Diploma Thesis

# General movements in very low birth weight pre-term infants at time of discharge

## Analysis of results with respect to neurodevelopmental outcome


submitted by

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Matric. Num.: 0533360


for the degree of

**Doctor of Medicine**

**(Dr. med. univ.)**

at the

**Medical University of Graz**

completed at the

**Department of Pediatrics and Adolescence Medicine**

**Division of Neonatology**

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Graz, 20th September 2010 Christoph Bauer

# *Affidavit*

*Herewith I, Christoph Bauer, declare that I have written the present diploma thesis fully on my own and without any assistance from third parties. Furthermore, I confirm that no sources have been used in the preparation of the thesis other than those indicated in the thesis itself.*

*Graz, 20th September 2010* *Christoph Bauer*

# Acknowledgement

First and foremost, I would like to express my sincere thanks to my parents and my sister who always supported me on my way. I am grateful for their love and trust.

Furthermore, I want to acknowledge my supervisor Professor Berndt Urlesberger, for giving me the opportunity to work on this topic and for thoughtfully assisting me in writing the thesis. In addition, I want to thank Professor Christa Einspieler for training me in Prechtl´s method on the qualitative assessment of general movements and for the time she spent discussing tricky cases. My gratitude goes to my friends Mr. Phillip Seif, Mr. Sebastian Dietl and Mr. Georg Grasegger for correcting the English.

Finally, I want to thank my colleague, Katrin Ellrott who assisted me in filming, GM assessment and data collection.

# Abstract

**Background:** During the last two decades Prechtl´s method on the qualitative assessment of general movements (GMs) has repeatedly been proven to be a highly sensitive and specific diagnostic tool for the early diagnosis of brain impairment. Compared to other techniques, e.g. magnetic resonance imaging cranial ultrasound, and traditional neurological examination it is quick, non-invasive, non-intrusive and cost-effective. However, despite these advantages longitudinal GM assessment is not yet widely introduced in clinical practice everywhere.

**Objective:** The aim of this study was to describe and analyse the relation between GM assessment performed only once at time of discharge and later neurodevelopmental outcome.

**Patients and Methods:** Between July 2006 and June 2009 GMs of 72 very low birth weight pre-term infants admitted to the Division of Neonatology at the Medical University Graz were filmed once at time of discharge. The recordings were assessed retrospectively according to Prechtl´s method. The results were compared with neurodevelopmental outcome that was measured at the specific time frame of 1-2 years using the Touwen Infant Neurological Examination, the Gross Motor Function Classification System and the Bayley Scale of Infant Development.

**Results:** Our findings widely go along with previously published data as we found a strong relation between certain GM patterns and neurological test results on the one hand and developmental test results on the other hand. 42 (95%) of 44 infants with normal pre-term movements had a normal neurodevelopmental outcome. Cramped-synchronized or poor-repertoire was followed by neurological abnormalities in 10 (36%) of the 28 infants (6 had CP and 4 had other neurological or developmental disorders). Sensitivity and negative predictive value were quite high (83% and 95%, respectively) whereas specificity and especially positive predictive value were somewhat lower (70% and 36%, respectively).

**Conclusion:** Longitudinal GM assessment should be preferred to a single shot assessment at 36 weeks as it has a limited power to predict later neurological outcome properly. In particular, a large number of false positives resulting in low specificity during pre-term period is responsible for the limited use.

# Zusammenfassung

**Hintergrund:** Während der vergangenen zwei Jahrzehnten wurde Prechtls Methode der qualitativen Beurteilung von General Movements (GMs) als hoch sensitives und spezifisches diagnostisches Mittel zur frühen Diagnose von Hirnschädigungen wiederholt bestätigt. Im Vergleich zu anderen Techniken, allen voran Magnetresonanztomographie, Ultraschall und traditionellen neurologischen Untersuchungen, kann sie schnell, ohne Manipulation und kosteneffizient durchgeführt werden. Trotz dieser Vorteile ist die Beurteilungen longitudinaler GMs noch nicht in allen Kliniken etabliert.

**Ziel:** Ziel dieser Studie war es die Beziehung von einmaliger GM Beurteilung, die zum Entlassungszeitpunkt durchgeführt wurde, und dem späteren entwicklungsphysiologischen Ergebnis zu beschreiben und zu analysieren.

**Patienten und Methoden:** Zwischen Juli 2006 und Juni 2009 wurden GMs von 72, auf der Neonatologie des LKH Graz behandelten, frühgeborenen Kindern einmalig zum Zeitpunkt der Entlassung gefilmt. Die Aufzeichnungen wurden zu einem späteren Zeitpunkt retrospektiv gemäß der Prechtl Methode ausgewertet. Die Ergebnisse der GM Analyse wurden mit den entwicklungsneurologischen Ergebnissen, die im Alter von 1-2 Jahren mittels Touwen Infant Neurological Examination, dem Gross Motor Function Classification System and dem Bayley Scale of Infant Development ermittelt wurden, verglichen.

**Resultate:** Unsere Ergebnisse entsprechen weitgehend den bereits publizierten Daten, da wir eine starke Beziehung zwischen einzelnen GMs und neurologischen Testergebnissen einerseits und Entwicklungsergebnissen andererseits feststellen konnten. 42 (95%) der 44 Kinder mit normalen pre-term GMs zeigten ein normales entwicklungsneurologisches Ergebnis. Abnormale GMs (cramped-synchronized, poor-repertoire) wurden bei 10 (36%) von 28 Kindern von neurologischen Auffälligkeiten gefolgt: 6 davon hatten Zerebralparese, 4 hatten andere neurologische Auffälligkeiten oder Rückstände in der Entwicklung. Die Sensitivität (83%) und der negativer prediktiver Vorhersagewert (95%) waren sehr hoch

wohingegen die Spezifität (70%) und speziell der positive prediktive Vorhersagewert (36%) etwas niedriger waren.

**Fazit:** Eine longitudinal angelegte GM Beurteilung sollte einer Einzelbeurteilung im Alter von 36 Wochen vorgezogen werden, da eine einmalige Beurteilung neurologische Ergebnisse nur bedingt vorhersagen kann. Im Speziellen scheint die hohe Anzahl an falsch positiven Testergebnissen den einmaligen Einsatz bei Frühgeborenen zu limitieren.

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## List of Abbreviations

| | |
|---|---|
| AGA | Appropriate for Gestational Age |
| BSID | Bailey Scale of Infant Development |
| CP | Cerebral Palsy |
| CPG | Central Pattern Generator |
| CS | Cramped-Synchronized |
| D | Disease |
| FMs | Fidgety Movements |
| GA | Gestational Age |
| GMFCS | Gross Motor Function Classification System |
| GMs | General Movements |
| GW | Gestational Week |
| H | Health |
| HIE | Hypoxic Ischemic Encephalopathy |
| IRDS | Infant Respiratory Distress Syndrome |
| IVH | Intraventricular Haemorrhage |
| LGA | Large for Gestational Age |
| MDD | Mild Developmental Delay |
| MND | Minor Neurological Dysfunction |
| MNS | Minor Neurological Signs |
| NA | Not Assessable |
| NEC | Necrotizing Enterocolitis |
| ND | Normal Development |
| NDD | Neurological or Developmental Disorder |
| NNE | Normal Neurological Examination |
| NO | Normal Outcome |
| NPT | Normal Pre-term GMs |
| PR | Poor-Repertoire |
| PVH | Periventricular Haemorrhage |
| PVL | Periventricular Leukomalacia |

| | |
|---|---|
| ROP | Retinopathy of Prematurity |
| SD | Standard Deviation |
| SDD | Severe Developmental Delay |
| SGA | Small for Gestational Age |
| TINE | Touwen Infant Neurological Examination |
| WM | Writhing Movements |

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# 1 Introduction

Recent progress in both prenatal assistance and neonatal intensive care has led to a great reduction in neonatal mortality rate over the past few decades.[1] Perinatal morbidity has not yet improved equally well as survival rates. Therefore, more and more infants born before term and especially very low birth weight infants are still at high risk of developing disabilities as a result of prenatal or perinatal brain lesions.[2] According to Volpe[3], 5% to 15% of very low birth weight infants (newborn infants with birth weights below 1500g) show severe neurological abnormalities mainly cerebral palsy (CP) and a further 25% to 50% more subtle cognitive and behavioural deficits. The resulting augmentation in total numbers of neurodevelopmental disabilities leads to an increasing need for early recognition of those infants who are at risk of developing such deficits.

Many different approaches have been developed in order to apply therapeutic intervention as early as possible. These strategies include neurological examinations, neurodevelopmental tests up to ultrasound (US), computer tomography (CT) and magnetic resonance imaging (MRI). However, in the first few weeks after birth all of these methods have failed to be sensitive and specific enough or available to be used exclusively in clinical practice.

In the early 1990s a completely new assessment technique which was based on the investigation of spontaneous movements was introduced by Heinz F. R. Prechtl and his co-workers: The assessment of general movements (GMs). After two decades of research numerous studies have repeatedly proven that GM assessment is a reliable and valid diagnostic tool for detecting brain dysfunction early in life.[4, 5]

The present study is about this new promising method. After a brief historical retrospection and a short survey on the topic of spontaneous movements which forms the fundamental of a deeper understanding of GM assessment it dwells on the description of Prechtl´s method, its performance, its strengths and limitations. The aim of the conducted study was to describe and analyse collected data of 72 pre-term infants in order to set requirements for the creation of further hypothesis.

## *1.1 A new approach in the early detection of brain dysfunction: The qualitative assessment of spontaneous motor activity*

There used to be a time when functional assessment of the young nervous system was all about testing reflexes and tone. Over years these classical stimulus response investigations shaped the opinion about the function of the human nervous system as being a passive rather than an active organ. Studies on reflexes and all kinds of sensory stimulation were most notably performed on spinal preparations and de-cerebrated animals. This gimmick made it possible to study the quantitative relationship between the sensory input and the motor output without the annoying nuisance of the interfering spontaneous activity of supra-spinal inputs.[4]

These work groups did not note that the nervous system is one of the most complex and complicate organs of any animal and that obviously these spontaneous activities, as the expression of spontaneous neural activity, seems to be an important substrate of proper brain function.[4, 6]

Therefore, reflexes are found to be poor indicators of brain function and dysfunction. This explains why classic neurological examination lacks the power to make a specific prognosis of later neurological outcome.[4, 6]

However, in the late 1950s and the early 1960s Prechtl being aware of these misjudgement tried to find a new technique for the early neurological assessment which should have a higher individual predictive power, should be quick and easy to learn. Inspired by the shortcomings of the former neurological investigations his attention was soon attracted by the many specific spontaneous motor patterns he was able to recognise during his observation studies on normal pre-term infants in 1979. Soon similar observations on high risk pre-term infants followed. Their first expectation was to find differences in the incidence of the various specific motor patterns between these two groups. However, it was not the case. Being convinced to be on the right track they soon realized that what really counted were not the quantitative differences but the qualitative differences in movements. This marked the beginning of a completely new approach: The qualitative assessment of spontaneous motor activity.[4]

From the beginning the main focus was on general movements, a certain type of spontaneous movements that occurs most frequently and lasts long enough to be proper observed.[4, 6]

And indeed, it turned out that these spontaneous movements were the key to the new technique which should approve to be an excellent marker for early brain impairment and dysfunction: Prechtl´s method on the qualitative assessment of general movements in pre-term, term and young infants.[4]

## *1.2 Spontaneous motility in foetuses, pre-term and term infants*

The change in paradigm from a passive to an active and endogenously generating central nervous system had far reaching consequences. From this time onward the human nervous system was suspected to be able to create a variety of motor patterns by itself, meaning without being constantly triggered by specific sensory inputs.[4] But how are such spontaneous movements generated? Although this question is not yet fully resolved central pattern generators seem to play an important roll.[7]

### 1.2.1 The roll of central pattern generators

Central pattern generators (CPGs) are networks of neurons which produce specific rhythmic movements without receiving sensory or descending inputs that carry specific timing information.[7, 8] Well known CPGs exist for walking, breathing, flying and swimming.[4] The circuits involved in the control of vital functions such as breathing, chewing and swallowing are located in the brain stem, whereas those for locomotion are placed in the spinal cord.[8]

General principles of the organisation of these circuits are peacemaking neurons and reciprocal inhibition, which are responsible for spontaneous activity. However, to meet the environmental requirements CPGs are modulated by supraspinal, sensory and neuromodulatory influences.[7]

Supraspinal centres such as the sensorimotor cortex, the cerebellum and the basal ganglia were identified to fulfil five major tasks in the control of locomotion: activating spinal locomotor CPGs, controlling the intensity of CPG operation,

maintaining equilibrium during locomotion, adapting limb movement to external conditions, and coordinating locomotion with other motor acts. Research showed that when the spinal cord of animals was transsected the characteristic features of the walking pattern still maintained but it lacked the refinement.[8]

These findings seem to be important for the understanding of Prechtl´s method because they suggest that any impairment of supra-spinal structures like the sensorimotor cortexas well as its descending pathways can affect CPGs and lead to changes in the quality of spontaneous movements.

### 1.2.2 The concept of onto-genetic adaptation

One of the most significant new paradigms of developmental neurology on the functional development of the human nervous system in the 1980s is the concept of onto-genetic adaptation. This model proceeds on the assumption that during the development of the individual, the functional repertoire of the developing neural structures have to meet the requirements of the organism and its environment.[4] Therefore, no phases of amorphic and random movements exist so that the individual is properly adapted to the environment at any time.[9]

As a consequence at different ages we are dealing with qualitatively different nervous systems in structure and function as well as specific vulnerability. Thus age specific signs and symptoms require age-adequate diagnostic procedures. Prechtl´s method of qualitative assessment of general movements is trusted to meet fully this requirements.[4]

### 1.2.3 Prenatal development of spontaneous movements

Once the many spontaneous motor patterns seen in newborns came to Prechtl´s attention he was wondering about their prenatal development. He was sure that birth could not be the starting point. The very first studies dealing with foetal movements were carried out by Minkowsky in 1928 and Hooker in 1952 on aborted foetuses.[4] As they were strictly conducted in the tradition of reflexology and behaviourism, endogenously generated spontaneous motor activity was totally overlooked or wrongly interpreted.[9] What they described were rather abnormal

movement patterns of dying foetuses and movements evoked by artificial tactile stimuli.[4]

In the 1980s technical achievements, especially the creation of more advanced ultrasound equipment, allowed Prechtl to study the undisturbed foetus in its natural environment. A series of longitudinal studies on the development of foetal movements were then performed which form the basis of our knowledge about the motor repertoire of the foetus as described below.[4, 9] For a brief outline see Table1.

*Table 1: Foetal motor repertoire (from Einspieler[4])*

| 10 weeks | 12 weeks | 14 weeks | 20 weeks |
|---|---|---|---|
| Startle | Startle | Startle | Startle |
| GMs | GMs | GMs | GMs |
| Isolated arm ms | Isolated arm ms | Isolated arm ms | Isolated arm ms |
| Isolated leg ms | Isolated leg ms | Isolated leg ms | Isolated leg ms |
| Hiccup | Hiccup | Hiccup | Hiccup |
| | Breathing ms | Breathing ms | Breathing ms |
| | Hand-to-face contact | Hand-to-face contact | Hand-to-face contact |
| | Head retroflexion | Head retroflexion | Head retroflexion |
| | Head anteflexion | Head anteflexion | Head anteflexion |
| | Head rotation | Head rotation | Head rotation |
| | Stretch | Stretch | Stretch |
| | Yawn | Yawn | Yawn |
| | | Sucking and swallowing | Sucking and swallowing |
| | | | Eye ms |

**Abbreviations:** GMs general movements, ms movements

Today we know from non-invasive ultrasound observations that distinct foetal movements occur as early as 8 weeks of post-menstrual age.[9] All data of the following description are counted from the first day of the last menstruation before the amenorrhoea.

The first movement that can be seen emerges at 7½ to 8 weeks post menstrual age. It is sidewards *bending of the head*.[9]

Soon afterwards at 9 to 10 weeks post menstrual age two kinds of complex and generalized movements occur. They both involve the whole body but differ in speed and complexity. While the *startles* are quick phasic movements of all limbs, trunk, and neck, *general movements* are slower and have a complex sequence of involved body parts.[9]

Contrary to previous opinions *isolated arm and leg movements* emerge at the same time and can be seen from 10 to 11 weeks onwards. It must be noted that arm movements occur more frequently than leg movements what might have been overlooked for a while. The delay in isolated movements is surmised to be due to a more difficult production of isolated movements than of global motor activity.[9]

Around the same time the *hiccup pattern* emerges. It is caused by repetitive short contractions of the diaphragm. During episodes of hiccups the whole foetus is being passively moved in the amniotic fluid.[9]

The next patterns that emerge at around 11 weeks are *head retroflexion*, *head anteflexion* and *head rotations*. Together with arm movements they produce hand to face contacts that are, however, considered accidental rather than intentional.[9]

*Breathing movements* are starting to appear episodically at 11 to 12 weeks. They are an exception because unlike all other movements breathing is related to the maternal glucose level.[9]

A very striking phenomenon in foetal motor development is the early emergence of *stretches* and *yawns* at 12 weeks. Both are complex movements which tend to maintain throughout the whole life without changing their form and pattern.[9]

Shortly after the 12$^{th}$ week rhythmical *sucking movements* and *swallowing* persuade allowing the foetus to drink amniotic fluid. By the end of pregnancy he drinks up to 1 litre per 24 hours.[9]

At last *slow eye movements* emerge at 20 weeks. They are followed by rapid eye movements at about 22 weeks.[9]

Within the concept of onto-genetic adaptation all of these motor patterns have an

effective function during prenatal life. Trunk movements, general movements and alternating leg movements for example lead to changes in the inter-uterine position of the foetus. Such changes are frequent and may run up to 25 per hour during the first half of pregnancy. Other movement patterns such as breathing movements, smiling and eye movements anticipate postnatal functions. They develop early and are ready for their specific function after birth.[9]

### 1.2.4 Postnatal continuity of foetal movements

Most of the foetal movements develop early during the first half of pregnancy and continue far above and beyond birth. Thus, besides some exceptions in the first few weeks after birth there are hardly any changes in form and pattern of the movements. It seems that there is a continuity from prenatal to early postnatal life.[4, 9]

Newly introduced movements are most notably depending on ventilation and include reflexes such as sneezing and coughing as well as the communication sign of crying. On the other hand some spontaneous movements gradually come under the control of sensory triggers. A good example is rooting. During pregnancy it is irrelevant when and where the foetus starts sucking because he is drinking amniotic fluid anyway. Postnatal on the other hand sucking is only useful in the proper feeding situation. So rooting has to be triggered and becomes directed towards the stimulated perioral area.[4, 9]

What is conspicuous in humans compared to other infra-human primates is the poor adaptation to the extra-uterine environment during the first few weeks of life on the one hand and its relatively late recompense on the other hand.[4, 9] This fact may be explained best by a concept based on allometric measurements. Compared to body size, brain size, basal metabolism, maternal-neonatal body weight relation and life span, the human pregnancy of 40 weeks is relatively short compared to other primates.[9] This may have developed because of evolutionary pressures on the higher demands on energy metabolism caused by the relatively rapid brain growth and the huge amount of white fat in the human neonate. Maybe the first few weeks of infancy can be understood as a continuation of gestation.[4]

### 1.2.5 The major transformation of neural functions at three months

However, at around three months after term a major transformation of many motor and sensory patterns occurs making the infant much fitter for the requirements of the extra-uterine environment.The time of transformation is not related to the extra-uterine life span but to the post-menstrual age. This means that the time of birth seems to be irrelevant. What counts is the corrected age for pre-term birth.[4, 9]

By this time the infant increases its muscle power. The ability to overcome gravity leads to a proper head control and a change of body posture from a body orientated to a space orientated control. Moreover, the sucking pattern changes, social smiling and pleasure occur and control of visual attention and binocular vision develops. But the most notable change happens in form of general movements. The heretofore dominating writhing character of GMs gradually becomes removed by a new pattern, the fidgety movements (FMs).[4]

### 1.2.6 Post-term development of spontaneous movements

FMs may frequently be seen together with a range of other spontaneous movements including wiggling-oscillating arm movements, swiping movements, mutual manipulation of fingers, manipulation of clothing, reaching and touching, legs lift, trunk rotation and axial rolling. For a detailed classification see Table 2. It is taken from Einspieler[4] and is based on the first systemic description by Hopkins & Prechtl (1984). FMs are present till 20 to 25 weeks. At this time intentional and anti-gravity movements start to dominate.[4]

## *1.3 General Movements*

There exists a great variety of distinct movement patterns the young human nervous system is able to generate endogenously and which occur during the whole course of development from foetus to the young infant.[6] Some of the most prominent and complex movement patterns observed are general movements. They have been selected because they are the most complex movements, occur frequently and last long enough to be observed properly.[4]

Table 2: Spontaneous movement patterns that may be seen together with fidgety movements (from Einspieler[4])

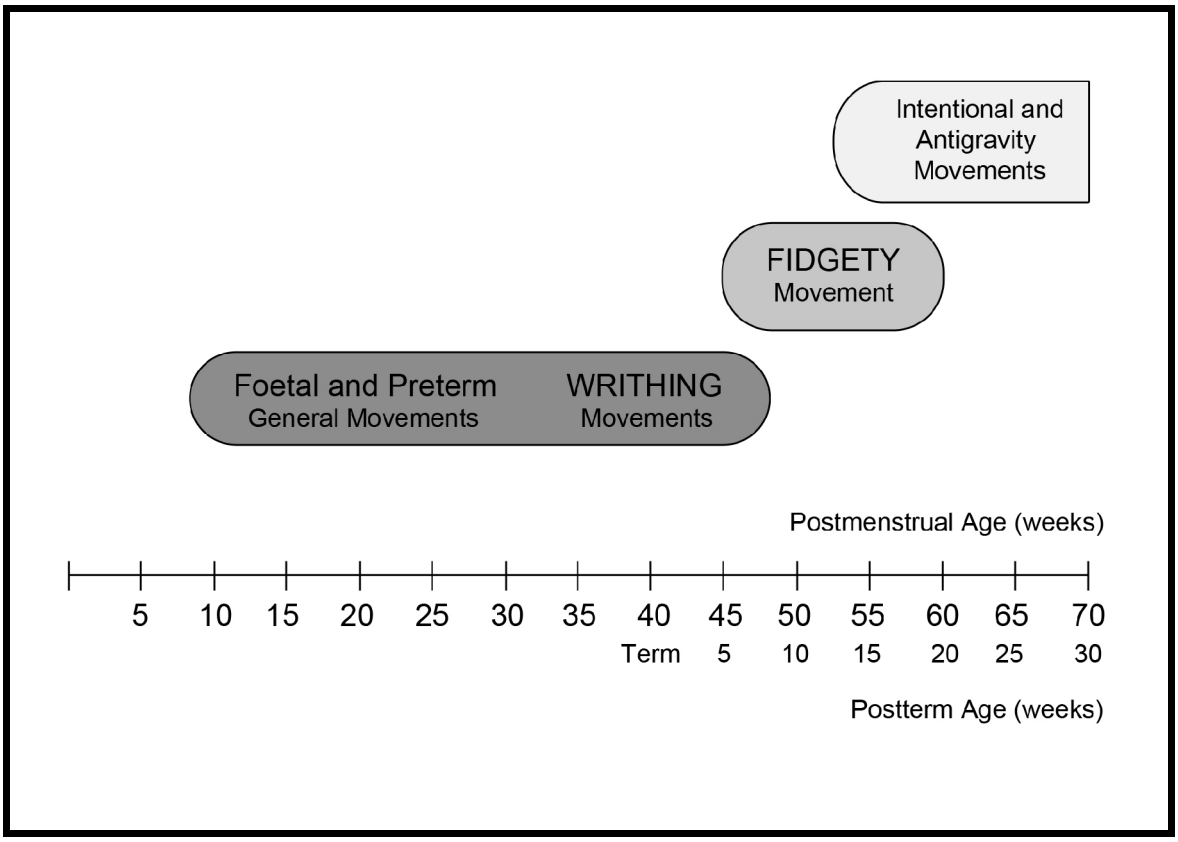
| Movement pattern | Definition | Period of occurrence |
|---|---|---|
| Wiggling-oscillating arm movements | Irregular, oscillatory, waving like movements; most noticeable in partially or fully extended arms, where they have a frequence of 2 to 3 Hz; small amplitude and moderate speed; should be clearly distinguished from tremendous movements, which are less smooth in appearance and have more regular rhythm | 6 to 14 weeks post-term |
| Saccadic arm movements | Jerky, zigzag movements, which continually vary in direction; most noticeable in partially or fully extended arms; moderate to large amplitude and moderate speed | 6 to 15 weeks post-term age |
| Swiping movements | Movements with a sudden but fluid onset and smooth offset with a ballistic-like appearance; can go in downward or upward direction; most noticeable in extended arms, but also in partially or fully extended legs; large amplitude and high speed | 6 to 20 weeks post-term age |
| Mutual manipulation of fingers | Both hands are brought together in the midline and the fingers of both hands repetitively touch, stroke or grasp each other | From 12 weeks postterm age onward |
| Manipulation (fiddling) of clothing | The fingers of one or both hands repetitively touch, stroke or grasp some object or the clothing | From 12 weeks postterm age onward |
| Reaching and touching | One or both arms extend to some object in the immediate environment. The fingers contact the surface of the object | From 12 weeks postterm age onward |
| Legs lift | Both legs lift vertically upward; partial or full extension at the knees; hips are slightly tilted upward; one or both hands touching or grasping the knees; sometimes with anteflexion of the hand | From 15 weeks postterm age onward |
| Trunk rotation | As a result of the soles of the feet pushing down on the lying surface, one side of the hips is lifted and rotated | From 12 weeks postterm age onward |
| Axial rolling | The whole body is turned from supine to prone lying in a movement started by the head. Sometimes the infant returns to prone lying | From 18 weeks postterm age onward |

By definition GMs are gross and slow movements which may last from a few seconds to several minutes.[10, 11] They involve the whole body in a variable sequence of arm, leg, neck, and trunk movements. What is particular about them

is the variability and fluctuation of intensity, force and speed of motor performance. They have a gradually beginning and end. Slight changes in direction of the movements as well as superimposed rotations make the movements fluent and elegant and create the impression of complexity and variability.[12]

From the 9th week post menstrual age onward when GMs can be observed first to the 5th month post term age when GM disappear and anti-gravity and intentional movements start to dominate these movements slightly change their character. Altogether three different periods can be distinguished: Foetal and pre-term GMs, writhing GMs and GMs of fidgety character. Figure 1 displays the developmental course of general movements.[6]

*Fig.1: Developmental course of general movements (from Prechtl[13])*




The description of GMs and their abnormal appearance given below is based on the terminology and definitions settled in 1998 by an international committee of experts and the definitions which the GM Trust founded in 1997 has agreed upon.[13–15] Table 3 provides an overview of all normal and abnormal GM patterns.

*Table 3: Definition of GMs and their abnormal appearance officially agreed upon by the GM Trust (from Prechtl[13])*

| | Normal general movements | Abnormal general movements |
|---|---|---|
| **Prenatal and pre-term age** | Gross movements, involving the whole body. They may last from a few seconds to several minutes or longer. Variable sequence of arm, leg, neck, and trunk movements. Wax and wane in intensity, force, and speed, and have a gradual beginning and end. Majority of sequences of extension and flexion movements of arms and legs are complex, with superimposed rotations and often slight changes in the direction of the movement. These added components make the movements fluent and elegant and create the impression of complexity and variability. | **Poor-repertoire** of general movements: the sequence of the successive movement components is monotonous and the movements of the different body parts do not occur in the complex way seen in normal GMs.<br><br>**Cramped-synchronized general movements:** These appear rigid and lack the normal smooth and fluent character. All limb and trunk muscles contract and relax almost simultaneously.<br><br>**Chaotic general movements:** movements of all limbs are of large amplitude and occur in a chaotic order with no fluency nor smoothness. They consistently appear to be abrupt. |
| **Term age until 8 weeks` post-term age** | **Writhing movements** are characterized by small-to-moderate amplitude and by slow to moderate speed. Fast and large extension movements may occasionally break trough, particularly in the arms. Typically, such movements are elliptical in form. This component creates the impression of a writhing quality of movements. | |
| **6 to 20 weeks´ post-term age** | **Fidgety movements** are circular movements of small amplitude and moderate speed and variable acceleration of neck, trunk, and limbs in all directions. They are continual in the awake infant, except during focused attention. They may be concurrent with other gross movements, such as kicking, wiggling-oscillating and swiping of the arms or pleasure bursts. Fidgety movements may be seen as early as 6 weeks post-term but usually occur around 9 weeks and are then present until 15 to about 20 weeks. This age range holds true for term as well as for pre-term infants after correcting the age. Initially, they occur as isolated events (score: +), they gradually increase in frequency (score: ++) and then decrease once again (score: +). | **Absent fidgety movements:** fidgety movements are never observed from ages 6 to 20 weeks postterm. Other movements can, however, be commonly observed.<br><br>**Abnormal fidgety movements:** look like normal fidgety movements except that their amplitude, speed, and jerkiness are moderately or greatly exaggerated. |

### 1.3.1 Normal general movements

#### *1.3.1.1 Foetal and pre-term general movements*

GMs can be first seen in foetuses as young as 9 weeks of post menstrual age. Initially they are called foetal GMs and can be investigated during ultrasound recordings. After birth up to term age (38. week of gestational age [GA]) they become pre-term GMs. Despite the gross environmental changes at this transition, e.g. increase of force of gravity and maturation of the brain, the appearance of GMs is not affected at all. Solitary pre-term GMs may have occasionally large amplitudes and are often of fast speed.[6] But in general foetal GMs do not change in form at birth.[4]

#### *1.3.1.2 Writhing general movements*

During term age and during the first two months post-term the movements become elliptical in form. As they are creating the impression of a writhing quality they are commonly referred to as writhing movements (WMs). Furthermore, they are characterized by small-to-moderate amplitude and by slow-to-moderate speed. From time to time fast and large extension movements may break trough, particularly in the arms.[13, 14]

#### *1.3.1.3 Fidgety general movements*

At the “major third month transformation” a new more oscillating kind of movement occurs. Movements of this type are called fidgety movements. They gradually emerge within the second month, come to full expression at 3 to 4 months and then taper off again at the end of the fifth month. Although writhing GMs can be seen in sleeping infants until the sixth month, FMs soon become the predominant movement pattern. This age range holds true for term as well as for pre-term infants after correcting the age.[12, 13] FMs can be seen continual in the awake infant, except during periods of focused attention, fussing and crying.[6, 12]

Compared with WMs, FMs are circular movements of small amplitude and moderate speed and variable acceleration of neck, trunk and limbs in all directions. They may be seen with other gross movements as described before.

Their temporal organisation slightly changes in the course of development from rather isolated events in the beginning by continual to a decreased occurrence in the end.[14] Therefore, three temporal organisations can be defined: Continual FMs intermittent FMs and sporadic Fms.[13]

- ***Continual fidgety movements*** are scored (++) as they occur frequently and are only interspersed with short pauses.[4, 13]
- I***ntermittent fidgety movements*** are scored (+). Like the previous type they may occur regularly but the intervals between the FMs are prolonged so far as they are only present half of the time.[4, 13]
- ***Sporadic fidgety movements*** are scored (+/-). They are the kind of FMs with the longest pauses.[4, 13]

### 1.3.2 Abnormal general movements

If the nervous system is impaired GMs change their quality. They lose their complex and variable character and become monotonous and stereotype.[6] In particular it is a reduction in elegance and fluency, as well as a reduction in variability and fluctuation of intensity and speed of the motor patterns.[10]
During the pre-term, term and early post-term period three different types of abnormal GMs are known.

- ***Poor-repertoire GMs:*** The combination of the successive movement components is monotonous and there are no complex movements of the different body parts as seen in normal GMs.[4, 13]
- ***Cramped-synchronized GMs:*** These abnormal GMs appear rigid and lack the normal smooth and fluent character. All limbs and trunk muscles contract and relax almost simultaneously.[4, 13]
- ***Chaotic GMs:*** A kind of abrupt movement that occur in a chaotic order without any fluency nor smoothness. The amplitude of all limb movements is large.[4, 13]

Suspicious FMs can be either abnormal or absent. They can be seen from the major transformation onward.[4]

- ***Abnormal fidgety movements:*** This kind of movements look like normal FMs but their amplitude, speed and jerkiness are moderately to greatly exaggerated.[4, 13]
- ***Absence of fidgety movements:*** In case FMs are never seen from 9 to 20 weeks post-term the abnormality is classified as absent FMs. However, other movements may be observed commonly.[4, 13]

## *1.4 Individual developmental trajectories*

Developmental trajectories are based on longitudinal recordings and can improve accuracy of individual prediction of the later outcome. Altogether, at last two to three recordings of the pre-term period, one at term or alternatively early post-term age and finally one recording between 9 and 15 weeks post-term should be documented on a pre-assembled perform. If FMs are absent recording should be repeated at 12 to 15 weeks post-term age. Individual developmental trajectories allow to consider individual deteriorations as well as improvements of GMs at particular ages. This seems important as research showed the earlier and the more often an infant shows abnormal GMs the likelier it will later suffer neurological deficits. Therefore, prediction of the later outcome from a single recording should be avoided.[4, 12]

## *1.5 Global judgement versus detailed analysis*

Global judgement means that in a first step the assessor only distinguishes between a normal and abnormal quality of GMs. Abnormal GMs can than be furthermore specified as described before.[4] It is based on “Visual Gestalt Perception” which was investigated by Konrad Lorenz. Although “Visual Gestalt Perception” is considered to be very vulnerable when attention is focussed on details, it is a well working tool when complex phenomena are analysed. In particular, it is able to take a great variety of details and their relationships better into account.[12]

However, especially when movements are abnormal it might be worthwhile to look more precisely at different aspects and components of GMs. For a detailed analysis of GMs several different attempts have been described. Prechtl introduced a motor optimality score for semi-quantitative assessment. It is age specific and for the pre-term and writhing period it consists of eight different movement criteria. They can either be judged as optimal (score 2) or non-optimal (score 1). Thus the total score can vary between 8 and 16. High scores refer to an optimal quality of GMs and low scores to a reduced quality of GMs. However, there are two shortcomings of this strategy. On the one hand the procedure does not allow a re-synthesis from the description of the details to the total picture and on the other hand by focussing on details the power of global “Gestalt Perception” is lost. But there are advantages too. It might be helpful in describing any changes in the quality of GMs more precisely and in addition it can be used for statistical analysis and comparison with other measurements.[4]

## *1.6 Prediction of neurological outcome*

### 1.6.1 Cerebral palsy and its early diagnosis

The term cerebral palsy refers to a condition caused by various CNS lesions during the prenatal, perinatal or postnatal period and represents a symptom of many developmental disorders. It is used to describe the resulting movement or posture disorders that are neither progressive nor curable. Often it is combined with other developmental disorders such as sensory, perceptual and language disorders, mental retardation and behavioural disorders.[16]

Depending on the location of the impairment different manifestation of CP may occur. Typically, periventricular leukomalacia impairing periventricular white matter structures lead to spastic CP with an accentuation of the legs. By contrast ischemic infarction of the capsula interna most notably caused by circulatory disturbance of the arteria lenticulostriata, may cause spastic hemiplegia with a accentuation of the arms.[16]

Corresponding to their movement and posture capabilities infants with CP can be classified into five degrees of severity.[16, 17]

For a long time CP was diagnosed at around 8 to 12 months post-term age when the first signs of spasticity or pareses or any other specific symptom for CP was detected. As approximately 0.1% to 0.2% of all infants are diagnosed as CP strategies for the early diagnoses seems to be a worthwhile requirement.[16]

Prechtl´s method represents such a diagnostic tool that beside a sensitivity and specificity of 95% is quick, non-invasive, non-intrusive and cost-effective at the same time.[6]

It has been shown repeatedly that consistent cramped-synchronized GMs and the absence of FMs strongly predict later CP.[4]

Poor-repertoire GMs on the other hand have a very low predictive value. They are rather frequent in infants with brain ultrasound abnormalities and might refer to a temporary affection of the brain. But they can be followed by normal, abnormal or absent FM and therefore, outcome can be abnormal as well as normal.[6]

Chaotic GMs and abnormal FMs are both very rare. While the first often develop cramped-synchronized GMs after a few weeks the later has a low predictive value for later neurological impairments.[6]

Recently a systemic review on the predictive validity of GMs has been published comparing the results of 17 studies. The review confirms the roll of GM assessment especially during the FMs period for the early prediction of later neurodevelopmental disabilities.[18]

Numerous studies have been performed comparing GM assessment, neurological examination, neurobehavioural assessment and neuroimmaging techniques such as ultrasound and MRI.[2, 19–26] Especially for traditional neurological investigations and to a less extent for ultrasound findings GM assessment showed a superior predictive power.[4] Only during pre-term period ultrasound may have a better specificity than GM assessment.[2] The same holds true for MRI which shows a better specificity and accuracy at 36 weeks post-conceptional age.[23]

However, all studies emphasize the complementary use of GM assessment and not a replacement of other established methods. The integration of all techniques may improve the prognostic accuracy. Recently this approach was confirmed by a study which investigated the integrated application of a traditional neurologic examination and GM assessment. The authors found that early prediction of

neurodevelopmental outcome in pre-term infants can be improved by applying both methods.[21]

### 1.6.2 Minor neurological dysfunction

Abnormal FMs show a low predictive power for CP but have been discussed repeatedly in the context of the later development of minor neurological deficits.[27, 28] Although the predictive power of the quality of GMs at fidgety age for minor neurological dysfunction (MND) is not yet sufficiently cleared, a recent study demonstrated the strong association between the presence of abnormal FMs at 11 to 16 weeks and MNDs.[29] These findings are in line with previous studies that have investigated the quality of the motor repertoire in the early diagnosis of MNDs. The authors conclude that beside specific clinical risk scores and neuro-imaging GM assessment helps to identify infants at high risk for development of MNDs.[29]

## *1.7 Inter-observer agreement and the effectiveness of training in Prechtl´s method*

As the qualitative assessment of GMs is based on “Visual Gestalt Perception” the new technique does not offer the option to count and reproduce the differences in numbers. Therefore, it has often be blamed to be subjective.[4, 30] However, this presumption turned out to be a misjudgement. The inter-observer reliability of GM assessment has been repeatedly investigated by various groups and recently been proven in a review to be sufficiently high and reliable.[30]

Data came particularly from experts in the field of GM assessment but also from doctors, students and nurses untrained in GM assessment. In average the inter-scorer agreement is around 90%.[30]

Different GM patterns are not equally difficult to access. The age specific GM patterns most difficult to judge are poor-repertoire GMs (74% correct assessments), abnormal FMs (74% correct assessments) and cramped-synchronised GMs (78% correct assessments). The simplest but also the rarest pattern represents chaotic GMs (96% correct assessments). Correct identification of normal GMs (91% correct assessments) and absence of FMs (90% correct

assessments) lay in between but are still high. They are the two most relevant GM pattern for clinical purpose as they predict normal neurological development in 96% of cases (NGMs), dyskinetic and spastic CP (abnormal FMs).[30]

Besides it seems that infants around term were more difficult to access than pre-term infants or infants after the 3-months major transformation.[30]

Since 1997 a standardized training course has been offered by the GM Trust. It enables professionals in the field of infant neurology to learn the new assessment technique appropriate within 3 to 4 days of intense training.[30] After a course participants were able to assess 83% of all GM patterns properly and to discriminate between normal and abnormal GMs correctly in 92%. Additional training was able to increase the correct assessments significantly from 83% to 89%.[30]

## *1.8 Assessment and recording technique*

Although GMs can be observed directly with the unaided eye a standardized recording and assessment procedure has been developed in order to improve the reliability of the new technique. Recording is one of its main requirements. It allows the observer to review any sequence for several times even at different speeds. This can be very helpful. Another advantage of applying video tapes is the possibility of storage for documentation and future reference.[4]

As equipment a small video or digital camera without a blinking light is proper and should be placed high above the infant. It is important that the camera catches all limbs and the face. The latter is very important as the assessment is done without acoustic signals, which means that the decision, whether a rigid movement is due to crying or not, can only be made by observing the infant´s face.[4]

The influence of visual and acoustic stimulation turned out to have rarely any effect on the temporal organisation of FMs. In particular, a study carried out in 2002, showed that visual stimuli such as a red ring, unanimated acoustic stimulation as well as the interaction of the mother talking to her baby had no influence. Only a red puppet could attract a significance level of focussed attention and lead to a decrease of FMs.[1] However, as the presence of distracting objects

such as toys and the presence of the caretaker may interfere with the observer´s "Gestalt Perception" they both should be avoided to be present on the film.[4] Social interactions are still possible during FMs assessment.[1]

The duration of the recording is age-dependent. Pre-term infants are usually recorded 30 to 60 minutes while from the writhing period onwards 5 to 10 minutes of recording are sufficient. Finally three different GMs of each film are collected and copied onto a new assessment tape.[4]

The correct behavioural state is another important requirement. While pre-term infants (before 37 weeks) should be recorded when bouts of activity occur, irrespective of whether the infant is awake or sleeping, older infants should be recorded preferably during periods which are characterized by open eyes, irregular respiration, present movements and absence of crying.[4]

It is not necessary to take off all cloths while the infant is filmed. However, it is important that none of them restrict the infant´s agility. Prechtl suggests a small and non restrictive nappy for very young pre-term infants. Older infants should be dressed lightly and comfortable with all arms and legs being left bare. As the infant ´s behavioural state and movement quality is affected by changes in temperature, climate should be adapted to the infants age and clothing.[4]

Since nests have been introduced for their beneficial effects in most European neonatal intensive care units (NICUs) the question rose whether they may have any influence to motor behaviour. Even though a nest seems to affect posture and motility in pre-term and early post-term infants it does not affect the occurrence of abnormal GMs. Therefore, no evidence exists that infants have to be removed during recording.[31]

There are a few situations that should be avoided because they are known to affect GMs or the observer´s "Gestalt Perception". During prolonged episodes of fussing, crying or drowsiness recording should be paused or even rescheduled on an other day because the quality of movements changes. Sucking on a dummy results in the sucking posture with flexed arms, fisting and extended legs, making any judgement impossible. Prolonged episodes of high-ups should be avoided as they interfere with both the GMs as well as the observers "Gestalt Perception".[4]

Recently a modified version of Prechtl´s method on the qualitative assessment of GMs which do not employ video recordings has been discussed.[32] According to the study published in 2007, direct observation of GM shows like the standardized procedure a very high sensitivity for the prediction of CP. But it was found to show a lower specificity, particularly during the writhing period. The authors suggest to use the direct assessment when the standard video observation cannot be routinely applied and to restrain the use of video recordings to the abnormal or doubtful cases.[32]

## *1.9 The effects of systemic disease, seizure and drugs on GM assessment.*

Many studies demonstrate the robust character of GMs, suggesting that they can be hardly influenced by any environmental changes.[4] Neither "individualised developmental"- or "Kangaroo" care[4] nor sensory stimulus (visual,[1, 33] acoustic,[1] social and proprioceptive[34]) could sufficiently interfere with GMs to compromise GM assessment. Even under intensive care unit conditions GM assessment can be carried out smoothly as long as the interventions and medications such as artificial ventilation, infusion lines, or electrodes, allows the infant to move.[35] However, there are some conditions under which GM assessment may be more difficult to perform especially for the less experienced observer.

*Seizures*, for example, may represent a source of error as they can resemble abnormal GMs. Nevertheless, there are marked differences, most notably the extreme stereotypy of all sequences during periods of seizure that allow the experienced observer to distinguish accurately between these two conditions.[4]

*Systemic infections* do not mimic brain lesions but may have a limiting influence on the quality of GMs during the acute phase. A study published in 1997 by Bos[36] found that GMs of pre-term infants became sluggish and showed a reduction in speed. But they point out that it is possible to discriminate between abnormal GMs due to brain lesions and affected GMs due to systemic infections.[36]

The effects of some *drugs* on the quality of GMs have been described for Barbiturates, Indomethacin, Dexamethasone and Anticonvulsants. However, the

role of these drugs has not been yet clarified sufficiently. It seems that anticonvulsant therapy during pregnancy may lead to a reduction of GM optimality score at 7 days and 4 weeks.[37] For Indomethacin transient effects on the quality of spontaneous movements were described i.e. a reduction in incidence, duration and speed.[38] Dexamethason may be blamed for a reduction in speed and amplitude of GMs.[39]

## *1.10 Aim of the present study*

The aim of the study was first and foremost to describe and analyse collected data in order to set requirements for the creation of further hypothesis. A specific question that arose to me was whether a single recording of GMs of pre-term character at the time of discharge has any predictive power for later neurological and developmental outcome at the age of 1 to 2 years.

I regard this as an interesting and important question worth considering because under daily conditions the normal practised longitudinal surveys are often hard to achieve. This is on the one hand especially due to the amount of time longitudinal assessments require and on the other hand when discharged patients are often not available for further regular recordings. To customize this assessment technique for a wider amount of infants it might be of interest to minimize the efforts of the assessment technique.

# 2 Subjects and methods

## *2.1 Subjects*

Between July 2006 and June 2009 data of 137 pre-term infants, admitted to the Division of Neonatology at the Medical University Graz were collected. All of the infants, 76 male and 61 female, had a birth weight under 1500g and were therefore classified as very low birth weight infants. The local ethics committee has given approval to conduct this study.

The main inclusion criteria were:

I. pre-term infant < 37. GA

II. birth-weight < 1500g

The main exclusion criteria were:

I. parents disapproval

II. lack of neurological and developmental outcome data

III. diseases interfering with assessment technique (e.g. paraplegia)

## *2.2 Data collection*

Obstetric and neonatal data were provided retrospectively by medical records applied for long term documentation. The obstetric data being recorded included the following two variables: multiple pregnancies (e.g. twins or triplets), growth: birth weight below the $10^{th}$ percentile = small for gestational age (SGA); birth weight between the $10^{th}$ and the $90^{th}$ percentile = appropriate for gestational age (AGA); birth weight above the $90^{th}$ percentile = large for gestational age (LGA). The neonatal variables being obtained were the following: gender, birth weight, head circumference, umbilical cord pH, gestational age and weight at recording time and data about perinatal morbidity.

## 2.3 Recording of spontaneous movements

Recordings of all infants were made only once at time of discharge. This was most of the time around the 37th week. At first the babies had been recorded by a nurse during her daily work and later filming was continued by two students. In order to get a proper perspective of the whole infant we used a video-camera that we placed on a tripod. The infants either lay in an incubator or in a cot in supine position. Recording time greatly varied but was considered to be 1 hour before feeding. This should have guaranteed that the baby was still awake but not crying. However, recordings were made during periods of active wakefulness or during sleeping states and lasted 20 to 60 minutes.

## 2.4 Qualitative assessment of general movements

Initially all recordings were skimmed trough, using the fast forward function, to identify sequences of appropriate movements. Finally approximately three sequences of each tape were selected and transferred to the computer. We took care to select the longest and best sequences, preferably one at the beginning one at the end and one in the middle of the tape. For further assessment and documentation they were stored on a separate file for each infant. The number of collected sequences varied between 2 and 5 (mainly 3).

Subsequently all files were assessed by two different observers (Christoph Bauer. & Katrin Ellrott) who ,by the time, did not know the history of most of the infants. In case of disagreement, GMs were discussed until consent was reached. Tricky cases were re-assessed by Professor Christa Einspieler.

## 2.5 Follow-up

Children were assessed once at specific time frames: 4 to 6 months, 7 to 12 months and 1 to 2 years of (corrected) age by specialists in the field of developmental neurology at the outpatient department. The prober was aware of the infants´ clinical history as the investigations were performed as a routine follow up. Not all infants enrolled, necessarily went trough all assessments but at last trough the one provided at 1 to 2 years of age, this is presented within the study.

The examination consisted of a general examination, growth assessment, neurological assessment and developmental examination.

### 2.5.1 Neurological examination

The neurological examination was done according to Touwen.[40] On the one hand the implemented TINE (Touwen Infant Neurological Examination) evaluates several traditional neurological signs such as dysfunctional muscle tone regulation, abnormal reflexes and dysfunction of cranial nerves. On the other hand it includes the assessment of the quality of spontaneous motility in terms of variation and stereotypy.[41] It takes approximately 15 to 20 minutes for an advanced observer to do all the different investigations.

The “Gross Motor Function Classification System” was used to classify infants with CP (spastic quadriplegia, spastic diplegia or hemiplegia) into 5 degrees of severity of motor disability.[17] It represents a standardized system based on abilities and limitations in gross motor function rather than the quality of movements. It is somehow indicated by the need for assistive technology including mobility devices (walkers, crutches) canes and wheeled mobility. Therefore, it is highly relevant for everyday life and can be used to estimate the extent of mobility which will be reached at the age of 6 to 12 years.[17, 42] Each level is named after the characteristic method of locomotion within the level itself. Level 1: Walks without restrictions; Level 2: Walks without assistive devices; Level 3: Walks with assistive mobility devices; Level 4: Self-mobility with limitations; Level 5: Self-mobility is severely limited even with the use of assistive technology.[17]

On the basis of neurological investigations the infants were classified into the following three groups:

I. Cerebral Palsy (CP) was diagnosed as spastic tetraplegia, spastic diplegia or spastic hemiplegia.

II. Minor Neurological Signs (MNS) included neurological signs that were not classified as CP such as asymmetry and muscular hypo-tension.

III. Normal Neurological Examination (NNE) was defined as having no abnormal neurological signs.

### 2.5.2 Developmental assessment

The developmental assessment was based on Bayley Scale of Infant Development (BSID). The BSID, first published in 1969 by Nancy Bayley and revised in 1993, is designed for infants aged between 1 and 42 month to identify children with developmental delays or disabilities. The test measures an infant´s level of development in three different areas: cognitive development, motor development and behavioural development. During the test procedure motor aspects are evaluated in 111 items while mental aspects are represent in 178 items. Although the test was standardized to the U.S. population and therefore, has not been evaluated and normed yet for German relations it is widely used in research works. However, the test offers age-adapted tasks and can only be administered by experienced examiners specifically trained in BSID.[16]

Developmental outcome was classified into the following four groups:

I. Severe developmental delay (SDD) was defined as developmental scores lower than the 2nd standard deviation (SD).

II. Mild developmental delay (MDD) was diagnosed when developmental scores were between the 1st and the 2nd SD

III. Normal development (ND) was defined as having average developmental scores (within the 1st SD)

IV. Not assessable (NA): Infants with CP could not be tested with the BSID. Therefore, they were classified as not assessable.

## *2.6 Statistics*

To compare the results of the present study with previously published studies the following statistical values were calculated: Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV).

### 2.6.1 Sensitivity and specificity

To quantify the diagnostic ability of a test two well established statistical measures are often used: sensitivity and specificity.[43] They both help us to estimate whether

a certain test is good at identifying those with the disease and those without disease or not.

**Sensitivity** is the proportion of the diseased group the test correctly identified as having the disease. It is a value describing how good the test is working on diseased and is calculated as follows:[44, 45]

$$sensitivity = \frac{number\ of\ true\ positives}{number\ of\ true\ positives + number\ of\ false\ negatives}$$

**Specificity** is the proportion of the non-diseased group, the test correctly identified as having no disease. It is a value describing how good the test is working on not diseased and it is calculated as follows:[44, 45]

$$specificity = \frac{number\ of\ true\ negatives}{number\ of\ true\ negatives + number\ of\ false\ positives}$$

### 2.6.2 Positive predictive value and negative predictive value

Positive and negative predictive values are estimates of the probability that patients with positive and negative test results indeed have the disease.[44] They help us to estimate how good the test is at predicting the disease.[45]

Positive predictive value (PPV) is the proportion of patients with positive test results who are correctly diagnosed.[44, 46] It is calculated as follows:

$$PPV = \frac{number\ of\ true\ positives}{number\ of\ true\ positives + number\ of\ false\ positives}$$

Negative predictive value (NPV) is the proportion of patients with negative test results who are correctly diagnosed.[44, 46] It is calculated as follows:

$$NPV = \frac{number\ of\ true\ negatives}{number\ of\ true\ negatives + number\ of\ false\ negatives}$$

Classification of disease negative and disease positive on the one hand and test negative and test positive on the other hand lies in the hand of the beholder. Therefore, different classifications might be used in different studies. This holds true for both NPV, PPV as well as for sensitivity and specificity. To meet this circumstance I calculated estimates for three different points of view that have already been used in previous studies. However, most studies provided values for abnormal (CS and PR) and normal (NPT) GMs. Disease has mostly been regarded as CP or developmental retardation. If not otherwise mentioned all values in this text refer to this classification.

# 3 Results

Between July 2006 and June 2009 of all 1671 infants, being admitted to the Division of Neonatology at the Medical University Graz, altogether 251 infants met the major inclusion criteria of being born pre-term with a birth weight under 1500g. 31 of these infants died during hospitalisation. Overall mortality was 12% (31 out of 251 infants). Mortality was highest amongst the 100 infants with a birth weight under 1000g (28%; n=28) whereas only 3 of the remaining 151 infants with a birth weight between 1000g and 1500g did not survive (2%).

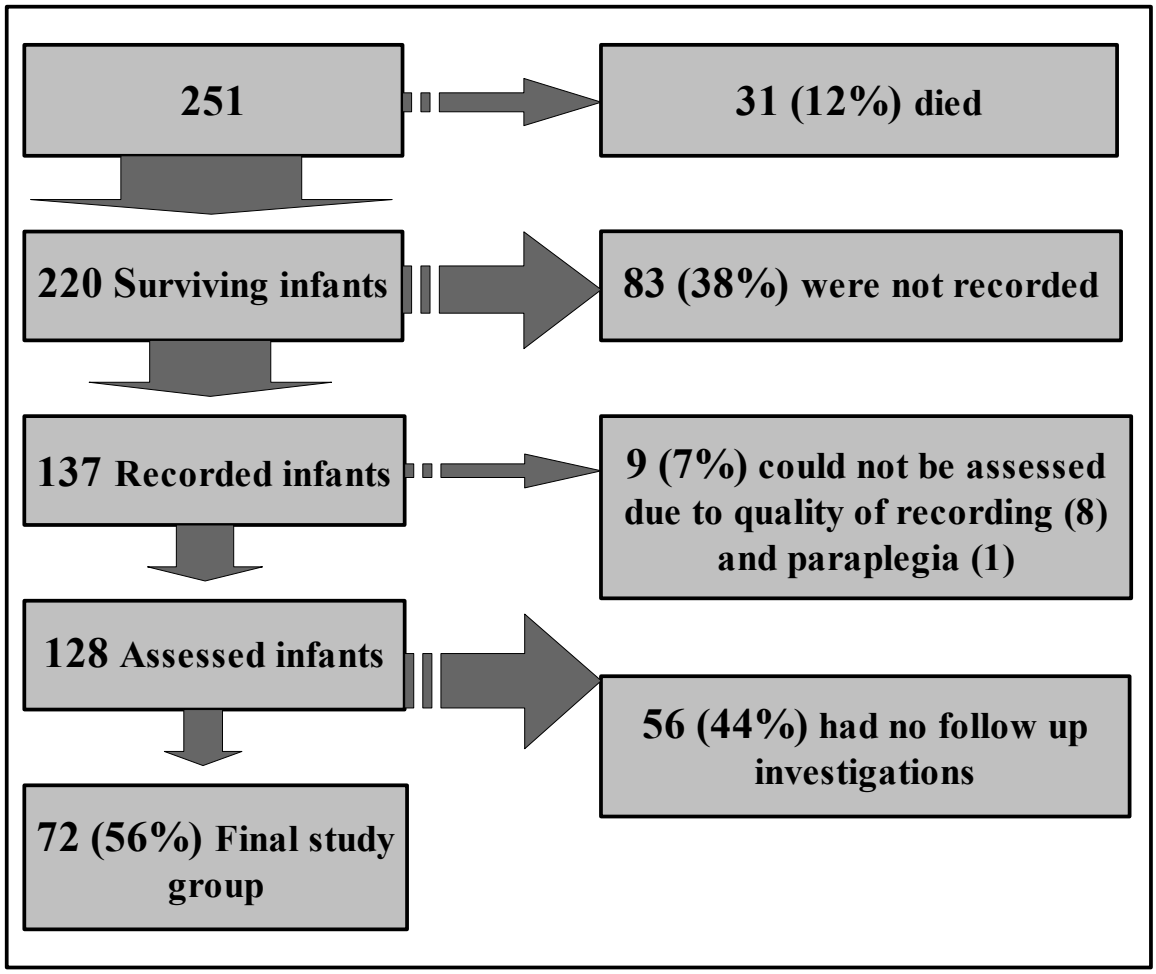
From the 220 surviving infants at last 137 were recorded (62%). In 83 infants recordings were not performed due to a variety of reasons: Parents´ disapproval, early transfer to a peripheral hospital, severe life-threatening conditions, or mechanic therapies like plasters which restricted movements and therefore, compromised assessment, or there was no staff available who could do the recordings.

However, from the 137 infants being recorded 9 (7%) had to be excluded later on. In 8 infants it was a matter of recording-quality. The recordings were either too short to catch assessable sequences or the infants were barely moving or they were crying during the whole recording period. In one further case an infant had to be rejected due to paraplegia, which made assessment impossible.

From the remaining 128 infants, neurological and developmental outcome were not available in 56 infants. These infants were either not old enough to have examinations > 1 year of age, or did not show up for neurodevelopmental assessment.

Hence, altogether 72 infants were finally enrolled in the study. For a graphical display of the study population see Figure 2.

*Fig.2: Final study group*




## *3.1 Clinical and basis data of the study group*

The study group finally consisted of 72 infants (41 male and 31 female) with a gestational age ranging 24 to 33 weeks (median 28,8 weeks), and a birth weight of 500 to 1500g (median 1075g). Table 4 provides a survey of the main data. Recordings were done only once at 34 to 43 weeks (median 37,0); at that time the infants had a body weight of 1572 to 2774g (median 2087g).

Further neonatal variables that we collected included umbilical cord pH (7,09 to 7,49; median 7,29), ventilation (13 needed no ventilation; 24 needed ventilation less than 8 days; 31 needed ventilation over 7 days, for 4 infants no data were available) and multiple births (n=24/ 33,3%).

*Table 4: Basis data and variables of all 72 included infants at time of birth and at time of recording*

| **Sex:** | **Male** | **Female** | | **SGA** | **AGA** | **LGA** |
|---|---|---|---|---|---|---|
| | **41** | **31** | **Total (%)** | **21 (30%)** | **49 (69%)** | **1 (1%)** |
| **Variables** | | | **Mean** | | **Range** | |
| Gestational age at birth (weeks) | | | 28,8 | | 24-33 | |
| Birth weight (g) | | | 1075 | | 500-1500 | |
| Head circumference (cm) | | | 25,9 | | 20,6-30,0 | |
| Umbilical cord pH | | | 7,29 | | 7,09-7,49 | |
| Gestational age at recording (weeks) | | | 37,0 | | 34-43 | |
| Weight at recording (g) | | | 2087 | | 1572-2774 | |

**Abbreviations:** SGA small for gestational age, AGA appropriate for gestational age, LGA large for gestational age

During neonatal period 21 infants suffered from septicaemia and one had a NEC (necrotizing enterocolitis). IRDS (infant respiratory distress syndrome) was diagnosed in 45 infants (IRDS 1+2: 22; IRDS 3+4: 23), ROP (retinopathy of prematurity) in 6 infants (ROP 1+2: 4; ROP >2: 2).

Brain ultrasound (US) revealed IVH (intra-ventricular haemorrhage) in 13 infants (IVH1: 5; IVH 2: 3; IVH 3: 5), 3 of these infants had PVH (periventricular haemorrhage). PVL (periventricular leukomalacia) was diagnosed in 5 infants (PVL 1: 1; PVL 2+3: 4). HIE (hypoxic ischemic encephalopathy) was not found.

## *3.2 Clinical and basis data of all 56 excluded infants*

Table 5 provides the basis data of the 56 infants who had to be excluded because their neurological and developmental data were not available. This group consisted of 56 infants (29 male and 27 female) with a gestational age ranging 24 to 37 weeks (median 29,0 weeks), and a birth weight of 410 to 1500g (median 1116g). The spectrum of all neonatal diseases as well as further neonatal variables was similar to that of the included group.

*Table 5: Basis data and variables of all 56 excluded infants at time of birth*

| **Sex:** | **Male** | **Female** | | **SGA** | **AGA** | **LGA** |
|---|---|---|---|---|---|---|
| | **29** | **27** | **Total (%)** | **19 (33%)** | **33 (59%)** | **1 (2%)** |
| **Variables** | | | **Mean** | | **Range** | |
| Gestational age at birth (weeks) | | | 29,0 | | 24-37 | |
| Birth weight (g) | | | 1116 | | 410-1500 | |
| Head circumference (cm) | | | 26,7 | | 21,5-34,7 | |
| Umbilical cord pH | | | 7,28 | | 7,07-7,40 | |

**Abbreviations:** SGA small for gestational age, AGA appropriate for gestational age, LGA large for gestational age

During the neonatal period 12 infants suffered from septicaemia and one even had a shock. IRDS was diagnosed in 32 infants (IRDS 1+2: 19; IRDS 3+4: 13), ROP in 1 infant (ROP 1+2).

Brain ultrasound revealed IVH in 6 infants (IVH 1: 5; IVH 2: 1), another infant had PVH. PVL was diagnosed in 3 infants (PVL 1: 1; PVL 2+3: 2) and HIE was found in one case.

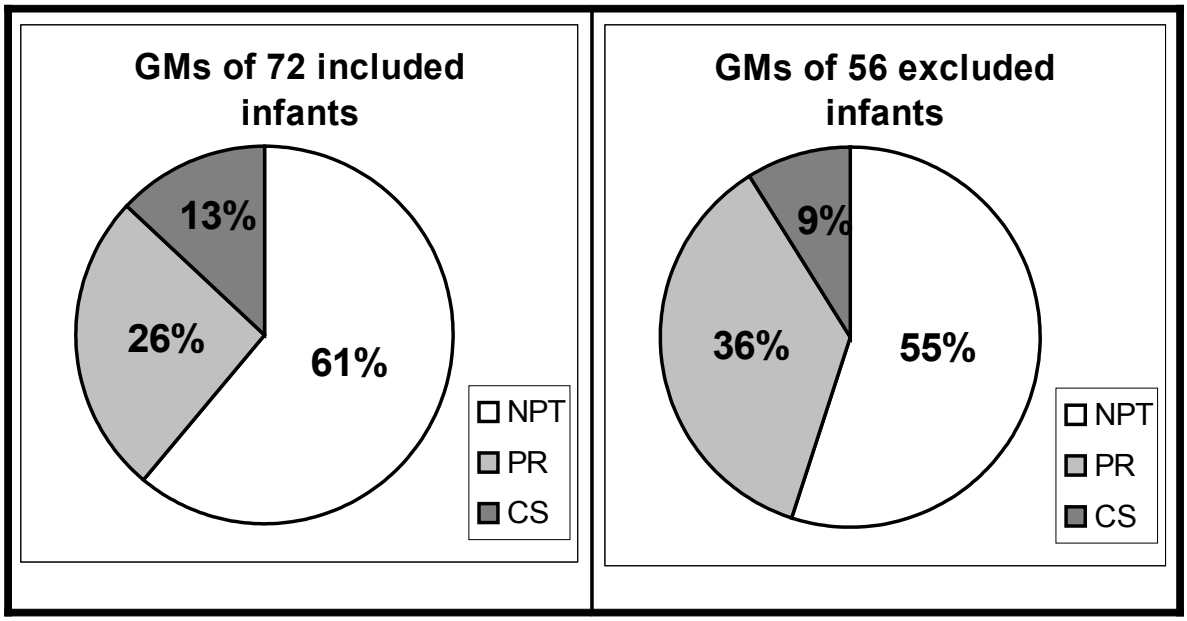
## *3.3 GM assessment at 36 weeks*

Altogether in 128 infants video recordings were done. But in 56 infants, where no neurodevelopmental outcome data were available no correlation of GMs with outcome was possible. For both groups we present the GM data.

Of all 72 enrolled infants a total of 44 (61%) infants showed a completely age-adequate normal GM pattern e.g. Normal pre-term GM, whereas 28 (39%) of the remaining infants had an abnormal movement pattern. In particular 19 (26%) infants were classified as PR and 9 (13%) as CS.

Amongst the 56 infants without neurodevelopmental data distribution of all GM categories was similar. 55% of all infants were judged as normal (31 infants), 45% were abnormal (25 infants) i.e. PR in 36% (20 infants) and CS in 9% (5 infants).

*Fig.3: Percentage of GMs*




**Abbreviations:** NPT normal pre-term GMs; PR poor-repertoire; CS cramped-synchronized; NA not assessable

## *3.4 Neurological outcome*

CP was diagnosed in 7 (10%) infants. 5 (7%) of these infants had spastic diplegia (GMFCS I, II, IV, an 2 V), one (1%) had a mild form of spastic hemiplegia (GMFCS I) and the last one (1%) had severe spastic tetraplegia (GMFCS IV).

Two infants had mild neurological signs (MNS), one because of asymmetry and another because of muscular hypo-tension. 63 infants (88%) however, had a completely normal neurological examination.

## *3.5 Developmental outcome*

On examination 55 infants (76%) had average scores on the developmental test (> 1$^{st}$ SD) (normal development), 6 infants (8%) reached scores between the 1$^{st}$ SD and the 2$^{nd}$ SD (mild developmental delay), 4 infants (6%) had scores < 2$^{nd}$ SD (severe developmental delay).

However, 7 infants (10%), who had CP, were not tested. Table 6 summarizes both the neurological and the developmental outcome.

*Table 6: Developmental and neurological outcome*

| Developmental outcome | Total | Percent | Neurological outcome | Total | Percent |
|---|---|---|---|---|---|
| ND | 55 | 76% | NNE | 63 | 88% |
| MDD | 6 | 8% | MNS | 2 | 3% |
| SDD | 4 | 6% | CP | 7 | 10% |
| NA (CP) | 7 | 10% | | | |

**Abbreviations:** ND normal development (> 1st SD), MDD mild developmental delay (1st SD-2nd SD), SDD severe developmental delay (< 2nd SD), NA not assessable because of CP, NNE normal neurological examination, MNS minor neurological signs, CP cerebral palsy

## *3.6 Comparison of GM assessment and neurodevelopmental outcome*

### 3.6.1 Neurological and developmental test results

We collected data of developmental and neurological outcome for all 72 infants. Table 7 lists the test results of each the neurological and the developmental tests separately. As for all other data too, additionally to total numbers, relative proportions of either the specific GM pattern or the outcome-category are provided in bar diagrams.

*Table 7: Relation of GMs to neurological and developmental test results*

| | Neurological test results | | | Developmental test results | | | |
|---|---|---|---|---|---|---|---|
| GM | NNE | MNS | CP | ND | MDD | SDD | NA (CP) |
| NPT (n = 44) | 43 | 0 | 1 | 40 | 2 | 1 | 1 |
| PR (n = 19) | 14 | 2 | 3 | 10 | 3 | 3 | 3 |
| CS (n = 9) | 6 | 0 | 3 | 5 | 1 | 0 | 3 |

**Abbreviations:** ND normal development (> 1st SD), MDD mild developmental delay (1st SD-2nd SD), SDD severe developmental delay (< 2nd SD), NA not assessable because of CP, NNE normal neurological examination, MNS minor neurological signs, CP cerebral palsy

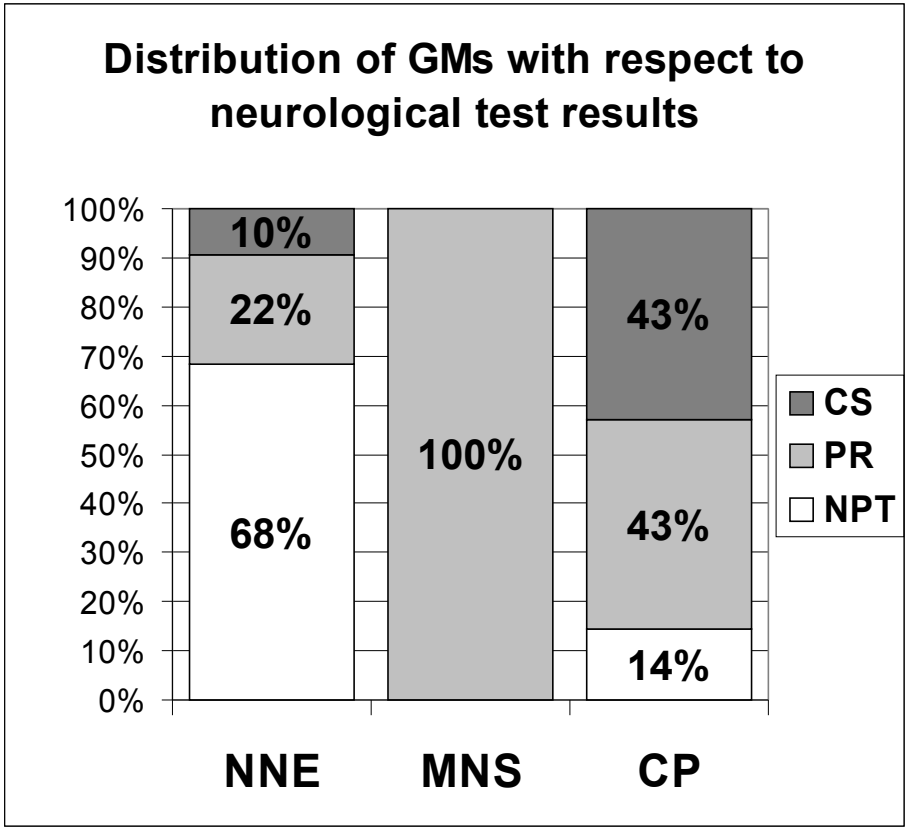



*Fig.4: Distribution of GMs with respect to neurological test results*

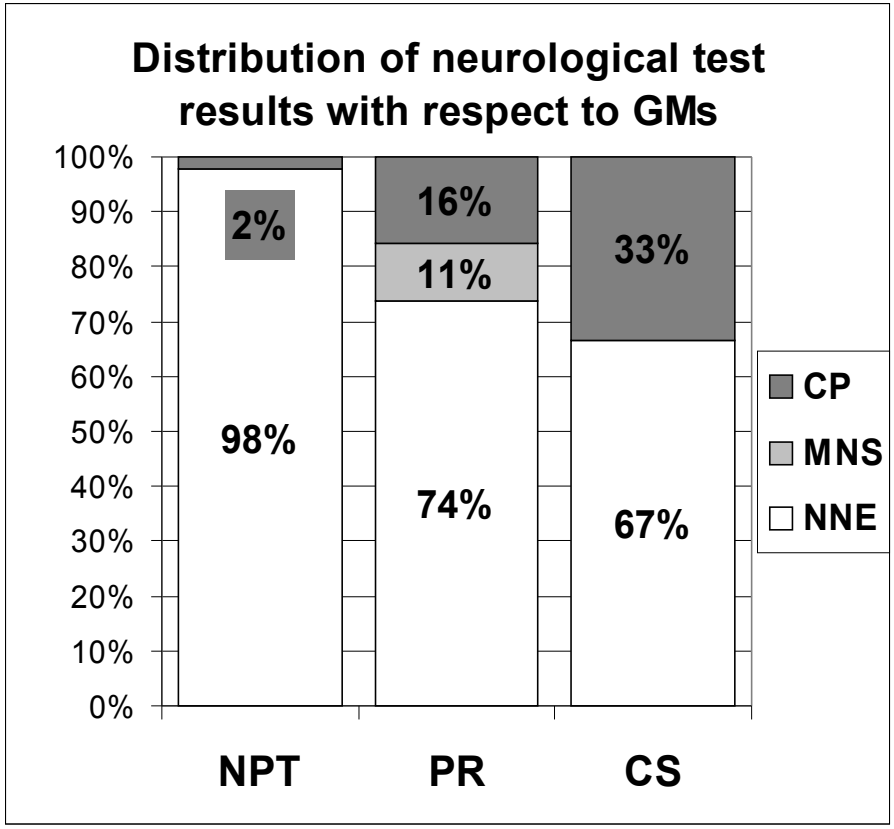



*Fig.5: Distribution of neurological test results with respect to GMs*

**Abbreviations:** ND normal development (> 1st SD), MDD mild developmental delay (1st SD-2nd SD), SDD severe developmental delay (< 2nd SD), NA not assessable because of CP, NNE normal neurological examination, MNS minor neurological signs, CP cerebral palsy

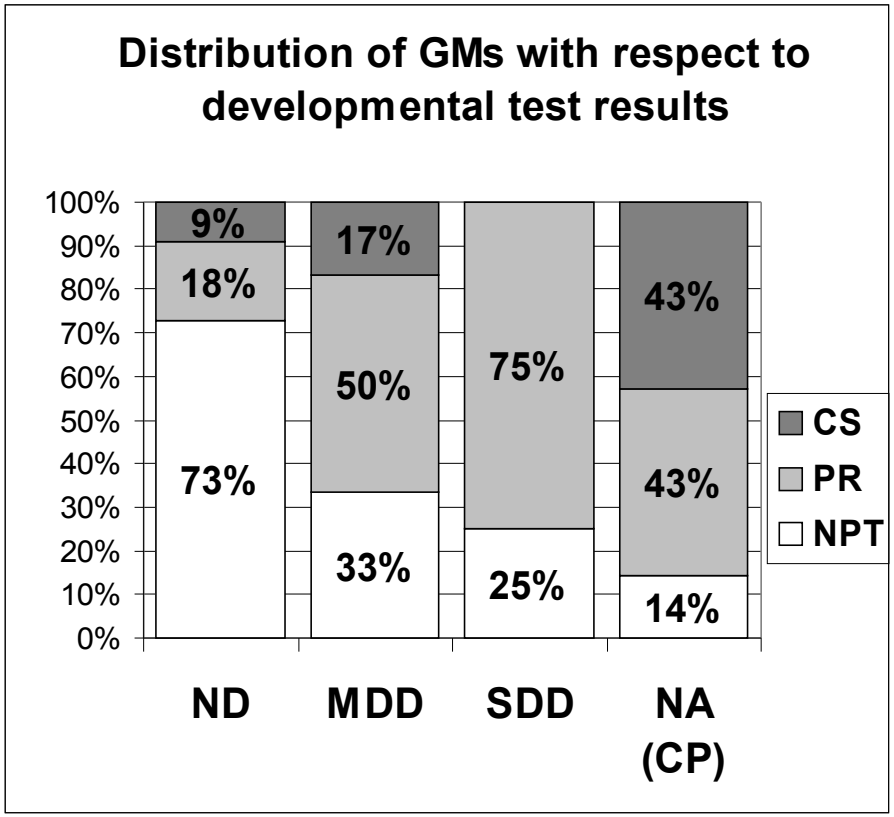



*Fig.6: Distribution of GMs with respect to developmental test results*

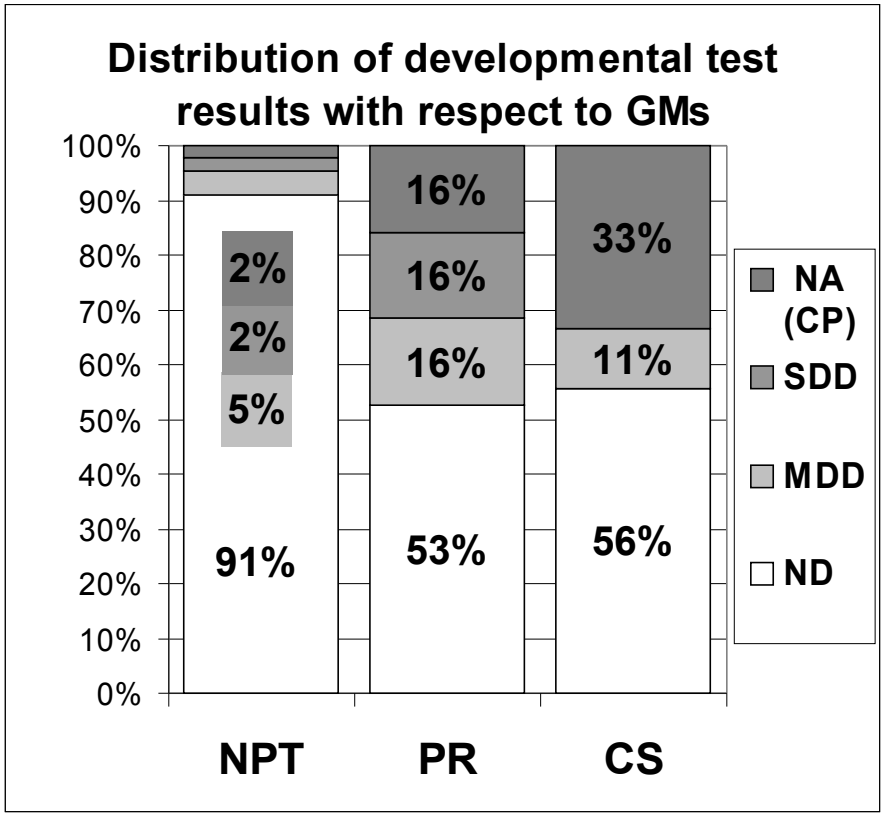



*Fig.7: Distribution of developmental test results with respect to GMs*

**Abbreviations:** ND normal development (> 1st SD), MDD mild developmental delay (1st SD-2nd SD), SDD severe developmental delay (< 2nd SD), NA not assessable because of CP, NNE normal neurological examination, MNS minor neurological signs, CP cerebral palsy

### 3.6.2 Overall outcome

Overall outcome was finally classified as: normal outcome (no abnormal neurological signs and ND or MDD); neurological or developmental disorder(NDD) (SDD or MNS); cerebral palsy (CP I-V).

Table 8: Relation of GMs to overall outcome

| GM | NO | NDD | CP |
|---|---|---|---|
| NPT (n = 44) | 42 | 1 | 1 |
| PR (n = 19) | 12 | 4 | 3 |
| CS (n = 9) | 6 | 0 | 3 |

**Abbreviations:** NO normal outcome = NN & (ND or MDD); NDD neurological or developmental disorder = SDD or MNS; CP = cerebral palsy

42 of all 44 infants with normal pre-term GMs (95%) were classified as normal outcome. They showed neither neurological nor developmental abnormalities. Of the remaining 2 infants with normal GMs 1 infant was categorized into NDD due to SDD (2%) and 1 had CP II (2%).

By contrast only 12 out of 19 infants with PR had a total normal outcome (63%), 4 were diagnosed as NDD (21%) and 3 had CP (16%). NDD was set due to MNS in 2 cases (asymmetry and muscular hypo-tension) and due to SDD in 2 cases. The 3 infants with CP had a severe form in 2 cases (IV) and a very mild form (I) in one case.

Infants with a CS movement pattern developed either totally normal (67%; n=6) or developed CP (33%; n=3). In detail, two infants had severe CP (V) and one from a very mild form of CP (I).

Figure 9 shows the distribution of GMs with respect to overall outcome. Abnormal GMs were only found in 18 out of all 60 infants who were classified as normal outcome. In particular 12 infants had PR and 6 had CS.

Only 5 patients were classified as NDD. 80% (n=4) of them had PR and the remaining (20%) showed a normal GM pattern.

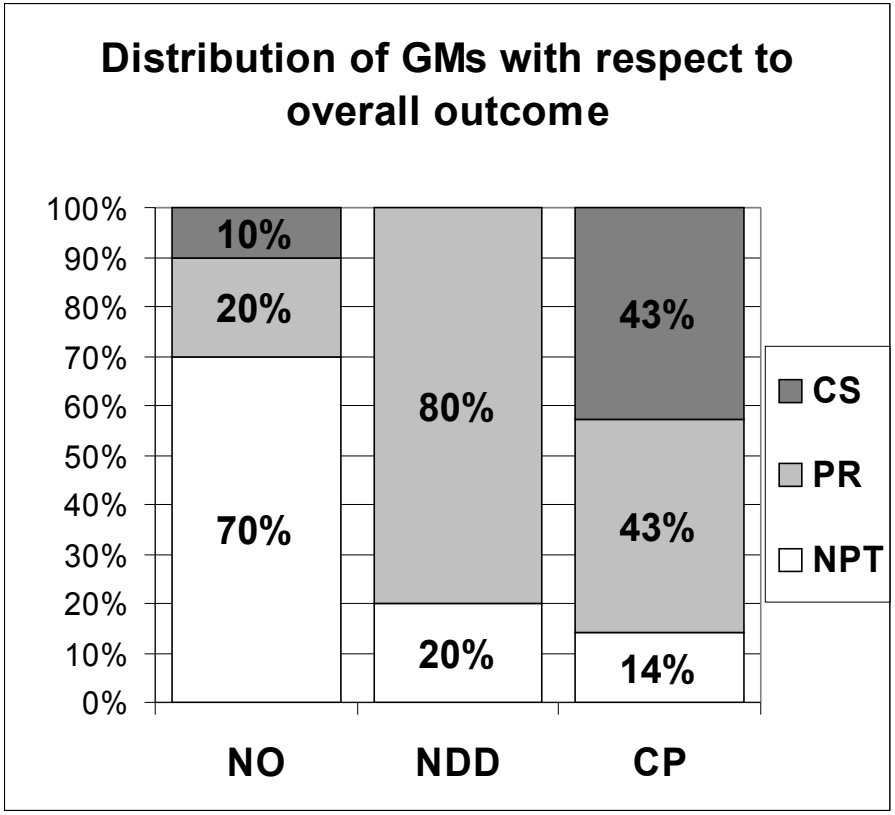



*Fig.8: Distribution of GMs with respect to overall outcome*

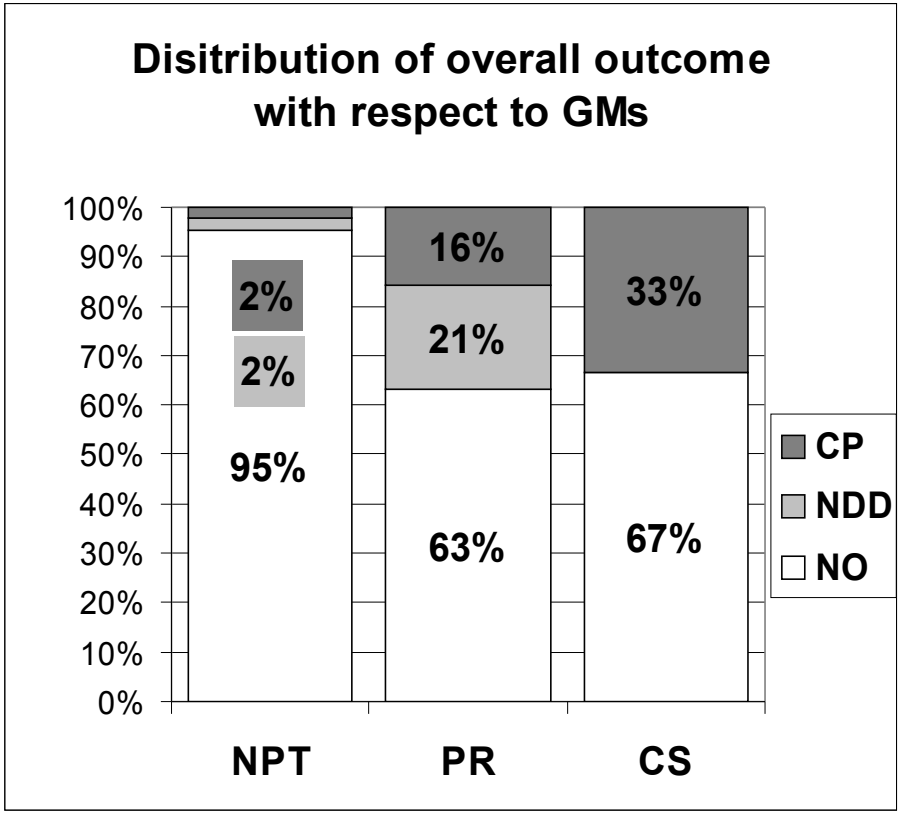



*Fig.9: Distribution of overall outcome with respect to GMs*

**Abbreviations:** NO normal outcome = NNE & (ND or. MDD); NDD neurological or developmental disorder = SDD or MNS; CP= cerebral palsy

Of the 7 infants who had CP only 3 (43%) showed CS movements, 3 infants (43%) showed PR, but only one infant (14%) normal GMs at 36 weeks post-menstrual age.

### 3.6.3 Predictive values

To meet the special needs of calculating sensitivities, specificities, PPV and NPV all infants were finally dichotomised into two groups. We used the following definition that is used in many other studies: Disease positive (D = disease) was defined as CP, MNS or SDD. Disease negative (H = health) was thus defined as having a normal neurology and either ND or MDD. Table 9 gives the data for this approach.

*Table 9: Relation of GMs to either normal or abnormal outcome*

| GM | H | D |
|---|---|---|
| NPT (n = 44) | 42 | 2 |
| PR (n = 19) | 12 | 7 |
| CS (n =9 ) | 6 | 3 |

When we calculated the values we regarded all abnormal GM patterns (i.e. CS and PR) as test positives. (Table 10)

*Table 10: Predictive values for CS/PR predicting CP, MNS or SDD*

| Sensitivity | Specificity | Positive predictive value | Negative predictive value |
|---|---|---|---|
| **83%** | **70%** | **36%** | **95%** |

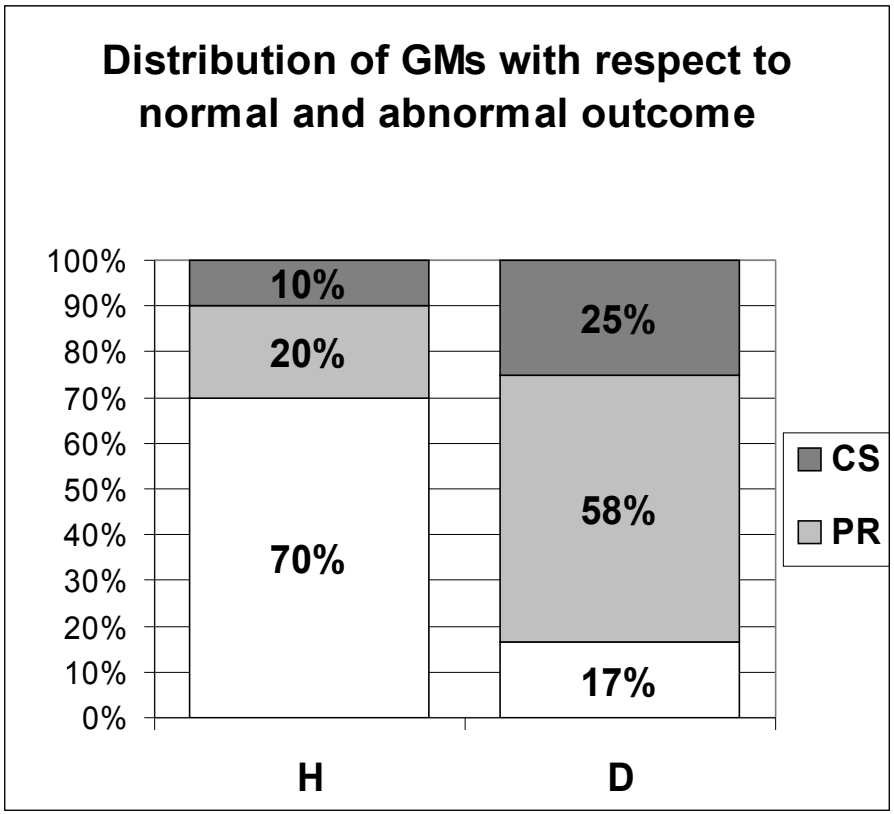



*Fig.10: Distribution of GMs with respect to normal and abnormal outcome*

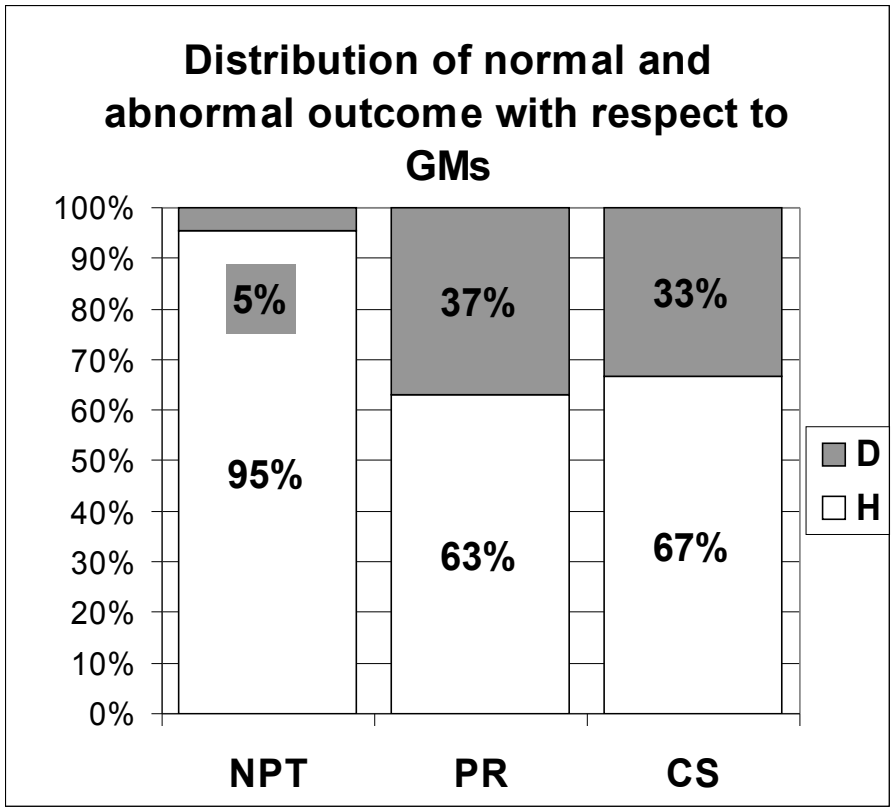



*Fig.11: Distribution of normal and abnormal outcome with respect to GMs*

**Abbreviations:** H health (disease negative) = NO = NNE & (ND or MDD); D disease (disease positive) = CP or NDD = CP or MNS or SDD

### 3.6.4 Deviating assumptions for predictive values

There are previous studies that are using different definitions for disease positive and test positive. Different assumptions are leading to different values and may reflect different applications depending on whether a maximum of diseased are wanted to be detected or the goal is to minimize wrong diagnoses. For the first approach you would need the test with the highest sensitivity which might be at the expense of specificity. For the latter you would prefer the test with the highest specificity.

However, values have been calculated for two further previously used definitions.

When abnormal outcome was restricted to CP and all other assumptions stayed like discussed before sensitivity increased slightly while specificity decreased slightly.

*Table 11: Predictive values for CS/PR predicting CP*

| Sensitivity | Specificity | Positive predictive value | Negative predictive value |
|---|---|---|---|
| **86%** | **66%** | **21%** | **98%** |

If furthermore a CS GM-pattern was solely regarded as test positive sensitivity dropped markedly while specificity increased.

*Table 12: Predictive values for CS predicting CP*

| Sensitivity | Specificity | Positive predictive value | Negative predictive value |
|---|---|---|---|
| **43%** | **91%** | **33%** | **94%** |

# 4 Discussion

The qualitative assessment of general movements in pre-term, term and young infants has repeatedly been proven to be a highly sensitive and specific diagnostic tool for the early diagnosis of brain impairment.[30] Furthermore it is widely seen as quick, non-invasive, non-intrusive and cost-effective compared to other techniques, e.g. MR, brain US, and traditional neurological examination.[6] Despite these advantages it is not yet widely introduced in clinical practice everywhere.

One reason might be the circumstance that the whole procedure of longitudinal conducted GM assessments, like it is suggested by the GM Trust, needs resources. On the other hand when discharged, patients are often not available for further regular recordings. To customize this assessment technique for a wider clinical use it might be of interest to minimize the efforts of the assessment technique further on.

The aim of this study was to describe and analyse the relation of GMs recorded only once at 36 weeks post-conceptional age to neurological and developmental test results at the specific time frame of 1 to 2 years, in order to set requirements for the creation of further hypothesis. Therefore, we have provided data on the quality of GMs observed in a group of 72 low birth weight infants recorded at time of discharge under routine conditions. The main results are discussed below.

## *4.1 Neurological and developmental test results*

Our findings widely go along with previously published data as we found a strong relation between certain GM pattern and neurological test results on the one hand and developmental test results on the other hand.

A normal age adequate GM pattern was followed by completely normal neurological test results in 98%. Only one infant (2%) later developed CP. Developmental test results for normal GMs were similar. 40 of all 44 infants (91%) had a completely normal development, two were classified as MDD and only one had SDD.

By contrast a cramped-synchronised GM pattern was followed by CP in only 3

infants (33%) while 6 infants (66%) had a normal neurological examination. 5 of these infants had normal developmental test results and only one had MDD.

Poor-repertoire was associated with normal neurological examinations in 74%, 16% had CP and 11% were classified as MNS. The relation of PR to developmental test results reflect the same tendency. 53% had normal developmental test results. MDD as well as SDD was diagnosed each in 16% of all infants.

## *4.2 Overall outcome*

Only 10 out of 28 infants with abnormal GMs during pre-term period (3 CS, 7 PR) had at last an abnormal outcome (CS, SDD or MNS) at 1 to 2 years. The remaining 18 infants with abnormal GMs (6 CS, 12 PR) showed a normal neurological and developmental outcome.

This large number of false positives is not unknown. Several studies reported similar findings.[1, 2, 23, 47, 48] The authors suggested that this circumstance was most notably because of the high number of infants with poor-repertoire GMs who later developed normal.[2] One explanation might reside in the plasticity and various number of neural subsystems converging on the CPGs of GMs. Different systems may be used at different ages and hence GM abnormalities at a young age might disappear when affected systems are removed by ones which are not compromised by the lesion after 2 to 3 months.[2]

What is conspicuous about our findings is the large number of false positives due to CS. CS GMs were found to contribute to false positives in approximately one third of all cases. With the exception of one case all of these infants suffered from either respiratory diseases (IRDS 1-2 in two cases, IRDS 2-4 in 3 cases, BPD in 2 cases) or severe ultrasound findings (PVL 2+3, IVH 2, IVH 3 each in one case) during neonatal period. Only one infant was completely inconspicuous with respect to neonatal morbidity. This circumstances might be of importance as Ferrari[49] already has shown several years ago that minor and transient ultrasound abnormalities, such as transient periventricular echodensity are linked to abnormal GMs. Moreover there are several reports of infants with transient CS movements

who later normalize.[2, 4]

In contrast only two of all 44 infants with normal pre-term GMs later showed an unfavourable outcome. In particular one was classified as spastic diplegia (GMFS II) and the other had SDD. It must be noted that both of them were diagnosed as MDD during the precedent investigation that was performed during the same age period and were later revised. The infant finally classified as CP had neither respiratory or any other severe diseases nor severe ultrasound findings during the whole neonatal period.

## *4.3 Composition of the study population*

When introducing a new diagnostic test into clinical practice one must be aware of the composition of the study population test values are based on. This might be of great interest because values indicative for accuracy like PPV and NPV are depending on the pre-test probability and, hence, on the prevalence of the disease in the evaluated group.[46]

Compared to other studies our study population consisted of infants whose outcome was in average better. This circumstance is reflected in the lower number of CP and ultrasound abnormalities that can be found in our population and may have led to the comparatively low positive predictive value. We found CP in 7 infants (10%) and ultrasound abnormalities in 18 infants (25%).

As opposed to this Ferrari[1] and Cioni[2] investigated high risk pre-term babies with much higher prevalence of abnormal outcome. 29 out of 66 infants (44%) in the former and 44 out of 84 infants (52%) in the latter had CP. ultrasound findings were equally higher. Inclusion criteria differed greatly from ours. Ferrari[1] required ultrasound abnormalities highly suggestive of brain parenchymal insult and the inclusion criteria Cioni[2] set led to a selection of infants at a higher risk of brain lesions and subsequent developmental disorders.

Two studies with roughly equal subjects were reported by Garcia[48] and Constantinou[23]. Garcia investigated 40 low birth weight pre-term infants with a birth weight between 630 and 1530g (mean 1100g) whose GA ranged from 26 to 34 weeks (mean 31 weeks). Of all 26 infants with follow up till 14 months 5 (19%)

were finally diagnosed as CP and 16 (62%) as normal. The remaining 5 infants (19%) were classified as having mild findings.

Constantinou recruited 130 infants with birth weight <1500g and applied video recordings for analysis that were made at 36 and 52 weeks post-conceptional age.

## *4.4 Patients that could not be included in the present study*

Patients can be lost due to many reasons. Sometimes it might be of interest to evaluate the causes of their withdrawal in order to prevent bias. Most infants who could not be included in our study were due to lack of recording. Although we attempted to record all low birth weight infants admitted to the intensive care unit 38% could not be filmed. We know little about these infants. They were lost due to lack of resources or parents disapproval. Only a few could not be recorded because the infants suffered severe life-threatening illnesses. Especially the latter could have had an impact on the prevalence of certain diseases and may indicate a limitation of the method in clinical practice. However, I regard the relevance of this circumstance as minor.

Another group of infants that could have contributed to a modification in prevalence are those who had no follow up. Some of them were not old enough at the end of our collecting period but in some cases parents did not show up for follow up investigations. In general the percentage of all collected perinatal diagnoses (sepsis; IRDS; ROP) and ultrasound findings (IVH; PVH; PVL) were slightly higher among the included group than compared to the excluded group.

*Table 13: Perinatal morbidity of included and excluded infants*

| | Sepsis | IRDS | ROP | IVH | PVH | PVL |
|---|---|---|---|---|---|---|
| Included infants | 29% | 63% | 8% | 18,% | 4% | 7% |
| Excluded infants | 22% | 60% | 2% | 11% | 2% | 5% |

**Abbreviations:** IRDS: infant respiratory distress syndrome, ROP: retinopathy of prematurity, IVH: intraventricular haemorrhage, PVH: periventricular haemorrhage, PVL: periventricular leukomalacia

Attention should be paid to the 8 infants who were recorded but who could not be assessed properly. At 1 to 2 years, 6 infants were completely normal, one had MDD and the remaining had asymmetry. There is hardly any marked association between recording-disability and later outcome. Therefore, it seems not likely that these infants had caused any relevant bias.

In sum it can be assumed that the study population is a representative sample of a contemporary Austrian neonatal intensive care unit population.

## *4.5 Comparison to previous studies*

There are a few differences between all published studies that make comparison difficult. First of all, there exists no consistent definition of outcome. Most papers regard CP or SDD as poor outcome and define normal outcome as absence of neurological findings. Ferrari,[1] however, restricted outcome to CP meaning that all infants with mild to moderate developmental delay were classified as healthy. Geerdink and Hopkins[50] defined disease positive as poor outcome according to neurological examination.[4]

Furthermore, the final neurological assessments used for defining outcome were performed at different ages and different tests were used as gold standard.[5] These tests included the Amiel-Tison, Denver Developmental Screening Test, Touwen, Griffiths Developmental Scales and the Bayley Scale.

The second difference involves the classification of test positives. Most studies distinguish abnormal and normal GMs. Abnormal GMs summarize PR and CS in most cases while normal GMs are referred to NPT GMs. Ferrari,[1] however, made use of a deviating classification. In addition to the previous he provide data for CS as the only test positive abnormal GM pattern during pre-term and term age.

However, the most commonly used classification is the one describing abnormal GMs by means of CS or PR with respect to poor neurodevelopmental outcome described by means of CP and developmental retardation.[5]

When using this classification sensitivity and negative predictive value calculated in our study were quite high (83% and 95%, respectively) whereas specificity and especially positive predictive value were somewhat lower (70%, 36%,

respectively). Previous studies report sensitivities between 62%[23] and 100%[48] and specificities between 44%[48] and 69%[23]. Hence, our findings are within the reported range. For a comparison of all studies see table 14.

*Table 14: Predictive values of GMs obtained from 6 different studies*

| Studies | Sensitivity | Specificity | PPV | NPV | Test positive | Disease positive |
|---|---|---|---|---|---|---|
| Ferrari et al., 1990[49] | 100 | 59 | 70 | 100 | abnormal GM | CP |
| Geerdink and Hopkins 1993[50] | 60 | 58 | | | | Poor outcome according to neurological examination[4] |
| Cioni et al.,1997[2] | 90,6 | 57,6 | 67,5 | 86,3 | CS+PR | CP or developmental retardation[4] |
| Ferrari et al., 2002[1] | 100 | 38 | 63 | 100 | CS/ CS+PR | CP |
| Garcia et al., 2004[48] [i] | 100 | 44 | 36 | 100 | CS+PR | Definite focal neurological abnormality, abnormal developmental profile, mild abnormalites |
| Constantinou et al., 2007[23] [i] | 69 | 62 | 29 | 90 | CS+PR | |
| [i] Studies with similar study population | | | | | | |

PPV and NPV are the two estimates who are capable to tell us how good a test is in predicting disease in clinical practice. Compared with previous studies showing PPVs of 67,5%[2] and 63%[1] our PPV is extremely low suggesting that only a third of all infants with positive test results later will develop neurological abnormalities. The NPV on the other hand lies within the previous reported values: 86,3%[2] and 100%[1, 48, 49].

When interpreting predictive values one must note that they depend on the prevalence of disease in the population. In general the rarer a certain abnormality can be found amongst patients the surer a negative test result indeed indicates absence of abnormality and the less sure a positive test result really reveals the disease.[44, 45]

As discussed before in terms of prevalence our study group is not comparable with

all other cited studies. Some investigated high risk pre-term infants which showed a higher prevalence of abnormal ultrasound findings as well as unfavourable outcome particularly CP.[1, 2] Hence, it is not surprising that despite the accordance in sensitivity and specificity our results for predictive values are varying from those previously reported.

## *4.6 Use of different classifications*

As shown by Ferrari[1] using CS as test positive and restricting outcome to CP lead to an increase in specificity and PPV from 38% and 63% up to 92% and 87%. Concurrently sensitivity and NPV decreased dramatically from both 100% to 46% and 62%. We have calculated values for equal classifications too and found partly similar findings. While sensitivity and specificity (43%, 91%) were almost identical our PPV was much lower (33%) and NPV was much higher (94%). However, the trend of all values was the same.

Hence, when Ferrari regarded CS movements as the only sign predicting later CP less than half of all infants are finally identified. In other words more than half of all infants being in great need of early intervention would not be diagnosed adequately. The same holds true for our findings.

In contrast when infants with CS and PR are regarded as test positive almost all infants with later CP would receive early intervention (sensitivity: 100% NPV 100%)[1]. But only two third of all infants being admitted to early intervention would have at last CP (specificity: 38%; PPV: 63%)[1]. These values were reported by Ferrari[1]. Our calculations were quite different as we found lower sensitivity(86%), NPV (98%) and PPV (21%) on the one hand and higher specificity (66%) on the other hand.

## *4.7 Longitudinal versus single GM assessment*

It is well known that quality of GMs, although it has been proved to be constant during one recording,[51] may vary over time.[1,2,4,12,48] Hence, many different developmental courses of GMs of an individual are possible and have already been reported. It has been shown that for later neurological outcome it is crucial if

abnormal findings are consistent or just transient phenomena.[1,12] Repeated assessments during different periods offer the opportunity to get individual developmental trajectories which help to improve the specific prediction of the individual outcome as they can take into account these informations.[4] Furthermore, longitudinal recordings include GMs of fidgety character which have repeatedly shown to have the best predictive power of all single GM assessments.[5] In addition Ferrari et a.,[1] reported that the severity of the functional impairment can be estimated as the earlier CS GMs appear the more severe is the degree of later functional impairment of CP.[1]

## *4.8 Strengths and limitations of the study*

There are some limitations to the present study. First we cannot provide a proper long term follow up. The time of the final investigation, determining outcome greatly varied from 1 to 2 years. As it is known that the clinical picture of CP is not always full expressed at the age of one and a half year, these strategy may have weakened the power to determine predictive validity.[41]

A second limitation of the study was the fact that the two assessors were not blind to all of the infants´ clinical histories. This was not avoidable because both of them were involved in recording of the infants in the hospital setting. However, as this applied only to few infants who were recorded at the end of the recruiting period most of them had to be excluded due to lack of follow up. Hence, this possible bias on the assessment of GMs should not be overvalued.

A third limitation might be the recording procedure that was on the one hand not always done as advised during state four and on the other hand in some cases it was very short. This might have limited the quality of some assessed sequences.

Furthermore, no proper statistic analysis were performed.

At last it should be mentioned that the two observers were not experienced in the field of neonatology.

However, the strength of the study might be the fact that the group of pre-term infants included in the study may be considered as a representative sample of an Austrian neonatal intensive care unit population during the last decade and that the results may be achieved under routine conditions.

## *4.9 Further hypothesis*

Regarding the presented results some new questions are prompted.

As the common inclusion criteria only involve very low birth weight pre-term infants the question arises if we catch all infants at risk for later brain dysfunction. Are there any other infants that we should take into account? Pharoah[52] reports that only 40% of all children with CP are born pre-term. So what are the most fitting inclusion criteria to catch all infants with later neurological disabilities?

What is the predictive power of GM assessment amongst these groups?

How does pre-screening with ultrasound improve accuracy.

It is reported that sensitivity and specificity are gradually increasing during infancy. The question arises if longitudinal GM assessment is not providable for a large number of infants would there be a better time for single GM assessment in clinical practice. To clarify these questions and confirm our results further more standardized studies are needed.

## *4.10 Conclusion*

Longitudinal GM assessment should be preferred to a single shot assessment at 36 weeks as it has a limited power to predict later neurological outcome properly. In particular a large number of false positives resulting in low specificity during pre-term period is responsible for the limited use.

However, when used additional to clinical history and other neurological investigations it might have still a beneficial effect. Especially the high NPV might help to identify those infants who do not need close surveillance. In contrast when infants display an abnormal GM pattern they should be supplied with close follow up including longitudinal GM assessment.

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Graz, 20th September 2010

# Curriculum vitae

## Personal information:

| | |
|---|---|
| First name: | Christoph |
| Surname: | Bauer |
| Date of birth: | born on 16th September 1985 |
| Place of birth: | Linz |
| Nationality: | Austrian citizen |
| Father: | Thomas Bauer, judge |
| Mother: | Sabine Bauer, teacher |
| Siblings: | 1 sister, psychologist |

## Education:

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|---|---|
| 1992 – 1996 | primary school, Stadlerstraße 45 |
| 1996 – 2004 | grammar school, Linz, Fadingerstrasse 4 |
| Summer 2004 | A-level |
| October 2004 – September 2005 | civilian service in Austrian Red Cross |
| Since October 2005 | study at the Medical University of Graz |
| September 2006 | first diploma exam |
| February 2010 | second diploma exam |

## Clerkship:

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|---|---|
| February 2007 | 4 weeks at the neurological section, BHB Linz |
| September 2007 | 4 weeks at the surgical section, UKH Linz |
| August/September 2008 | 4 weeks at the children ward, Dareda hospital/ Tanzania |

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| | 2 weeks at the maternity ward, Dareda hospital/ Tanzania |
| September 2009 | 2 weeks at the paediatric section, BHS Linz |
| | 2 weeks at the internal section, BHS Linz |
| March 2010 | 6-weeks at the general practiser Dr. Mertl |
| April/Mai | 8 weeks at the department for urology, BHS Linz |
| Juni/July | 6 weeks at the department for cardiology at the TMC hospital hill, Kansas City/ USA |

## Add-on education/Experience

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| July 2008 | 3-weeks experience as medical caretaker at the asthma and neurodermitis health program for children in Lignano/ Italy |
| November 2008 | workshop “Das Diagnosegespräch”, How to tell Parents a bad diagnosis of their child |

## Interests:

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|---|---|
| Hobbies: | Guitar, mountaineering, mountain biking, climbing, scouting, reading |
| Voluntary work: | Participation in Austrian Red Cross as a first aid attendant since October 2005 |
| | Participation in Austrian Scout Movement as a youth guide since 2003 |
| Languages: | English - written and spoken, French – good basic knowledge |
| Special Skills: | Great social engagement, efficiency, conscious of my duties and reliable |