of walking.[9-12] Infant factors, like neuromaturation, postural control and muscle strength play an important role in the development of walking skills.[13-15] The Alberta Infant Motor Scale (AIMS) measures early gross motor maturation[16] and the Test of Infant Motor Performance (TIMP) postural and selective motor control needed for functional performance in early infancy.[17] The concurrent validity of these instruments, both designed to apply early in life, and their ability to identify infants with a suspect motor development has been described as fair to good.[18-20] Considering the different constructs of both tests, the question was raised, which instrument has better clinical value predicting motor performance in neonatal follow-up. In the present study we analysed the predictability of gross motor maturation and independent walking in a birth cohort of infants born very preterm, comparing the two tests.

Objectives

1. To assess the concurrent validity and diagnostic agreement between the Test of Infant Motor Performance (TIMP) and the Alberta Infant Motor Scale (AIMS) used at 3 months CA in infants born very preterm.
2. To determine the ability of TIMP and AIMS to predict the level of gross motor maturation and independent walking at 15 months CA.
3. To explore risk factors associated with delayed onset of independent walking.

METHODS

The participants in this study were recruited as part of a longitudinal study on motor performance of infants born very preterm in or referred to a level three neonatal intensive care unit within one week of birth, from January 2009 through to October 2010. Inclusion criteria were: infants born with a GA <30 weeks or a BW <1000 grams, who participated in the neonatal follow-up program. Infants diagnosed with chromosomal, genetic, major neurological or sensory abnormalities were excluded. The Institutional Review Board previously approved the study and all parents provided informed consent prior to enrolment in the study.

In this prospective cohort study, all infants were examined three consecutive times by a pediatric physical therapist using the TIMP and/or AIMS. The first author (JN) performed the first assessment in their home setting at three months CA (T1).The next assessments, by one of three pediatric physical therapists (ICvH, MJCE or JN), took place in the neonatal follow-up clinic around six months (T2) and 15 months (T3) CA. All therapists had extensive experience with the assessment of preterm infants.

The TIMP is designed to identify infants with developmental delay prior to four months of age. The test examines postural and selective motor control needed for functional performance in daily life in infants between 34 weeks post-menstrual age to 17 weeks post-term. Within 25-35 minutes, 13 items have to be observed and 42 elicited.[17] The TIMP was used only at T1. The AIMS is a standardized norm-referenced test to assess the gross motor repertoire of infants between 0 and 19 months. It consists of observations reflecting the level of maturation in four positions: supine, prone, sitting and standing.[16] The instrument requires minimal handling and can usually be completed within 10-20 minutes. Norm values for infants born with a GA ≤32 weeks are also described.[21] The AIMS was performed three times: at T1, T2 and T3.

At the age of three months, the TIMP and AIMS raw-scores have been shown to have a significant correlation of 0.64 in a mixed population, indicating a shared variance of 41%.[19] According to the same study, a cut-off value of -0.5 standard deviation (SD) from the mean TIMP score identified 80% of the same infants categorized as above or below the AIMS cut-off (P10)[18] for prediction of abnormal developmental outcome. We wanted to examine whether these values for concurrent validity and diagnostic agreement were comparable in our cohort of infants born very preterm.

We used two individual items of the AIMS 'standing subscale' to identify the level of upright locomotion at T3, namely 'early stepping' and 'walks alone'. 'Early stepping'

is defined as the ability of the infant to take five independent steps. The position of the arms may vary from high to medium guard. According to the manual, 50% of the normative sample (n=2200 Canadian infants) received credit for this item between 11 and 12 months of age, while 90% of the 14-months-old infants successfully performed this item. 'Walks alone' is scored if the infant uses walking as the main method of locomotion. The walking pattern may still be immature. The frequency distribution of 'walks alone' is about three weeks later than 'early stepping'.[16] The definition of independent walking was: ≥5 steps walking without support. The age of onset of independent walking was monitored and recorded by the parents.

To explore additional factors to predict independent walking, demographic data (gender, ethnicity), perinatal data (GA, BW, mode of delivery, multiple birth, Apgar score at five minutes), and medical history (duration of admission, duration of mechanical ventilation, diagnosis of chronic lung disease [Grades I-II][22], necrotizing enterocolitis, sepsis, and cranial ultrasound findings during admission including intraventricular hemorrhage [Grades I-IV][23] and periventricular leukomalacia [Grades I–III][23,24]) were recorded. Ethnicity was defined based on the cultural background of the parents according to Statistics Netherlands (www.cbs.nl): Western (including Dutch) or non-Western (one or both parents).

Data analysis

Statistical analyses were performed in SPSS (version 20.0; SPSS Inc, Chicago, Illinois, USA). Frequencies, means, SDs, medians (interquartile range) and proportions were calculated where appropriate. The TIMP and AIMS raw-scores were converted into Z-scores. We analysed correlations of the raw-scores and Z-scores at 3 months CA (Pearson) and sensitivity/specificity of cut-off scores of both tests (Kappa [κ] and a receiver operating characteristic [ROC] curve). The AIMS full-term norm values were used for the concurrent analysis with the TIMP at T1. In the prediction analysis the preterm norm values of the AIMS were applied.[21] To determine predictive validity on the level of gross motor maturation and on walking skills, linear and logistic regression was used, respectively. Cox proportional hazard regression was applied in the analyses of age of independent walking, since the stage of this ability had not yet been established in some infants at the end of the study.

The incidence of plurality is high in cohorts of infants born preterm. Among twins and triplets a dependency in motor development is presumed.[25] Therefore we selected for

our analyses one of the infants born from multiple birth at random, in case there was more than one surviving infant.

RESULTS

During the study period, 158 infants born with a GA <30 weeks or a BW <1000 grams started the neonatal follow-up program around term-equivalent age. Due to social reasons or long distance to the hospital, the parents of 10 infants were not approached. Ten more parents declined to participate. From the remaining 138 infants, 17 (12.3%) had to be excluded due to medical conditions: two infants presented with a sensory system disorder (one auditory, one visual), seven with a congenital malformation or syndrome, and two with an obstetric brachial plexus lesion. Six infants were excluded due to severe brain abnormalities on the term-equivalent MRI and subsequently abnormal movement patterns or tone: three were diagnosed with a spastic unilateral cerebral palsy, one with severe psychomotor retardation, while in two infants the dystonia turned out to be transient. At T2 and T3, 3 and 5 infants respectively (8/121), no longer participated in the follow-up program and were subsequently excluded from all analyses. No significant differences were found in the characteristics of infants enrolled in the study compared with those whose parents declined participation.

The final study cohort consisted of 113 infants (Figure 6.1) with a mean GA of 28 ±1.6 weeks (minimum 24.7, maximum 32.0), and a mean BW of 1064 ±241 grams (minimum 570, maximum 1680). Six infants (5%) had a BW <1000 grams, while their GA was ≥30 weeks. Eleven (9.7%) were small for GA, which was defined as a BW <P10 according to the reference curves for birth weight by GA, gender and parity of the Netherlands Perinatal Registry. Other characteristics of the cohort are shown in Table 6.1.

In our cohort, 43 infants (38.1%) were part of a multiple birth. Eight of them were the only survivor. Eighteen infants were randomly excluded as described in the data-analysis section. The final sample for the analyses consisted of 95/113 (84.1%) infants. The mean ± SD corrected age at each assessment was 3.1 ± 0.14 months (T1), 6.5 ± 0.52 months (T2), and 16.3 ± 1.36 months (T3).

Concurrent validity TIMP versus AIMS

The average raw score on the TIMP for the 95 selected subjects at three months CA was 99.4 ± 12.99 (minimum 54, maximum 127). Simultaneously, the average raw-score

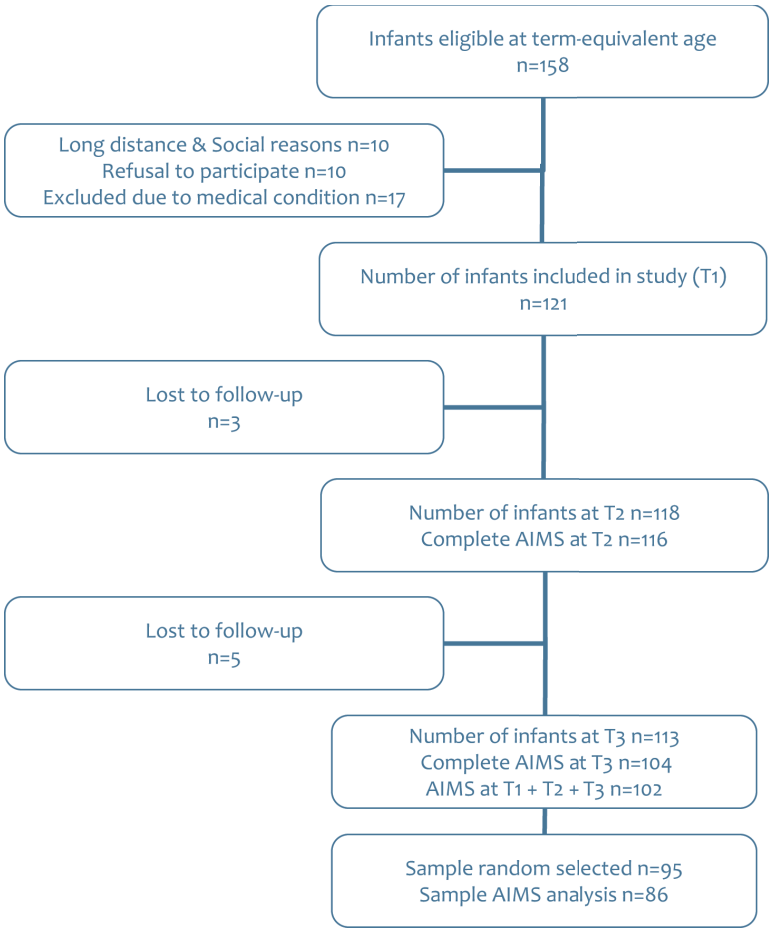

Figure 6.1 Flowchart of the study cohort. T1, T2, T3 = 3, 6, 15 months corrected age; AIMS = Alberta Infant Motor Scale; n = Number.

on the AIMS was 10.5 ± 2.18 (minimum 4, maximum 16). The mean Z-scores were -0.48 ± 0.68 on the TIMP, and -0.57 ± 0.68 on the AIMS. The Pearson correlation coefficient between TIMP and AIMS raw-scores was 0.82, and between Z-scores 0.71 ($p<0.000$). An ROC-curve was executed to compare TIMP Z-scores with a cut-off score on the AIMS (P10) regarding high risk for poor developmental outcome in 4-months old infants.[18] A cut-off Z-score of -1.0 on the TIMP had the best diagnostic agreement of 92% ($\kappa=0.67$, $p=0.000$) with an AIMS score <P10 (sensitivity 0.91; specificity 0.92). This value indicates a good agreement beyond change. The advised cut-off value of -0.5[19] provided in

Table 6.1 Characteristics of the cohort of infants born at <30 weeks of gestation and/or with a birth weight <1000 grams

Characteristics	Cohort	Sample with one infant per multiple birth
Included infants (n, %)	113 (100)	95 (100)
Gestational age		
Mean (SD), in weeks	28 (1.57)	28.1 (1.59)
Birth weight		
Mean (SD), in grams	1064 (241)	1061 (251)
Gender (n, %)		
Male	60 (53.1)	53 (55.8)
Female	53 (46.9)	42 (44.2)
Ethnicity (n, %)		
Western	93 (82.3)	78 (82.1)
Non-Western	20 (17.7)	17 (17.9)
Plurality (n, %)		
Singleton	70 (61.9)	70 (73.7)
Multiple birth (1 triplet)	43 (38.1)	25 (26.3)
Median duration of NICU/HC stay in days (IQR)	39 (29.5)	39 (32)
Median duration of mechanical ventilation in days (IQR)	3 (7)	3 (7)
Cranial ultrasound findings (n, %)		
IVH grade I	12 (10.0)	9 (9.5)
IVH grade II	25 (22.1)	21 (22.1)
IVH grade III	8 (7.1)	6 (6.3)
IVH grade IV	0 (	0 (
PVL grade I	40 (35.4)	36 (37.9)
c-PVL	0 (	0 (
PHVD	12 (10.6)	10 (10.5)
PHVD with VP-shunt insertion	2 (1.8)	1 (1.1)
Sepsis (n, %)		
Early onset	6 (5.3)	6 (6.3)
Late onset (>7 days)	24 (21.2)	20 (21.1)
Other medical conditions (n, %)		
CLD		
Grade I: >30 days O_2	42 (37.2)	36 (37.9)
Grade II: O_2 >36 weeks post-menstrual age	14 (12.4)	12 (12.6)
NEC	3 (2.7)	3 (3.2)

IQR = Inter-quartile range; NICU = Neonatal intensive care unit; HC = High-care; IVH = Intraventricular haemorrhage; (c)PVL = (Cystic) periventricular leukomalacia; PHVD = Post-haemorrhagic ventricular dilatation; VP = Ventricular-peritoneal; CLD = Chronic lung disease; NEC = Necrotising enterocolitis.

our cohort an equal sensitivity, but lower specificity of 0.67, leading to a decrease in diagnostic agreement (69%; κ=0.28).

Prediction gross motor maturation at T3

In one infant it was not possible to obtain a total AIMS-score at T2, and in two other infants at T3, all due to being irritable or tired. At T3, four infants were older than 19 months CA and two were not examined by the physical therapist due to understaffing. Eventually, 86/95 infants (90.5%) had completed all tests (Figure 6.1 and 6.2; Table 6.2), and their test-scores were used to analyse the predictive ability of the TIMP and the AIMS.

Neither TIMP nor AIMS Z-scores at T1 were associated with the outcome on gross motor maturation at T3. Only the AIMS Z-scores at T2 were significantly associated with AIMS-scores at T3 (B=0.53; 95% CI 0.29-0.77; *p*=0.000). The explained variance was

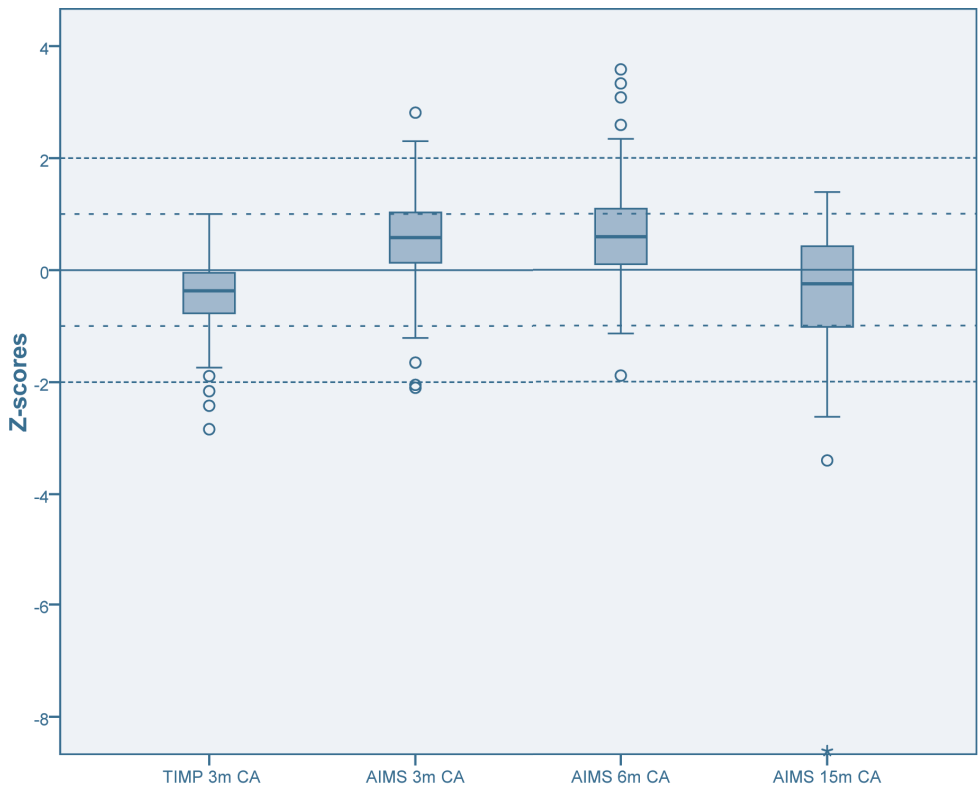

Figure 6.2 Boxplots of Z-scores on the TIMP and the AIMS at T1, T2 and T3 (n=86).

Table 6.2 TIMP and AIMS scores

n=86[a]	T1 TIMP	T1 AIMS[b]	T2 AIMS[b]	T3 AIMS[b]
Mean raw scores (min-max)	99.8 (54–127)	10.5 (4–16)	21.5 (10–38)	54.2 (26–58)
Mean Z-scores (SD)	-0.48 (0.70)	0.47 (0.97)	0.67 (1.04)	-0.41 (1.27)
Median Z-scores	-0.37	0.58	0.59	-0.25
Min-max Z-scores	-2.84 – +1.00	-2.84 – +2.81	-1.89 – +3.58	-8.61 – +1.39

n = Number; T1, T2, T3 = 3, 6, 15 months corrected age; TIMP = Test of Infant Motor Performance; AIMS = Alberta Infant Motor Scale.
[a] Only infants with three test scores were included in the analyses.
[b] Preterm norms of the AIMS were used for analyses of prediction.[21]

low: r^2=0.19, indicating that 19% of the variance in AIMS-scores at T3 could be explained by the scores at T2. At T3, 48/86 (55.8%) performed at least 'early stepping' and 29/86 (33.7%) 'walks alone'. Infants with a Z-score of +1 on the AIMS at T2 were more likely to show the individual items 'early stepping' (OR 2.5; 95% CI 1.43-4.43; *p*=0.000) and 'walks alone' (OR 3.2; 95% CI 1.76-5.86; *p*=0.000) at T3 compared to infants with a Z-score of 0.

Independent walking

The age of onset of independent walking was known in 90/95 (94.7%) infants at the end of the study. The median age was 15.7 months CA (95% CI 15.21-16.26). The hazard ratio of independent walking was 2.1 (95% CI 1.69-2.56; *p*=0.000) in infants with an AIMS Z-score +1 at T2 compared to infants with a Z-score of 0. None of the medical or demographical factors was significantly associated with the age of independent walking, except ethnicity. Seventeen of the 95 infants (17.9%) were of non-Western origin: seven North-African, two African, two Arabian, one Turkish, one Antillean, one Asian, and three of mixed origin. Despite the heterogenic composition of the non-Western group, age of independent walking was significantly earlier than in Western infants (median age 14.4 months CA, 95% CI 11.9–16.9 versus 15.9 months CA, 95% CI 15.3-16.4; *p*=0.041). Kaplan-Meier curves are shown in Figure 6.3. The hazard ratio of independent walking on a certain age of non-Western infants was almost twofold compared to Western infants (1.8; 95% CI 1.01-3.04; *p*=0.045).

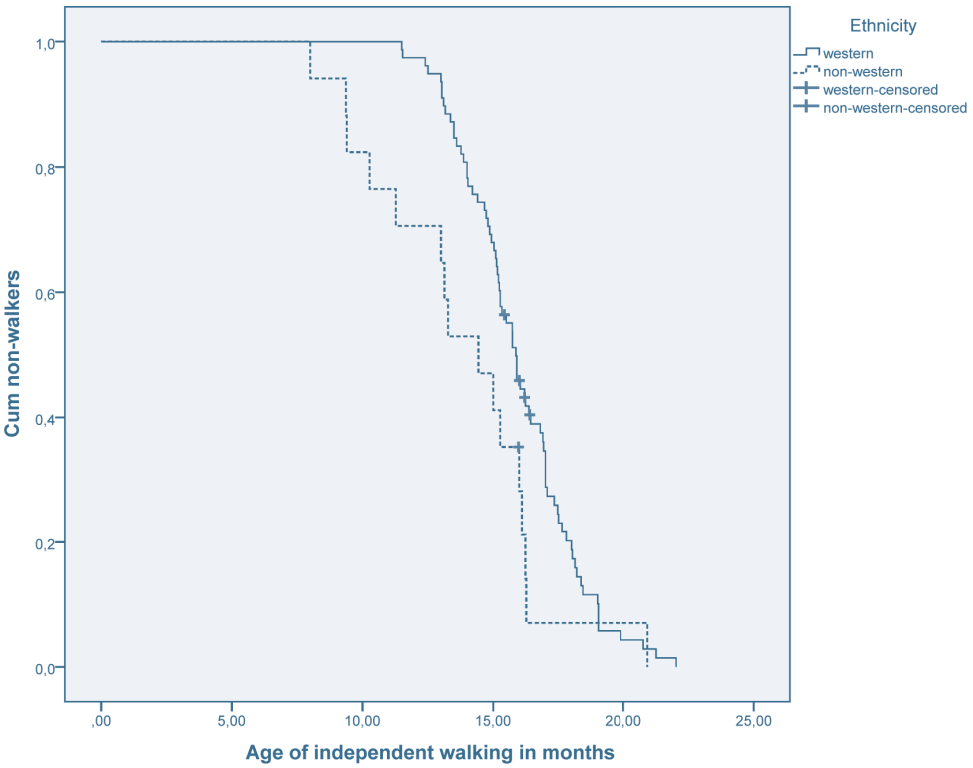

Figure 6.3 Kaplan–Meier curve of walking independently stratified by ethnicity, filtered on randomized one of multiple birth infants: n=95; 17 (17.9%) from non-Western origin, n=5 censored.

DISCUSSION

Fifty percent of infants born very preterm walked independently at 15.7 months CA. Compared to the norm values of term born infants, the median onset was more than three months later[16], even though their age was corrected for prematurity. In non-Western infants, independent walking emerged about six weeks earlier than in Western infants. The clinical characteristics in both sub-groups were comparable, so cultural differences or child-rearing practices might play a role in developing walking skills. Surprisingly, none of the other perinatal or medical factors was associated with the onset of independent walking. These findings suggest that the emergence of independent walking in relatively healthy infants born preterm is more related to cultural and individual variables, than to their medical history. Some[5,6,9,11], but not all[12] previous

studies have found a delay in the onset of walking. Among these studies the magnitude of delay varies (1-2 months), but we found a remarkably longer delay. Compared to our study, populations differ regarding GA (<37 weeks)[9], BW (<1500 grams)[5,6,9,11,12], ethnicity[9,11,12] or smaller numbers of infants included.[5,11]

Comparing the TIMP and the AIMS to measure motor development at a very early age, we found a good correlation in raw-scores and Z-scores at 3 months CA. The values were even higher than described in the study of Campbell et al.[19] We also determined a lower cut-off point to identify 92% of the same infants with abnormal developmental outcome compared to the AIMS. Our results differ from that of Campbell et al., which might be due to a difference in number of assessors and as such a possible bias: in the present study one versus 11 in Campbell's study. Next, in our study both tests were performed simultaneously, instead of at two separate visits. Furthermore, the cut-off point in our study was -1.0 SD from the (TIMP) norm population, while the -0.5 SD in the Campbell study was distracted from the mean of the sample of her study.[19] Although the TIMP and the AIMS are designed to measure complementary aspects of motor development, in casu postural control versus neuromaturation, the overlap and agreement in detecting infants with a low motor performance at 3 months CA is substantial. This raises the question whether these instruments, despite the distinctive constructs, might measure the same phenomena. In the neonatal follow-up clinic the AIMS might be preferable because of the short time needed and the hands-off structure as distinct from the TIMP where extensive handling is required. Nonetheless, clinicians might make different choices dependent on the circumstances in their hospital. Anyway, in the analyses to predict gross motor outcome and walking skills, the results on the TIMP and/or the AIMS at three months CA were not significantly associated with the outcome at six or 15 months CA in our sample.

The AIMS-scores at six months CA were significantly associated with the scores at 15 months CA. A stronger relation was found in predicting the items 'early walking' and particularly 'walking alone'. A plausible interpretation of this finding is, that infants with higher scores at six months CA are two- to threefold more likely to demonstrate advanced walking skills, compared to infants with one Z-score lower. However, the six-month CA scores must be interpreted with caution, because they explain only a fifth of the score at 15 months CA.

An important strength of the present study is that we examined a large cohort of infants born very preterm, of younger gestational ages than in previous studies. The successful follow-up (93% at 15 months CA), with only a few infants lost, reveals the

typical development of these vulnerable and immature infants regarding the onset of independent walking. To monitor walking skills, the follow-up around 15 months CA turned out to be an interesting age. Besides, we chose to select only one infant per twin for analysis, which is not often done. An advantage is that one eliminates the inter-twin dependency to strengthen the findings methodologically. A disadvantage is the smaller sample, but the findings between the samples were highly comparable.

One limitation was the missing data of independent walking in five infants, but a survival analysis was helpful to overcome this shortcoming. Another limitation was the actual age at the third assessment, 16 months CA on average instead of 15, due to cancelling of appointments by parents in combination with a busy schedule at the follow-up clinic. This postponement resulted in missing AIMS results of five infants at T3, who were too old for the test. Hence, this was in our study inevitable being part of usual clinical practice.

In future studies, it may be interesting to examine the ability of the AIMS (and TIMP) to predict gross motor outcome and walking skills at an older age, as well as quality of walking skills.

In conclusion, we found that infants born at <30 weeks of gestation start independent walking about three months later than term born infants, even with full correction for prematurity. The level of gross-motor maturation at six months CA, and ethnicity are associated with the age of independent walking, but not their medical history. Infant and cultural factors seem to determine the onset of walking skills. Despite good concurrent validity, neither the TIMP nor the AIMS at three months CA can reliably predict gross motor maturation or walking skills at 15 months CA in infants born very preterm. A clinical implication is that the age of three months might be too early to assess infants if the goal is to give any valid prediction on gross motor outcome. This indicates also that a more valid prediction about the age of independent walking could be given at the earliest age of six months CA.

Acknowledgements

We gratefully acknowledge Dr. Marian Jongmans for support in the examinations of the 15-months old infants, Cas Kruitwagen MSc for his advice on the statistical analyses of the study, and most importantly, all the families who participated in this study.

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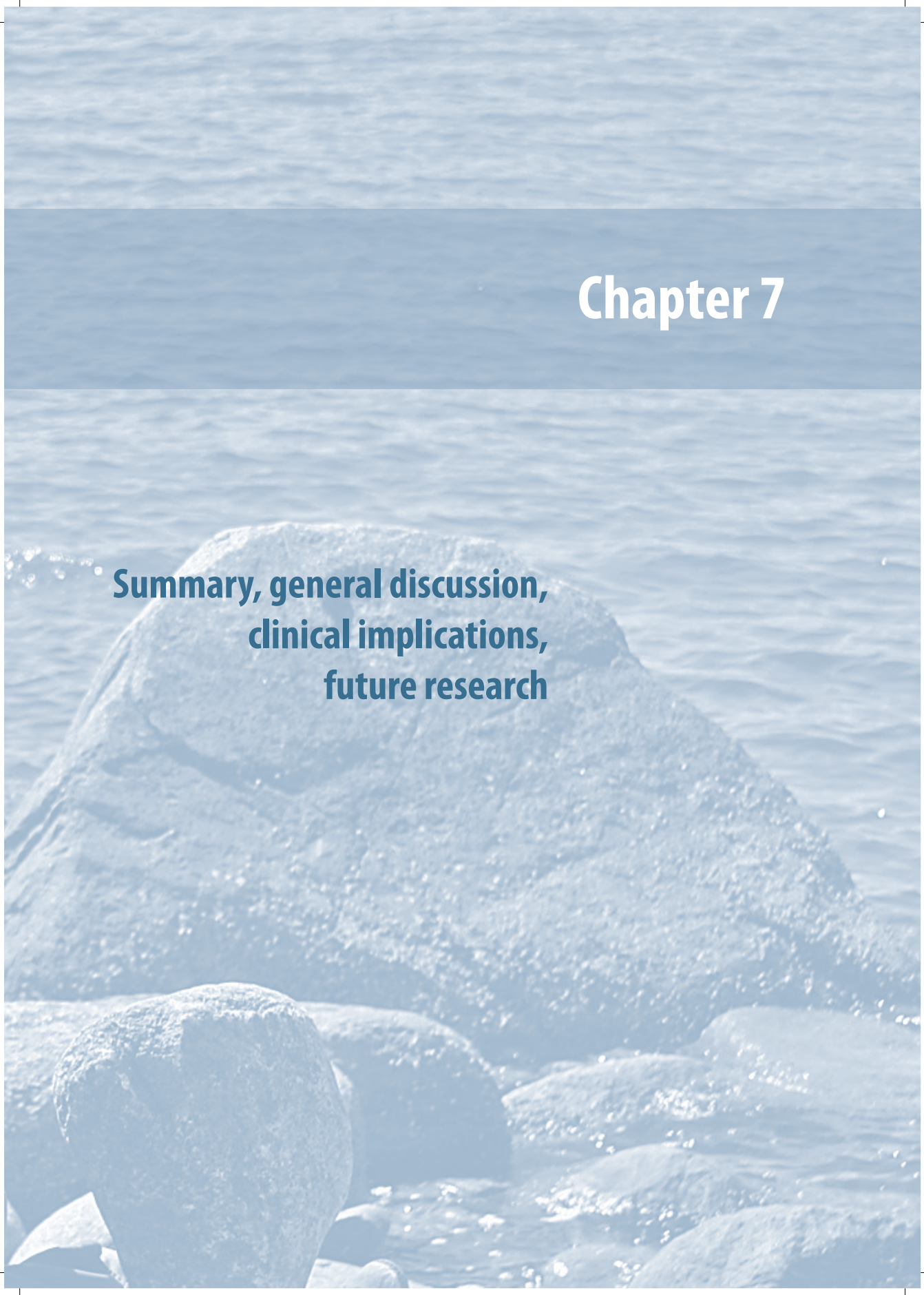
Chapter 7

Summary, general discussion, clinical implications, future research



SUMMARY

In this thesis five studies on motor performance of very young infants are presented, all within the domain of pediatric physical therapy. The topics in the studies meet the domain of pediatricians and are realised in close collaboration with the neonatology department of the Wilhelmina Children's Hospital, in Utrecht, The Netherlands.

The main aim of the thesis was to contribute to the diagnostic process and clinical decision making in very young infants with an atypical motor performance, influenced by both an asymmetric development, and a development according to a preterm birth.

In **Chapter 1**, an introduction provides information about the prevalence of asymmetry in full-term born infants, etiology and risk factors, and the role of pediatric physical therapists in the diagnostic process. Subsequently, the characteristics of infants born preterm are described, as a run-up to the studies about prevalence of asymmetry in infants born preterm. After a description of instruments used in the studies to measure early motor development, the chapter ends with a paragraph on theories of motor development.

In **Part I**, **Chapter 2**, a review of current literature is conducted on the incidence of disorders or dysfunctions possibly leading to a symptomatic asymmetry and accompanying signs that differentiate symptomatic asymmetry from idiopathic asymmetry in the first six months of life. A comprehensive literature search was done in peer-reviewed literature as well as in clinical textbooks from the various specialties. Although a great number of diagnoses were found, it turned out that prevalence / incidence was not always or inconsistently documented. We selected six diagnoses with a clear incidence rate (/1000): developmental dysplasia of the hip (40), perinatal fracture of the clavicle (35), congenital muscular torticollis (20), obstetric brachial plexus lesion (4), central nervous system disorder (2) and craniosynostosis (0.03). Besides, we defined several groups of disorders: congenital abnormalities or malformations (divided into musculoskeletal and chromosomal), sensory systems disorders (divided into ocular and hearing disorders), and a rest group of acquired asymmetry (e.g. due to an inflammatory condition). Regarding the acquired asymmetry, the signs and symptoms are less well known in physical therapy practice, but the consequences of missing these signs can be very serious. We derived from the literature a list of possible red flags.

Part I, Chapter 3 continues on the topic of differential diagnostics between symptomatic and idiopathic asymmetry. A qualitative study design was used to achieve the objective to develop a screening instrument for pediatric physical therapists applicable in the clinical evaluation of young infants with an asymmetric head posture. Two consensus methods were chosen: a two-round Delphi design and an expert meeting using nominal group technique. In the two Delphi rounds 13 experts, six medical specialists and seven pediatric physical therapists, were polled anonymously with a digital questionnaire on three topics: (1) completion and classification of a list of possible diagnoses leading to symptomatic asymmetry; (2) to value on a five-point scale clinical diagnostic criteria (CDC) to establish the degree of relevance relating to the diagnoses; (3) collection and rating of signs or symptoms considered to be a 'red flag'. After Round 1, a divergence in opinions came out and some valuable additions. Between the two rounds small revisions were made to the CDC. The experts were provided with tabulated responses of Round 1. The results after two rounds were: saturation of diagnoses and CDC and a clear convergence of rating of CDC. In most sets of CDC two criteria with a mean rate of relevance ≥4 could be distinguished. The consistency of the panel increased from Cronbach's-α =0.67 in Round 1 to 0.89 in Round 2. Based on these results, a draft version of the screening instrument was made, containing the 10 most frequently occurring symptomatic asymmetry diagnoses with the two most relevant CDC for each diagnosis, and a list of absolutely and relatively important red flags. This draft version was proposed to a new expert panel, consisting of eight pediatric physical therapists. In a face-to-face meeting, they discussed and considered carefully the choices that were made. The panel stated that with minor adaptations (1) the classification scheme was comprehensive for all known causes of symptomatic asymmetry in infants in the first six months of life; (2) concordance existed regarding the selection of the 10 most frequent occurring diagnoses with for each diagnosis the two most relevant CDC based on the results of the Delphi process; (3) life-threatening diagnoses were sufficiently excluded by using the eight selected red flags; (4) the established instrument is useful and efficient for pediatric physical therapists. Finally, a differential diagnostic screening instrument containing a classification scheme, the CDC for differential diagnostics, and a list of red flags was established, on the basis of literature search and expert consensus. Cross-validity and reliability of the instrument have to be investigated in future research.

In **Part II**, the focus of this thesis shifts from symptomatic asymmetry toward idiopathic asymmetry, more specific in a preterm born population.

Part II, Chapter 4 explored retrospectively the prevalence and determinants of idiopathic asymmetry in a birth cohort of infants born at a gestational age (GA) <32 weeks or with a birth weight (BW) <1000 grams. The three objectives were: (1) to explore the prevalence of an idiopathic asymmetry defined as a positional preference of the head and/or deformational plagiocephaly (DP) at term-equivalent age (TEA) and at 6 months corrected age (CA); (2) whether demographical, perinatal, and medical factors were predictors of the asymmetry; (3) differences in motor maturation at 6 months CA between infants with and without asymmetry measured with the Alberta Infant Motor Scale (AIMS). The data were abstracted from individual electronic patient files, medical correspondence, and pediatric physical therapy charts of 192 infants. All infants were admitted in 2006 to the neonatal intensive care unit of the Wilhelmina Children's Hospital in Utrecht, and visited the neonatal follow-up clinic at TEA and around 6 months CA. Sixteen infants with a diagnosis of a symptomatic asymmetry were excluded. At TEA, the prevalence rate of a positional preference of the head was 44.8% (86/192); 10.4% (20/192) had an (often minimal) DP. At 6 months CA, no infants with a positional preference were observed, but in 13% (25/192) a DP was reported. From all putative prediction factors, only positional preference at TEA (OR 3.0; 95% CI 1.23-7.39), multiple birth (aOR 3.2; 95% CI 1.28-7.31) and male gender (aOR 3.2; 95% CI 1.14-9.15) predicted significantly (p<0.05) the presence of DP at 6 months CA. In infants with a positional preference at TEA, a significant lower AIMS-score was found at 6 months CA. Between infants with and without DP at 6 months CA the difference in Z-scores on the AIMS was not significant (T-test). We concluded that in infants born at a GA <32 weeks, a positional preference of the head was found in nearly half of the studied cohort at TEA, which is substantially higher than reported in literature on full-term born infants. The finding, that at 6 months CA the gross motor maturation was less well developed, indicates that motor maturation plays a role in this transient phenomenon. The high prevalence requires extra alertness to prevent the development of DP, especially in boys and twins.

The findings in the retrospective study of Chapter 4 legitimised a prospective study to get more insight in the natural course of idiopathic asymmetry in infants born preterm. Moreover we wanted to know more about the role of motor behaviour and postural control, which are presumed to be different in infants born very preterm. **Part II, Chapter 5**, reports a prospective study from birth up to 6 months CA in infants born with a GA <30 weeks or a BW <1000 grams. The objectives were to describe the natural course of a positional preference of the head and DP, and to explore predictive factors for the persistence of these phenomena. The eligible infants were born between January

2009 and October 2010, admitted to the neonatal intensive care unit of the Wilhelmina Children's Hospital in Utrecht and visited the neonatal follow-up clinic at TEA. Sixteen infants had to be excluded due to a diagnosed symptomatic asymmetry. The parents of 120 infants consented to the study. The infants underwent 3 assessments in a six-month period, at TEA and 6 months CA at the follow-up clinic, and at 3 months CA at home. The presence of DP, evaluated using the Argenta classification, and a score of 1-6 on an asymmetry performance scale were primary outcome measures at 6 months CA. Demographic and perinatal data, and medical history were recorded. The social environment and child-rearing practices were examined via digital questionnaire. At TEA a general movements (GMs) assessment and the screening version of the Test of Infant Motor Performance (TIMP) were performed. GMs, TIMP and AIMS were used at the CA of 3 months. At 6 months only the AIMS was applied. The prevalence of a positional preference of the head at TEA was 65.8% (79/120) and 36.7% (44/120) at 3 months CA. DP was observed in 30% (36/120) and 50% (60/120), respectively. At 6 months CA, 15.8% (19/120) scored ≥2/6 on the asymmetry scale and a DP with minimal Argenta degree II was found in 23.3% (28/120). The presence of a DP at 3 months CA predicted an asymmetric motor performance at 6 months CA. Chronic lung disease and/or slow gross motor maturation at 3 months CA predicted the persistence of DP up to 6 months CA. All other factors, including child-rearing practices, had no statistically significant influence on the persistence of the idiopathic asymmetry at 6 months CA. We concluded that in very preterm born infants, a positional preference of the head at TEA seems to be a normal aspect of their motor repertoire, with limited ability to predict the persistence of asymmetric motor performance. The high prevalence of DP, as seen at 3 months CA, had more than halved by 6 months CA, except in infants with a history of chronic lung disease grade II and or a slow gross motor maturation at three months CA.

Since we had studied prospectively a large and relatively healthy cohort of infants born very preterm in the asymmetry study, we decided to continue the follow-up through to the 15-months assessment to be able to analyse gross motor outcome. In **Part III, Chapter 6**, we examined the concurrent validity of the two motor performance instruments that were used at 3 months CA (TIMP and AIMS) and the ability of both instruments to predict gross motor outcome around 15 months CA and the age of walking independently. From the original cohort, 113 infants completed all tests at 3, 6 and 15 months CA. Concurrent validity was analysed with Pearson correlation coefficient of raw-scores and Z-scores on TIMP and AIMS, and a cut-off point for diagnostic agreement was determined. Linear and logistic regression was used to determine predictive validity. With Cox regression

we analysed the age of independent walking, because the stage of this ability had not yet been established in all infants at the end of the study. The incidence of plurality in cohorts of infants born very preterm is high and a dependency in motor development is presumed. Therefore we randomly selected a sample with only one of the twin infants for our analyses. The correlation between TIMP and AIMS raw-scores was 0.82, and between Z-scores 0.71. A cut-off Z-score of -1.0 on the TIMP had a diagnostic agreement of 92% (κ=0.67) with an AIMS score <P10. Neither TIMP nor AIMS scores at 3 month CA were associated with gross motor outcome at 15 month CA. The AIMS scores at 6 months CA predicted the AIMS scores at 15 months CA (B=0.53; 95% CI 0.29-0.77; *p*=0.000), and the items 'early stepping' (OR 2.6; 95% CI 1.55-4.47; *p*=0.000) and 'walks alone' (OR 3.2; 95% CI 1.86-5.65; *p*=0.000). The explained variance (r^2=0.19) indicated that the scores at 6 months CA could explain 19% of the variance in AIMS-scores at 15 months CA. The median age of independent walking was 15.7 (95% CI 15.21-16.26) months CA. None of the demographical or medical factors was related to the age of independent walking, except ethnicity. Non-Western infants walked significantly earlier than Western infants (14.4 versus 15.9 months CA; *p*=0.041). The hazard ratio of independent walking at a certain age of Non-Western infants was almost twofold compared to Western infants (1.8; 95% CI 1.01-3.04; *p*=0.045). In conclusion, we found that infants born at <30 weeks of gestation start independent walking about three months later than full-term born infants, even with full correction for prematurity. The level of gross motor maturation at 6 months CA, and ethnicity are associated with the age of independent walking, but not their medical history. Infant and cultural factors seem to determine the onset of walking skills. Despite good concurrent validity, neither the TIMP nor the AIMS at three months CA can reliably predict gross motor maturation or walking skills at 15 months CA in infants born very preterm. A clinical implication is that the age of three months might be too early to assess infants if the goal is to give any valid prediction on gross motor outcome. This indicates also that no valid prediction about the age of independent walking could be given prior to six months CA using the AIMS.

CONCLUSIONS

The following conclusions based on the studies in this thesis can be drawn:

- A differential diagnostic screening instrument to distinguish symptomatic from idiopathic asymmetry in the first six months of life was established. The instrument contains a classification scheme, CDC for differential diagnostics, and a list of red

flags, based on a literature search and expert consensus. An expert panel stated that the instrument is useful and efficient for pediatric physical therapy practice in the clinical evaluation of asymmetry in infancy. (Part I, Chapter 2 and 3)

- In very preterm born infants substantially higher prevalence rates of positional preference and DP were found at TEA and 3 months CA than reported in literature on full-term born infants.
- A higher prevalence in boys and twins was not consistently demonstrated. (Part II, Chapter 4 and 5)
- At 6 months CA, 15.8% (19/120) scored ≥2/6 on the asymmetry scale. A DP with minimal Argenta degree II was found in 23.3% (28/120). The presence of a DP at 3 months CA predicted an asymmetric motor performance at 6 months CA. Chronic lung disease and/or slow gross motor maturation at 3 months CA predicted the persistence of DP up to 6 months CA. All other factors, including child-rearing practices, had no significant influence on the persistence of the idiopathic asymmetry at 6 months CA.
- In very preterm born infants, a positional preference of the head at TEA seems to be a normal aspect of their motor repertoire, with limited ability to predict the persistence of asymmetric motor performance. (Part II, Chapter 5)
- Despite good concurrent validity, neither the TIMP nor the AIMS at three months CA could reliably predict gross motor maturation or walking skills at 15 months CA in infants born very preterm.
- AIMS-scores at 6 months CA explained 19% of the variance in AIMS-scores at 15 months CA.
- The level of gross motor maturation at 6 months CA, measured with the AIMS, and ethnicity were associated with the age of independent walking, but their medical history was not.
- The median age of independent walking in infants born <30 weeks of gestation was 15.7 months CA. They start independent walking about three months later compared to the norm population of the AIMS. (Part III, Chapter 6)

GENERAL DISCUSSION

Clinical reasoning

Clinical reasoning is considered to be the foundation of professional clinical practice.[1] A range of clinical reasoning strategies are used by physical therapists, depending of the field they work in, their experience, knowledge and reflective competency, and the clinical question involved.[2] Generally these strategies are hypothesis-oriented and collaborative.[1] In the Dutch situation, patients have direct access to physical therapy, which stresses the diagnostic competency of the therapists. Moreover, it requires transparency of the used procedures.[3] In the diagnostic process both hypothesis deduction and pattern recognition are of importance. Physical therapists must be aware of and able to distinguish expected from unusual patterns. Besides, they have to recognise biomedical factors that contraindicate physiotherapy as clinical 'red flags', suggesting the presence of serious organic pathology.[4,5] The Hypothesis Oriented Algorithm for Clinicians version II (HOAC-II)[6] supports physical therapists in this diagnostic process. With our differential diagnostic instrument we defined criteria that can be used in assuming or rejecting hypotheses assessing an asymmetry in young infants, a health condition frequently seen in pediatric physical therapy practice. For novice pediatric physical therapists it creates a methodical instrument, while in more experienced colleagues it may prevent automatic pattern recognition of idiopathic asymmetry if the asymmetry is symptomatic of nature. (Part I, Chapter 2 and 3)

Clinical decision-making

Another approach of clinical reasoning is decision making regarding intervention and case management. Considering the need and intensity of an intervention, the strategy is more collaborative[1], as context factors, as well as motor behaviour of the infant in question are of equal value as the degree of asymmetry. In our studies on idiopathic asymmetry in infants born very preterm, we determined that these infants are clearly a risk group, with high prevalence rates. Nevertheless we think that intervention is only needed in the more complex cases. A number of factors support this opinion. At first, the large amount of infants having a positional preference at TEA and the finding that gross motor maturity at six months CA was significantly less well developed in the same infants, indicate that an asymmetry in posture at TEA is related to the level of neuromaturation. Hence the association of a positional preference at TEA with

the persistence of DP at six months CA was rather low. Therefore, to give all these infants with a positional preference physical therapy intervention is unrealistic and unnecessary. Secondly, although the degree of DP has not been measured exactly, we established that only a small number of infants had an obvious, easy to see deformation at six months CA. This was also visible in the small number of infants referred for helmet treatment. And most importantly, because all infants had overcome very serious health problems in the first months of their lives, parents often considered a discrete plagiocephaly of minor importance. To make decisions about the need of intervention, pediatric physical therapists have to weigh the asymmetry parameters and the ability to act upon these, the gross motor development so far, the presence of predictors like chronic lung disease, but also the family system and their amenability. (Part II, Chapter 4 and 5)

Ability to predict motor development

In our study on the ability to predict walking skills and gross motor outcome based on early measurements with TIMP and AIMS, we found that the measurements at three months CA had no significant predictive value, while measurements at six months CA had an increasing predictive value.

The idea to be able to predict motor development at a very early age can be traced back to a more traditional perspective with a preposition that developmental shape

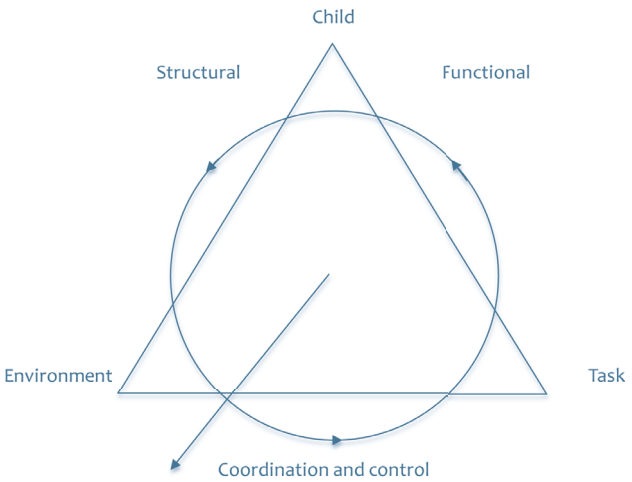


Figure 7.1 Newell's (1986) model of constraints.

is linear of nature. To date, theoretical approaches on motor development no longer support this view. Adolph described the variety of developmental shapes, based on numerous observations and research.[7,8] The Newell model illustrates, from an ecological perspective, that the emergence of (more coordinated) motor skills are influenced by continuous interaction between constraints of the particular infants (both structural and functional), and environmental and task constraints (Figure 7.1).[9] A good example is the intra-uterine compared to the extra-uterine environment. This change in constraints has a huge influence on motor performance, as infants born preterm demonstrate. Besides, many researchers emphasize the importance of repeated measurements regarding motor development. In a longitudinal design, remarkable differences are observed between cross-sectional and longitudinally obtained data.[10-16] The differences reflect intra-individual variability and the influence of changing constraints. From this perspective, repeated measurements during follow-up and careful interpretation of early results are crucial in developmental surveillance of infants at risk.

CLINICAL IMPLICATIONS

The diagnosis idiopathic asymmetry can only be made after excluding pathology. The differential diagnostic screening instrument is regarded useful and efficient for pediatric physical therapists in the clinical evaluation of young infants with an asymmetry. The reduction in items created a practical, no time-consuming instrument. The instrument can be used to formulate and verify hypotheses during the diagnostic process. Our advice is to use the 'red flag' list in the first intake to exclude serious pathology. After that, the clinical diagnostic criteria can easily be completed in the first assessment. In doubt, the infants must be referred to a pediatrician to confirm the diagnosis.

Our findings on idiopathic asymmetry in infants born very preterm confirm that these infants are clearly at risk for the development of DP. A majority of infants have a positional preference at TEA, and 50% a DP at 3 months CA. On the other hand, following the infants prospectively we found that positional preference at TEA was not associated with persistence of DP at 6 months CA. The question is which infant needs intervention and for whom is a wait-and-see policy supported with preventive advices enough? There are indications that infants who needed oxygen >1 month after birth, and even stronger that infants with oxygen dependency beyond 36 weeks post menstrual age, are the infants eligible for timely intervention. For the remaining infants it will depend on the course of motor development, as well as on variability of positioning they

show, whether intervention is needed. Providing advices to the parents regularly and consistently regarding positioning is of major importance for all infants.

The conclusions of the study on predictive validity of AIMS and TIMP imply that the age of 3 months CA might be too early to assess very preterm born infants, if the goal is to give any valid prediction on gross motor outcome. This indicates also that no valid prediction about the age of independent walking could be given prior to 6 months CA using the AIMS.

The delay on emergence of independent walking compared to a full-term norm population is substantial. We suggest to explain parents that this delay is normal for infants born very preterm.

DIRECTIONS FOR FUTURE RESEARCH

1. On the topic of differential diagnostics regarding symptomatic asymmetry in young infants, the differential diagnostic screening instrument needs to be (cross-) validated. Diagnostic value (specificity and sensitivity) of the selected 'red flags' and clinical diagnostic criteria needs to be confirmed.
2. Regarding the high prevalence of asymmetry in infants born preterm, the focus of future research might best be on primary or secondary prevention of DP, especially in infants diagnosed with chronic lung disease.
3. Motor developmental trajectories of infants studied prospectively, with a high assessment frequency, may contribute to a better understanding of (variation in) motor profiles of typically developing infants born full term and preterm. We have started the analysis of the data obtained in our prospective study to describe within-subject gross motor trajectories measured with the AIMS. Subsequently, we have started to undertake a research project to establish Dutch norm values of the AIMS, in cooperation with the developers of the AIMS in Canada. Furthermore, exploration of the need of updating AIMS-preterm norms can be part of this project. At the same time, longitudinally obtained scores on the AIMS might be an interesting novelty.

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Nederlandse samenvatting (Summary in Dutch)

In dit proefschrift worden vijf studies over motoriek van zeer jonge kinderen gepresenteerd passend binnen het domein kinderfysiotherapie. De onderwerpen van de studies hebben raakvlakken met het domein kindergeneeskunde en zijn tot stand gekomen in nauwe samenwerking met de afdeling neonatologie van het Wilhelmina Kinderziekenhuis in Utrecht.

Het generieke doel van het proefschrift was een bijdrage te leveren aan het diagnostisch proces en het nemen van klinische beslissingen bij zeer jonge kinderen met een atypische motoriek, die zowel door een asymmetrische ontwikkeling als door een ontwikkeling passend bij vroeggeboorte beïnvloed wordt.

De introductie in **hoofdstuk 1** geeft informatie over de prevalentie van asymmetrie bij voldragen kinderen, zichtbaar in een te sterke voorkeurshouding van het hoofd en/of een schedelvervorming (deformerende plagiocephalie, DP), twee verschijnselen die elkaar beïnvloeden. Oorzaken en risicofactoren van zo'n asymmetrie en de rol van de kinderfysiotherapeut in het diagnostisch proces worden beschreven. Vervolgens worden kenmerken van te vroeg geboren kinderen beschreven, als opmaat naar de studies over prevalentie van asymmetrie bij te vroeg geboren kinderen. Na de beschrijving van de gebruikte meetinstrumenten naar vroege motorische ontwikkeling, eindigt het hoofdstuk met een paragraaf over motorische ontwikkelingstheorieën.

In **deel 1**, **hoofdstuk 2**, is een literatuuronderzoek uitgevoerd naar de incidentie van aandoeningen en disfuncties die mogelijk kunnen leiden tot een symptomatische asymmetrie en over de daarbij horende kenmerken die de symptomatische asymmetrie onderscheiden van een idiopathische in de eerste zes levensmaanden. De uitgebreide zoekstring omvatte zowel peer-reviewed literatuur als medische handboeken van de verschillende specialismen. Weliswaar zijn veel mogelijke diagnoses gevonden, maar de prevalentie / incidentie werd niet altijd of soms inconsistent beschreven. We selecteerden zes diagnoses met een duidelijk beschreven incidentie (/1000): dysplastische heupontwikkeling (40), perinatale claviculafractuur (35), congenitale myogene torticollis (20), obstetrische plexus brachialis lesie (4), centraal neurologische aandoening (2) en craniosynostose (0.03). Daarnaast definieerden we enkele groepen aandoeningen: aangeboren afwijkingen of misvormingen (onderverdeeld in musculoskeletaal en chromosomaal), aandoeningen van het zintuiglijk systeem (visus en gehoor), en een restgroep verworven asymmetrie ten gevolge van interne problematiek (bijvoorbeeld ten gevolge van een infectie of tumor). Tekens en symptomen van deze verworven asymmetrieën zijn minder goed bekend binnen de fysiotherapie, maar het

missen van deze signalen kan ernstige gevolgen hebben. Hiervoor hebben wij hebben een lijst met mogelijke 'rode vlaggen' opgesteld, die zijn afgeleid uit de gevonden literatuur.

Deel 2, hoofdstuk 3 gaat verder met de differentiaaldiagnostiek tussen symptomatische en idiopathische asymmetrie. Het doel was een screeninginstrument te ontwikkelen voor kinderfysiotherapeuten, dat zij kunnen gebruiken bij het onderzoeken van jonge kinderen met een asymmetrische hoofdhouding. Hiervoor is een kwalitatief design gebruikt, bestaande uit twee consensusmethoden: een Delphistudie (twee rondes) en een expertbijeenkomst waarbij nominale groepstechniek werd toegepast. In de twee Delphirondes werden 13 experts, zes medisch specialisten en zeven kinderfysiotherapeuten met een digitale vragenlijst anoniem bevraagd over drie onderwerpen: (1) volledigheid en indeling van een lijst diagnoses die mogelijk kunnen leiden tot een symptomatische asymmetrie; (2) het waarderen van een set met 4-6 klinisch-diagnostische criteria (CDC) op een vijf-puntschaal om de mate van relevantie van elk criterium voor de betreffende diagnose vast te stellen; en (3) het verzamelen en waarderen van signalen of symptomen die gezien kunnen worden als 'rode vlag'. Na ronde 1 liepen de meningen van de experts nog uit elkaar. Zij gaven enkele waardevolle aanvullingen op de diagnoselijst en de sets CDC. Tussen de twee rondes zijn kleine aanpassingen gedaan aan de CDC. De experts kregen de uitkomsten van ronde 1 te zien. Hen werd gevraagd de items opnieuw te scoren. Het resultaat na ronde 2 was een verzadiging qua diagnoses en CDC en een duidelijke convergentie in waardering van de CDC. Bij de meeste sets CDC konden twee criteria onderscheiden worden met een gemiddelde relevantiewaarde van ≥4. De interne consistentie van het panel nam toe van Cronbach's α=0.67 in ronde 1 tot 0.89 in ronde 2. Gebaseerd op deze uitkomsten werd een conceptversie van het instrument gemaakt met daarin de 10 meest voorkomende symptomatische asymmetrie-diagnoses met de twee meest relevante CDC voor elke diagnose, en een lijst met absolute en relatieve 'rode vlaggen'. Deze conceptversie werd voorgelegd aan een nieuw expertpanel, bestaande uit acht kinderfysiotherapeuten. Tijdens een gestructureerde face-to-face-bijeenkomst bespraken en overwogen zij zorgvuldig de genomen beslissingen. Het panel stelde vast dat, met kleine aanpassingen, (1) het classificatieschema volledig was wat betreft nu bekende diagnoses, die mogelijk leiden tot symptomatische asymmetrie bij kinderen in de eerste zes levensmaanden; (2) er overeenstemming was betreffende de selectie van de 10 meest voorkomende diagnoses met voor elke diagnose de twee meest relevante CDC, gebaseerd op de uitkomsten van het Delphiproces; (3) het signaleren van levensbedreigende diagnoses

voldoende kon worden uitgesloten met de acht geselecteerde rode vlaggen; en (4) het vastgestelde instrument zinvol en efficiënt is voor kinderfysiotherapeuten. Uiteindelijk is een differentiaaldiagnostisch screeninginstrument vastgesteld, bestaande uit een classificatieschema, de CDC voor differentiaaldiagnostiek en een lijst met 'rode vlaggen', gebaseerd op literatuuronderzoek en consensus onder experts. (Kruis)validiteit en betrouwbaarheid van het instrument moeten in de toekomst nog onderzocht worden.

In **deel II**, verschuift het onderwerp van dit proefschrift van symptomatische naar idiopathische asymmetrie, in het bijzonder in een prematuur geboren populatie.

Deel II, hoofdstuk 4, verkende de prevalentie en voorspellende factoren van idiopathische asymmetrie retrospectief in een cohort kinderen geboren na een zwangerschapsduur van <32 weken of met een geboortegewicht <1000 gram. De drie te onderzoeken doelen waren: (1) de prevalentie van een idiopathische asymmetrie, gedefinieerd als een voorkeurshouding van het hoofd en/of een DP, op à terme leeftijd (TEA) en op 6 maanden gecorrigeerde leeftijd (CA); (2) of demografische, perinatale of medische factoren voorspellers van de asymmetrie waren; en (3) verschillen in motorische rijping tussen kinderen met en zonder asymmetrie gemeten op 6 maanden CA met de Alberta Infant Motor Scale (AIMS). De gegevens werden gehaald uit elektronische patiëntendossiers, medische correspondentie en kinderfysiotherapeutische statussen van 192 kinderen. Alle kinderen waren in 2006 opgenomen op de neonatale intensive care unit van het Wilhelmina Kinderziekenhuis in Utrecht en bezochten de neonatale follow-up poli op TEA en rond 6 maanden CA. Zestien kinderen werden geëxcludeerd omdat zij een symptomatische asymmetrie hadden. De prevalentie van een voorkeurshouding van het hoofd op TEA was 44.8% (86/192); 10.4% (20/192) had een (vaak minimale) DP. Op 6 maanden werd bij geen van de kinderen nog een voorkeurshouding van het hoofd gezien, maar bij 13% (25/192) wel een DP. Van alle potentiële voorspellende factoren waren alleen een voorkeurshouding op TEA (OR 3.0; 95% CI 1.23-7.39; *p*=0.20), meerlingschap (aOR 3.2; 95% CI 1.28-7.31; *p*=.020) en mannelijk geslacht (aOR 3.2; 95% CI 1.14-9.15; *p*=.030) significante voorspellers voor de kans op aanwezigheid van DP op 6 maanden CA (p<0.05). Bij kinderen met een voorkeurshouding op TEA werd een significant lagere score op de AIMS op 6 maanden CA gevonden. Tussen kinderen met en zonder DP op 6 maanden CA was het verschil in Z-scores op de AIMS niet significant (T-test). We concludeerden dat bij bijna de helft van het bestudeerde cohort kinderen geboren na een zwangerschapsduur van <32 weken een voorkeurshouding van hoofd werd gezien op TEA: een substantieel hoger aantal dan beschreven wordt in de literatuur

over voldragen kinderen. De bevinding dat bij hen op 6 maanden CA de grofmotorische rijping minder goed ontwikkeld was, is een indicatie dat motorische onrijpheid een rol speelt in dit, doorgaans weer voorbijgaand, fenomeen. Het hoge prevalentiecijfer vraagt echter om extra alertheid om de ontwikkeling van schedelvervorming te voorkomen, in het bijzonder bij jongens en meerlingen.

De resultaten uit de retrospectieve studie van hoofdstuk 4 rechtvaardigden een prospectief onderzoek om meer inzicht te krijgen in het natuurlijk beloop van idiopathische asymmetrie bij prematuur geboren kinderen. Bovendien wilden we meer weten over de rol van bewegingsgedrag en de posturale controle, waarvan men veronderstelt dat die anders zijn bij prematuur geboren kinderen. **Deel II, hoofdstuk 5**, brengt verslag uit van een prospectieve studie bij kinderen geboren na een zwangerschapsduur van <30 weken en/of een geboortegewicht van <1000 gram vanaf de geboorte tot en met 6 maanden CA. De doelstellingen waren het beschrijven van het natuurlijk beloop van een voorkeurshouding van het hoofd en van DP, en het verkennen van voorspellende factoren voor het persisteren van deze verschijnselen. De kinderen die hiervoor in aanmerking kwamen waren geboren tussen januari 2009 en oktober 2010, opgenomen op de neonatale intensive care unit van het Wilhelmina Kinderziekenhuis in Utrecht en bezochten de neonatale follow-up poli op TEA. Zestien kinderen moesten geëxcludeerd worden vanwege een gediagnosticeerde symptomatische asymmetrie. De ouders van 120 kinderen gaven schriftelijk toestemming voor deelname aan de studie. De kinderen ondergingen drie keer een onderzoek in een periode van 6 maanden, op TEA en op 6 maanden CA tijdens de follow-up poli, en daar tussenin op 3 maanden CA aan huis. De aanwezigheid van een DP, aangegeven met de Argentaclassificatie, en een score van 1-6 op een asymmetrieschaal voor motoriek waren de primaire uitkomstmaten op 6 maanden CA. Relevante demografische en perinatale gegevens, alsmede de medische voorgeschiedenis werden vastgelegd. De sociale omgeving en de wijze van hanteren en positioneren van het kind werden nagevraagd met een digitale vragenlijst. Op TEA werden de general movements (GMs) onderzocht en werd de screeningsversie van de Test of Infant Motor Performance (TIMP) afgenomen. GMs, TIMP en AIMS werden gebruikt op 3 maanden CA en op 6 maanden alleen nog de AIMS. De prevalentie van een voorkeurshouding van het hoofd was 65.8% (79/120) op TEA en 36.7% (44/120) op 3 maanden CA. DP werd gezien bij respectievelijk 30% (36/120) en 50% (60/120). Op 6 maanden CA scoorde 15.8% (19/120) ≥2/6 op de asymmetrieschaal, terwijl bij 23.3% (28/120) nog een DP van minimaal Argenta-II werd gezien. Het hebben van een DP op 3 maanden CA voorspelde de kans op een asymmetrie in de motoriek op 6 maanden

CA (OR 3.3; 95% CI 1.12-9.99; *p*=.030). Chronische long problematiek postnataal (aOR 4.5; 95% CI 1.46-13.58; *p*=.009)) en/of een trage grofmotorische rijping op 3 maanden (aOR 0.4; 95% CI 0.20-0.86; *p*=.018) CA voorspelden de kans op het persisteren van DP bij 6 maanden CA. Alle andere factoren, inclusief hanteringen en positioneringen, hadden geen statistisch significante invloed op het blijven bestaan van de idiopathische asymmetrie op 6 maanden CA. We trokken de conclusie dat bij zeer vroeg geboren kinderen een voorkeurshouding van het hoofd een normaal aspect van hun motorisch repertoire lijkt te zijn, waarbij de mogelijkheid om het persisteren van die asymmetrie te voorspellen beperkt is. De hoge prevalentie van DP die gezien werd op 3 maanden CA, was teruggebracht tot minder dan de helft tegen de 6 maanden CA, behalve bij kinderen die een CLD hadden doorgemaakt of een trage motorische rijping lieten zien op 3 maanden CA.

Aangezien we prospectief een groot en relatief gezond cohort prematuur geboren kinderen hadden onderzocht in de asymmetriestudie, besloten we de dataverzameling door te laten lopen tot en met het 15-maands onderzoek op de neonatale follow-up poli om de grofmotorische uitkomsten op die leeftijd te analyseren. In **deel III, hoofdstuk 6** onderzochten we de concurrerende validiteit van de twee motoriekinstrumenten die gebruikt zijn op 3 maanden CA (TIMP en AIMS) en het vermogen van beide instrumenten om het grofmotorisch niveau rond 15 maanden CA alsmede de leeftijd van loslopen te voorspellen. Van het oorsponkelijke cohort hebben 113 kinderen alle testen op 3, 6 en 15 maanden ondergaan. De concurrerende validiteit werd geanalyseerd met de Pearson correlatiecoëfficiënt van zowel ruwe scores als Z-scores op de TIMP en de AIMS. Tevens werd een afkappunt voor diagnostische overeenstemming vastgesteld. Lineaire en logistische regressie werden gebruikt om de voorspellende validiteit te bepalen. Omdat aan het eind van de studie nog niet alle kinderen dit stadium bereikt hadden, analyseerden we de leeftijd van loslopen met een Coxregressie. In een cohort te vroeg geboren kinderen komen relatief veel meerlingen voor. Deze verwantschap veronderstelt een onderlinge afhankelijkheid qua motorische ontwikkeling. Om dit effect uit te sluiten hebben we willekeurig één kind van elke meerling geselecteerd voor onze analyses. De correlatie tussen de ruwe scores van de TIMP en AIMS was 0.82, en tussen de Z-scores 0.71. Een Z-score van -1.0 op de TIMP als afkappunt had 92% (κ=0.67) diagnostische overeenstemming met een AIMS score van <P10. Noch de TIMP-scores, noch de AIMS op 3 maanden CA liet een significante samenhang zien met het grofmotorisch niveau op 15 maanden CA. De AIMS-scores op 6 maanden CA voorspelden de AIMS-scores op 15 maanden CA (B=0.53; 95% CI 0.29-0.77; *p*=.000), en de items 'early stepping' (OR 2.6; 95%

CI 1.55-4.47; *p*=.000) en 'walks alone' (OR 3.2; 95% CI 1.86-5.65; *p*=.000). De verklaarde variantie (r^2=0.19) geeft aan, dat de AIMS-scores op 6 maanden CA 19% van de variantie in AIMS-scores op 15 maanden CA kunnen verklaren. De mediane leeftijd waarop de kinderen los gingen lopen was 15.7 (95% CI 15.21-16.26) maanden CA. Geen van de demografische of medische factoren had invloed op de leeftijd van loslopen, behalve etniciteit. Niet-Westerse kinderen liepen significant eerder dan Westerse kinderen (14.4 tegenover 15.9 maanden CA; *p*=.041). De toevalskans van loslopen op een bepaalde leeftijd was voor niet-Westerse kinderen bijna twee keer zo groot als voor Westerse kinderen (HR 1.8; 95% CI 1.01-3.04; *p*=.045). De conclusie was dat kinderen geboren na <30 weken zwangerschap gemiddeld ongeveer drie maanden later gaan loslopen dan op tijd geboren kinderen, zelfs wanneer de leeftijd gecorrigeerd wordt voor de vroeggeboorte. Het niveau van grofmotorische rijping op 6 maanden CA en de etniciteit hingen samen met de leeftijd van loslopen, de medische voorgeschiedenis niet. Kindfactoren en culturele factoren lijken het los gaan lopen te bepalen. Ondanks goede concurrerende validiteit, kan noch de TIMP noch de AIMS op 3 maanden CA de grofmotorische rijping of de loopvaardigheid op 15 maanden CA voorspellen bij te vroeg geboren kinderen. Een klinische gevolgtrekking hiervan is dat de leeftijd van 3 maanden CA te vroeg is om kinderen te testen wanneer het doel is een valide uitspraak te doen over de latere grofmotorische uitkomst. Dit wijst ook uit dat er, gebruikmakend van de AIMS, voor 6 maanden CA geen valide voorspelling gedaan kan worden over de leeftijd waarop een kind gaat loslopen.

CONCLUSIES

De volgende conclusies kunnen worden getrokken gebaseerd op de studies in dit proefschrift:

- Een differentiaaldiagnostisch screeningsinstrument is vastgesteld om een symptomatische asymmetrie te onderscheiden van een idiopathische in de eerste zes levensmaanden. Het instrument bevat een classificatieschema, klinisch-diagnostische criteria voor de differentiaaldiagnose, en een lijst 'rode vlaggen', gebaseerd op literatuuronderzoek en consensus onder experts. Een expertpanel stelde vast dat het instrument zinvol en efficiënt is voor kinderfysiotherapeuten bij het klinisch onderzoek van asymmetrie op jonge leeftijd. (Deel I, hoofdstuk 2 en 3)
- Bij zeer vroeg geboren kinderen werden substantieel hogere prevalentiewaarden gevonden voor een voorkeurshouding van het hoofd en DP op à terme leeftijd en op 3 maanden CA dan beschreven wordt in de literatuur over op tijd geboren kinderen.

- Een hogere prevalentie onder jongens en meerlingen werd niet consistent aangetoond. (Deel II, hoofdstuk 4 en 5)
- Op de gecorrigeerde leeftijd van 6 maanden scoorde 15.8% (19/120) ≥2/6 op een asymmetrieschaal. Een DP met minimaal Argentagraad II werd gezien bij 23.3% (28/120). De aanwezigheid van een DP op 3 maanden CA voorspelde een grotere kans op een asymmetrische motoriek op 6 maanden CA. Chronische longproblematiek en/of trage grofmotorische rijping op 3 maanden CA voorspelden de kans dat de DP nog aanwezig is op 6 maanden CA. Alle andere factoren, inclusief hantering en positionering, hadden geen significante invloed op het blijven bestaan van de idiopathische asymmetrie op 6 maanden CA.
- Een voorkeurhouding van het hoofd op à terme leeftijd lijkt bij zeer vroeg geboren kinderen een normaal aspect van hun bewegingsrepertoire, waarvan niet met zekerheid te zeggen is dat dit zal leiden tot het blijven bestaan van die asymmetrie. (Deel II, hoofdstuk 5)

- Ondanks goede concurrerende validiteit, kan noch de TIMP noch de AIMS op 3 maanden CA de grofmotorische rijping of de loopvaardigheid op 15 maanden CA voorspellen bij te vroeg geboren kinderen.
- De AIMS-scores op 6 maanden CA verklaren 19% van de variantie in AIMS-scores op 15 maanden CA.
- Het niveau van grofmotorische rijping op 6 maanden CA, en de etniciteit hingen samen met de leeftijd van loslopen, de medische voorgeschiedenis niet.
- De mediane leeftijd waarop kinderen geboren na <30 weken zwangerschap los gingen lopen was 15.7 maanden CA. Zij liepen ongeveer drie maanden later vergeleken met de normpopulatie van de AIMS. (Deel III, hoofdstuk 6)

AANBEVELINGEN VOOR DE KLINISCHE PRAKTIJK

De diagnose idiopathische asymmetrie kan alleen gesteld worden door pathologie uit te sluiten. Het differentiaaldiagnostisch screeningsinstrument wordt gezien als een zinvol en efficiënt instrument voor kinderfysiotherapeuten toepasbaar bij het klinisch onderzoek van jonge kinderen met een asymmetrie. De reductie in te onderzoeken items zorgde ervoor dat het instrument praktisch is en weinig tijd kost. Het instrument kan

gebruikt worden om hypotheses te formuleren en te testen tijdens het diagnostisch proces. Ons advies is om de rode vlaggenlijst te gebruiken bij de start van anamnese / onderzoek om ernstige pathologie uit te sluiten. Daarna kunnen de CDC eenvoudig uitgevoerd worden tijdens het eerste onderzoek. Bij twijfel moeten de kinderen verwezen worden naar een (kinder)arts om de diagnose te kunnen bevestigen.

Onze bevindingen wat betreft idiopathische asymmetrie bij zeer vroeg geboren kinderen bevestigen duidelijk dat zij een risicogroep zijn voor het ontwikkelen van een DP. De meerderheid van deze kinderen heeft op TEA een voorkeurshouding en 50% een DP op 3 maanden CA. Daarentegen vonden we ook, doordat we de kinderen prospectief vervolgden, dat het hebben van een voorkeurshouding op TEA niet betekende dat dezelfde kinderen ook op de leeftijd van 6 maanden CA nog een DP lieten zien. Maar welke kinderen hebben nu interventie nodig en bij welke kinderen volstaat het om af te wachten en preventieve adviezen te geven? Er zijn aanwijzingen dat kinderen die langer dan 1 maand na de geboorte zuurstof nodig hebben, en nog sterker bij kinderen die nog zuurstofafhankelijk zijn na 36 weken postmenstruele leeftijd, de kinderen zijn bij wie tijdige interventie op zijn plaats is. Voor de andere kinderen geldt dat het zowel afhangt van het verloop van de motorische ontwikkeling, als van de variabiliteit die het kind laat zien in houdingen of interventie nodig is. Voor alle kinderen is het van groot belang om regelmatig en consistent adviezen te geven aan de ouders over positionering.

De conclusies van de studie over voorspellende waarde van TIMP en AIMS impliceren dat de leeftijd van 3 maanden CA te vroeg is om kinderen te testen wanneer het doel is een valide uitspraak te doen over de latere grofmotorische uitkomst. Dit wijst ook uit dat er, gebruikmakend van de AIMS, voor 6 maanden CA geen valide voorspelling gedaan kan worden over de leeftijd waarop een kind gaat loslopen.

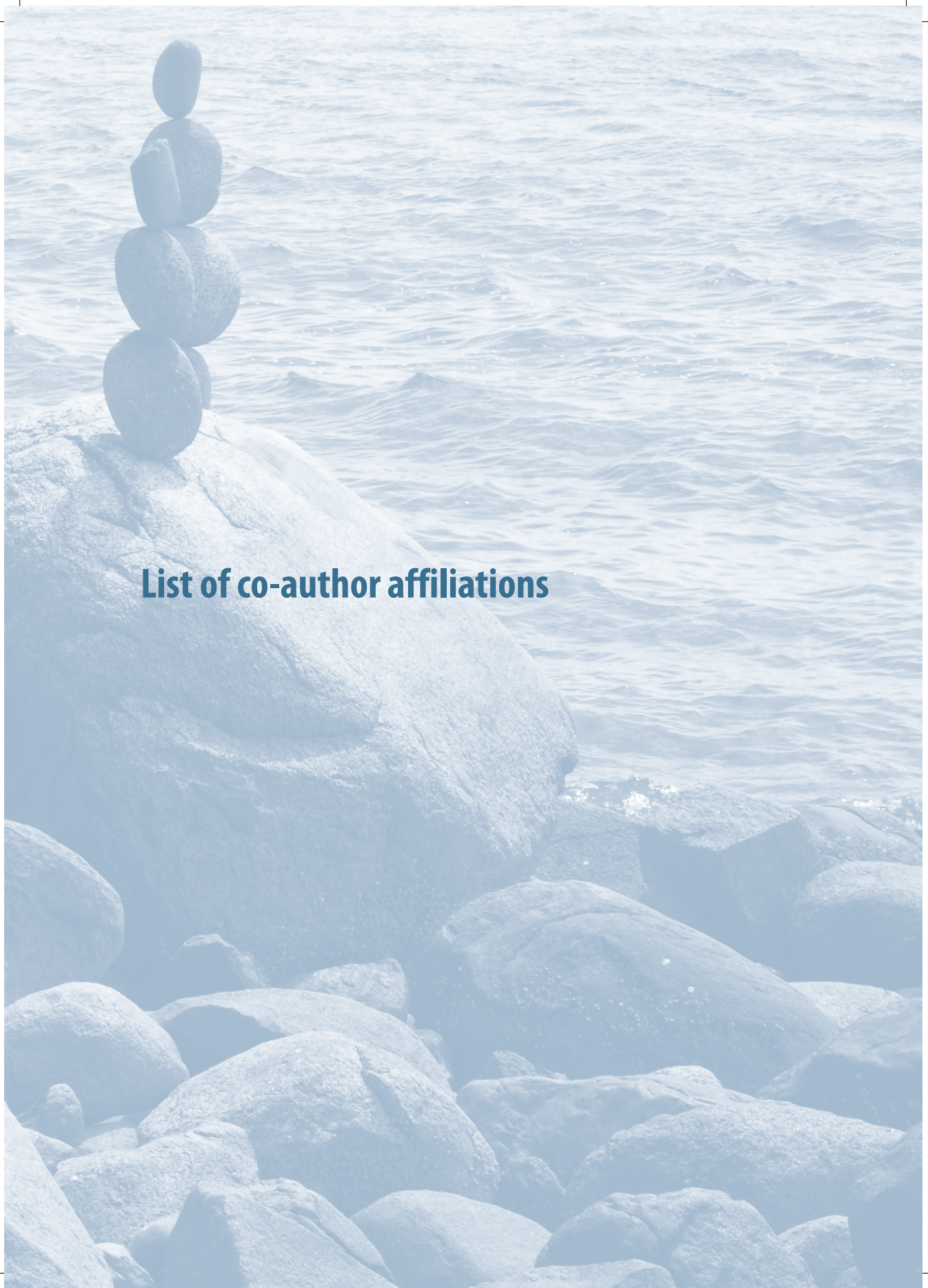
De vertraging in de start van het loslopen ten opzichte van een à terme geboren populatie is aanzienlijk. We bevelen aan om aan de ouders uit te leggen dat deze vertraging normaal is voor zeer vroeg geboren kinderen.

AANBEVELINGEN VOOR TOEKOMSTIG ONDERZOEK

1. Wat betreft de differentiaaldiagnostiek van symptomatische asymmetrie bij jonge kinderen: het differentiaaldiagnostisch screeningsinstrument beschreven in dit proefschrift zal gevalideerd moeten worden. De diagnostische waarde (specificiteit en sensitiviteit) van de geselecteerde rode vlaggen en de klinisch-diagnostische criteria moeten bevestigd worden.

2. Gezien de hoge prevalentie van idiopathische asymmetrie bij prematuur geboren kinderen kan toekomstig onderzoek zich het beste richten op primaire of secundaire preventie van DP, in het bijzonder bij kinderen met chronische longproblematiek.

3. Het prospectief, met een hoge frequentie, bestuderen van motorische ontwikkelingstrajecten van kinderen kan bijdragen aan het beter begrijpen van (variatie in) motorische profielen van typisch (normaal) ontwikkelende kinderen. Wij analyseren nu de data uit onze prospectieve studie om intra-individuele grofmotorische trajecten te beschrijven, gemeten met de AIMS. We zijn daarnaast gestart met het opzetten van een onderzoeksproject om Nederlandse normwaarden voor de AIMS vast te stellen, in samenwerking met de ontwikkelaars van de AIMS in Canada. Tevens kan als onderdeel van dit project uitgezocht worden of updaten van de (Nederlandse) prematurennormen nodig is. Vervolgens zou het, gezien de intra-individuele variabiliteit, een interessante innovatie kunnen zijn om te kijken naar longitudinaal verkregen normwaardes voor de AIMS.



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Dankwoord (Acknowledgements)

Een proefschrift schrijven en verdedigen is een proeve van bekwaamheid als wetenschappelijk onderzoeker. En bij wie kun je dit vak beter leren dan bij twee meesters in dit genre: prof.dr. P.J.M. Helders en prof.dr. L.S de Vries, mijn beide promotoren. Paul, jij hebt mij vanaf mijn eerste eenvoudige onderzoeksplan tijdens de studie Fysiotherapiewetenschap gestimuleerd en geïnspireerd om dit pad op te gaan en mij als 'buitenpromovendus' de kansen geboden om deze onderzoeken binnen het Kinderbewegingscentrum van het Wilhelminakinderziekenhuis te doen. Hoe snel kan het gaan? Vijf jaar geleden haalde je wat mensen bij elkaar en na een uurtje lag er een onderwerp en een rolverdeling. Ik heb nog wat oude blaadjes liggen met je grove schetsen tijdens de eerste gesprekken. Het klopt aardig met hoe het uiteindelijk gelopen is. Dank voor je sturing op hoofdlijnen, maar ook voor je rotsvaste vertrouwen in het eindresultaat. En Linda, jij was voor mij de stille kracht op de achtergrond, met altijd relevante opmerkingen over de geschreven manuscripten en uitleg over wat ik niet kende rondom de neonatologie. Dank voor alle tijd die je in mijn onderzoeken geïnvesteerd hebt – feedback doorgaans op zondagmiddag! – in jouw onvoorstelbaar drukke programma.

Een bijzondere rol is er bij promotietrajecten voor de co-promotor, formeel de directe begeleider op de werkvloer. In mijn geval uiteindelijk zelfs twee personen, dr. J. van der Net en dr. I.C. van Haastert. Janjaap, met eindeloos geduld en creatieve oplossingsgerichtheid stond je open voor al mijn vragen, ook al was het onderwerp van mijn studies voor jou geen vertrouwd terrein. Veel dank ook voor je hulp bij vastlopende manuscripten. Inge-Lot, jij was voor mij de laagdrempelige inhoudsdeskundige. Ook zonder dat ik een vraag stelde dacht je al mee. Onze samenwerking in wetenschappelijk onderzoek startte in 2004 tijdens de FW studie, waarbij jij mijn eerste vraagbaak was bij het opzetten van het kwalitatieve onderzoek naar aandoeningen die asymmetrie konden veroorzaken. We hebben samen heel wat uurtjes gezeten om al die rondes voor te bereiden en keuzes te maken. Vervolgens kon ik voor de retrospectieve studie gebruik maken van jouw legendarische statussen. Intussen ben je zelf gepromoveerd met een prachtig proefschrift over jouw 'kinderen', de high risk infants van de neonatale follow-up poli. En iedereen die je kent weet hoeveel tijd en energie je hierin gestoken hebt. Ondanks dat, heb je altijd klaar gestaan als ik een sparringpartner nodig had om goede keuzes te kunnen maken. En er kwam geen manuscript terug van jou zonder minutieuze correcties. Hopelijk kunnen we nog veel leuke dingen samen doen, rondom onze plannen voor de AIMS-normering. Of gewoon weer eens naar Hartlooper voor een mooie film.

De leden van de leescommissie prof.dr. F. van Bel, prof.dr. E.E.S Nieuwenhuis, prof.dr M.J. Jongmans, prof.dr. J.I.P. de Vries en dr. R.J. Vermeulen wil ik bedanken voor de aandacht die zij aan mijn proefschrift hebben besteed.

Dr. T. Takken, beste Tim, jij was mijn afstudeerbegeleider bij FW en medeauteur van de eerste twee artikelen. Ook al stond het onderwerp ver af van jouw werkzaamheden, dank voor de rol die je erin speelde. Mede dankzij jou zijn het van onderwijsproducten wetenschappelijk relevante studies geworden.

Een speciaal woord van dank ook hier voor de experts van de Delphi-studie: de medici dr. M. Boere-Boonekamp, dr. A. Bulk-Bunschoten, drs. W. Eskes, prof.dr. I. Mathijssen, drs. I. Russell, dr. R. Severijnen, prof.dr. N. Schalij-Delfos en de kinderfysiotherapeuten H. Crombag, J. Deenen-van Zon, dr. R. Engelbert, P. van Essen, dr. L. de Groot, dr. I. van Haastert, drs. M. Loeters, dr. P. van Schie, dr. M. Schoenmakers, F. Sleijpen, A. Vermeulen en dr. L. van Vlimmeren.

Dr. C. Koopman-Esseboom, neonatoloog en hoofd van de neonatale follow-up poli, beste Corine, wat geweldig dat je mij de kans hebt gegeven bij jou op de neo-poli al die kinderen te kunnen zien en gebruik te kunnen maken van de gegevens die jullie verzamelden. Mooi om te zien met hoeveel vakmanschap en aandacht de kinderen door jullie gevolgd worden. Inge-Lot, Rian Eijsermans en later ook Maaike Sprong, bedankt voor alle metingen die jullie als kinderfysiotherapeuten extra en zorgvuldig hebben gedaan om de prospectieve dataverzameling zo compleet mogelijk te krijgen. Rian, jij hebt met je jarenlange ervaring bij prematuur geboren kinderen inhoudelijk ook veel meegedacht bij de voorbereiding van de longitudinale studie en bij de klinische interpretatie van de onderzoeksgegevens. Jammer dat je voor een rol als paranimf moest bedanken wegens persoonlijke omstandigheden. Ik wil je extra hartelijk bedanken voor je onbaatzuchtige en altijd positieve inbreng.

Dit brengt me bij de hoofdpersonen in de laatste twee studies uit dit proefschrift, de ruim 120 zeer vroeg geboren kinderen en hun ouders die ruimhartig toestemming gaven te participeren in weer een onderzoek. Een vaak gehoorde reden was: "Natuurlijk doen we mee, want als er geen wetenschappelijk onderzoek was geweest was ons kind er vast niet zo goed uitgekomen". En vervolgens ontving u mij gastvrij bij u thuis toen de kinderen 3 maanden oud waren (gecorrigeerd voor de vroeggeboorte) met fotoboeken en koffie of thee, soms zelfs met Brabantse worstenbroodjes of een Afghaanse maaltijd! Indrukwekkend om de verhalen te horen en te zien hoe goed de kinderen het dan doen na die spannende tijd in het ziekenhuis. In twee jaar tijd reed ik 6538 km tussen Hoorn

en Alphen (dat in het zuiden van Noord-Brabant bleek te liggen) en Gouda en Deventer. Gelukkig kon ik ook vaak op de fiets als het gewoon in Utrecht was.

Enkele personen wil ik graag speciaal bedanken voor hun inbreng bij de studies of de manuscripten: Carla Tims van het Juliuscentrum, wat fijn dat ik bij je terecht kon om het databeheer goed op te zetten. Het heeft goed geholpen om zo overzicht te houden in de databerg. Eric Stutterheim, collega van de HU, bedankt voor de digitale enquête die je voor mij hebt gemaakt. Het liep als een trein! En als laatste Cas Kruitwagen, als reddende engel kwam je dit jaar een dag per week als statisticus op de HU werken en was je mijn vraagbaak voor een goede interpretatie van de statistiek in het laatste half jaar van de studie. Fijn dat ik gebruik van je mocht maken (geregeld door dr. Harriet Wittink, lector aan het Kenniscentrum van de HU). Heel veel dank hiervoor en wat kun jij toch goed uitleggen!

Naast de persoonlijke ondersteuning op de Faculteit Gezondheidszorg van Hogeschool Utrecht, mijn werkgever, is er ook een bescheiden ondersteuning geweest in de vorm van tijd, een dagdeel in de week gedurende drie jaar en het laatste jaar een hele dag, om deze promotie af te kunnen ronden. Ik bedank de directeur mr. Harm Drost, voor deze mogelijkheid. Mieke Klootwijk, de directeur van het Instituut voor Bewegingstudies en drs. Rob van Dolder, mijn opleidingsmanager, ben ik zeer dankbaar voor hun mentale steun en waardering voor mijn zelfgekozen project en voor het meedenken in kleine oplossingen om het toch te kunnen faciliteren. Fijn dat we werken aan mogelijkheden om het ontwikkelingsonderzoek bij jonge kinderen, zo waardevol voor een masteropleiding kinderfysiotherapie, voort te kunnen zetten.

Gedurende de afgelopen vijf jaar heb ik me in twee teams buitengewoon thuis gevoeld. Het eerste team was op de HU, met de MFO collega's Ina Bettman, Rutger IJntema, François Maissan, Jorrit Rehorst, Roland van Peppen, Kitty Meijer, Jaap Dronkers, Selma May, Milou van Oostrum, Dammis Vroegindeweij en eerder Jan Pool, Bas Honselaar, Martijn Janssen en Jacqueline Outermans, en met de kinderfysiotherapiedocenten Ida Bosga-Stork, Ron van Empelen, Manon Bloemen, Bert Halfwerk, Marion Diepstraten, Cocky Mesman- Ruigrok, Marike Boonzaaijer en Femke Kooijmans. Inspirerende en enthousiaste collega's met veel hart voor de masteropleiding en haar studenten.

Het tweede team was in het WKZ, kinderbewegingscentrum op de onderzoeksdagen, dinsdag en vrijdag, en als het even kon op de donderdaglunch bij de patiënt- en researchbesprekingen. Collega's Marja Schoenmakers, Rian Eijsermans, Ron van Empelen, Lianne Verhage, Janjaap van der Net, Patrick van der Torre, Bart Bartels,

Maaike Sprong, Erik Hulzebos, Tim Takken, Marco van Brussel, Jeroen Jeneson; de (voormalige) mede-promovendi Janke de Groot, Wim Groen, Martijn Pisters, Maarten Werkman, Mirjam Kruijsen, Bart Bongers, Johannes Noordstar, Rogier de Knikker, en Esther Habers; en de onvolprezen dames van het secretariaat Sonja Raaff, Annemieke Apeldoorn en Carla van Rooijen. Met zoveel verschillende en zo gedreven personen, kunt u zich voorstellen wat een kritische bende het kon zijn tijdens de donderdagmiddagpresentaties. Maar altijd inspirerend! Ik kijk met veel genoegen terug op deze periode met een gastaanstelling. Ik hoop nog vaak te gast te kunnen zijn, zodat onze samenwerking in onderzoek, kliniek en onderwijs verder uitgebouwd wordt.

Sommige mensen passen niet in deze rijtjes maar hebben toch een speciale rol gespeeld. Eén van die mensen is Dr. Nico van Meeteren, toenmalig hoofd van de studie Fysiotherapiewetenschap en een van mijn eerste tutoren. Nico, bedankt dat je mij dat zetje hebt gegeven om van mijn allereerste onderzoeksproject een artikel te gaan maken voor het Tijdschrift voor Fysiotherapie. Ik herinner me dat we zelfs een avond bij jou thuis zin voor zin aan de inleiding zijn gaan werken. Je was superkritisch en bleef me maar bevragen waarom ik iets vond of koos. Dit heeft mijn academische capaciteiten geprikkeld en wakker geschud. Bijzonder!

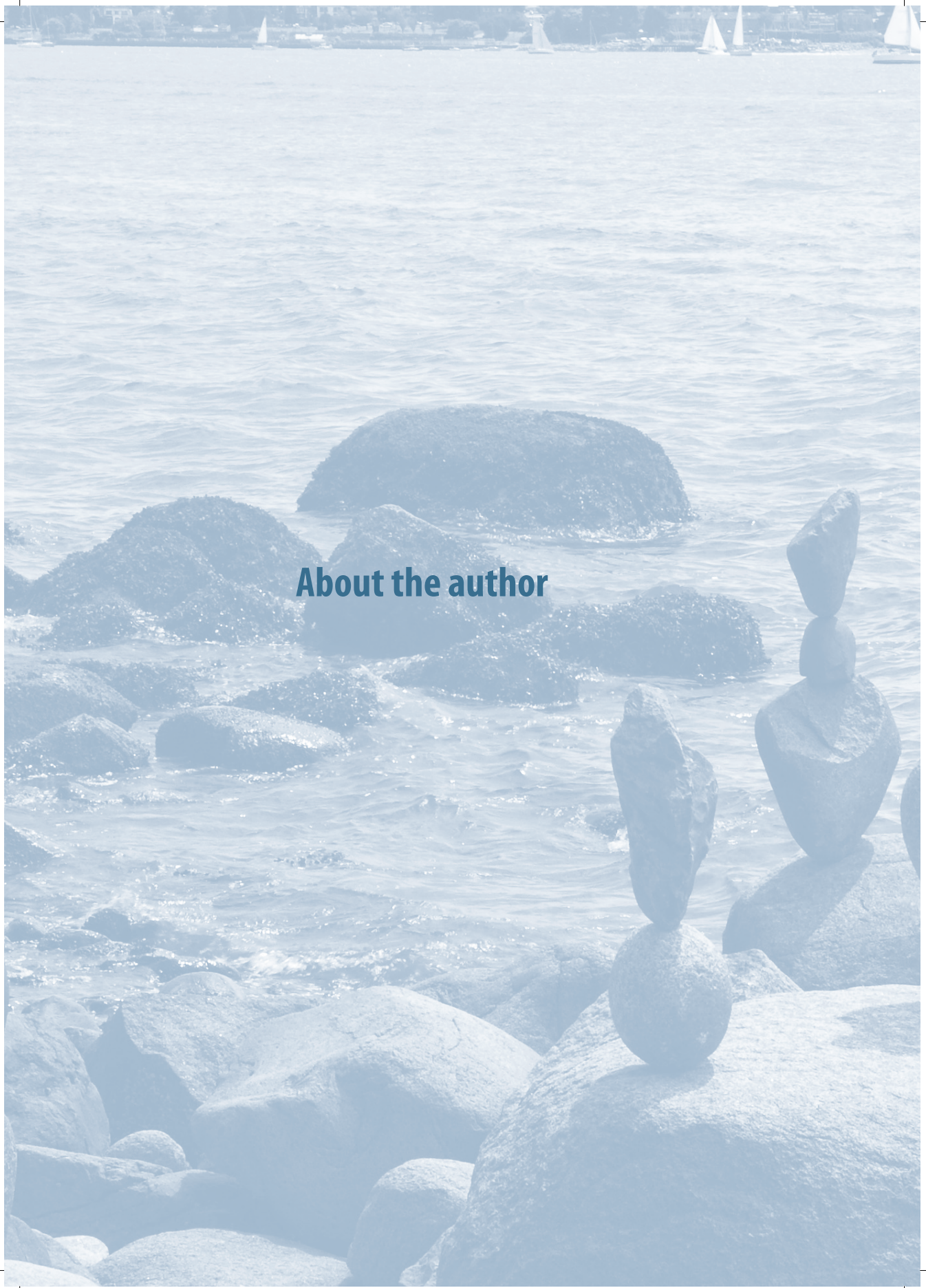
Een andere rol speelde prof.dr. Marian Jongmans. Bij jou kon ik, in het laatste jaar, enkele keren terecht als ik eens in meer algemene zin wilde reflecteren op hoe het promotietraject ging. Naast alle inhoudelijke focus kan ik dit iedere promovendus aanraden. Veel dank voor je tijd, je oprechte interesse en je relevante vragen.

Het proefschrift zelf, het 'boekje' is zo mooi geworden dank zij de voortreffelijke hulp van Renate Siebes, bij het verzorgen van de lay-out en door mij achter de broek te zitten wanneer ik nog even over iets wilde nadenken. En door Joëlle Boef die de foto's prachtig bewerkt heeft voor de omslag.

Bij een promotie horen twee paranimfen. Ook al is dit een ceremoniële rol, ik vind het toch fijn dat twee mensen die belangrijk voor mij zijn dit op zich willen nemen. Ina Bettman, hartelijke en zorgzame collega, belangstellend en ondernemend. Onze hilarische kookclub en etentjes, samen met Jacqueline O. en soms de mannen waren plezierige niet-onderzoeksgebonden activiteiten. Het hoogtepunt, na het zwijntje uit Duitsland, was toch wel de herfstvakantiereis naar de Parijse keuken! Er zijn vast nog meer keukens te ontdekken. Al is het maar om O. nu te ondersteunen bij haar promotietraject.

En de ander is Ron van Empelen. Het is een wederdienst, ik mocht bij jou ook paranimf zijn. Jij was het die mij, nadat jouw vervolgcursus over statistiek en kritisch lezen niet genoeg deelnemers had, uitnodigde om jou te assisteren bij je onderzoek naar kinderen met epilepsie. Het smaakte naar meer en je kwam met de brochure voor FW. De rest is inmiddels geschiedenis.

De laatste alinea is voor de belangrijkste mensen in mijn leven. Elise, mijn jongste dochter, maakte en bewerkte samen met Mike de mooie foto's van de balancing stone sculptures in Stanleypark, Vancouver. Een prachtig beeld van asymmetrie die toch volkomen in balans is. Marlous, mijn oudste dochter, altijd bereid te helpen met het Engels en 'feestmeester' op de promotiedag. En Jo, al 35 jaar mijn stoere partner en soulmate. Gelukkig kwam je na je bijzondere reis met Marlous naar de Anapurna, weer heelhuids terug naar beneden om samen de afronding van de promotie te vieren. Mogen we nog heel veel mooie reizen maken samen.



About the author

CURRICULUM VITAE

De auteur van dit proefschrift is geboren op 18 augustus 1953 te 's-Gravenhage. Zij bezocht daar het Christelijk gymnasium Sorghvliet, maar behaalde haar gymnasium-β diploma, na verhuizing naar Bilthoven, op Het Nieuwe Lyceum aldaar in 1971. Van 1971-1975 volgde zij de opleiding Fysiotherapie in Utrecht. Direct na het behalen van de bevoegdheid tot fysiotherapeut ging zij werken bij revalidatiecentrum De Hoogstraat, toen nog in Leersum (hoofd T. Andeweg). In deze periode volgde zij o.a. de opleiding Haptokinesie in Overasselt. Zij werkte de eerste drie jaar met volwassen revalidanten met complexe neurologische en orthopedische problematiek. Vervolgens was zij drie jaar werkzaam op de dwarlesie-afdeling.

In 1981 werd het tijd voor een ander perspectief en ging zij werken in de eerstelijn, in de praktijk voor fysiotherapie in Bussum van C. van den Berg aan de Huizerweg. Na enkele jaren ontstond de behoefte aan inhoudelijk een ander focus binnen de fysiotherapie en ging zij scholing volgen voor het behandelen van kinderen (NDT, MBD, sensorische integratie, FOK en meerdere korte cursussen). Tegelijkertijd zette zij in Bussum een kinderfysiotherapiepraktijk op en later tevens in haar toenmalige woonplaats Amersfoort. Na het volgen van de zogenaamde aanvullingscursus (Pediatrie) in Utrecht kan zij zich in 1992 laten registreren als kinderfysiotherapeut. Tegelijkertijd ontplooide zij meer bestuurlijke activiteiten, eerst als bestuurslid en voorzitter van de Werkgroep Kinderfysiotherapie Midden-Nederland. In deze periode zette zij in deze grote regio 10 kinder-IOFs op. Vanaf 1999 tot 2005 was zij bestuurslid en vice-voorzitter van de beroepsvereniging van kinderfysiotherapeuten, de NVFK, met als belangrijkste portefeuille het organiseren van congressen, de commissie wetenschap en het penningmeesterschap.

In 2002 startte in Utrecht de nieuwe universitaire deeltijdstudie Fysiotherapiewetenschap (hoofd dr. N. van Meeteren, hoogleraar prof.dr. P.J.M. Helders), waarvoor zij zich aanmeldde. Voor de eerste groep duurde de studie nog vier jaar, zodat zij in 2006 haar bul in ontvangst kon nemen met een masterthesis over 'Differential diagnostic screening in young infants with asymmetry'. In het laatste jaar van de studie is zij gevraagd te komen werken bij Hogeschool Utrecht als tutor en als coördinator van de specialisatie Kinderfysiotherapie van de nieuwe opleiding master Fysiotherapie. Hier werkt zij nog steeds.

In september 2007 startte zij daarnaast een promotietraject in het WKZ bij prof.dr. P.J.M. Helders en prof.dr. L.S. de Vries over asymmetrie en prematuren, dat 5 jaar later, op 11 oktober 2012 uit zal monden in de verdediging van dit proefschrift.

Jacqueline Nuysink is getrouwd met Jo Althoff. Zij wonen in het centrum van Utrecht. Zij hebben samen twee volwassen dochters, Marlous (1983) en Elise (1985).

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