Early motor repertoire and long-term neurological outcome
Bruggink, Janneke Leontien Maria

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Pilot use of the early motor repertoire in infants with inborn errors of metabolism: outcomes in early and middle childhood

Janneke LM Bruggink¹
Francjan van Spronsen²
Barbara J Wijnberg-Williams³
Arend F Bos¹

¹Department of Pediatrics, Division of Neonatology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.
²Department of Pediatrics, Division of Metabolic Diseases, University Medical Center Groningen, Groningen, the Netherlands.
³Department of Medical Psychology, University Medical Center Groningen, Groningen, the Netherlands.

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Chapter 6

Abstract

**Background:** Predicting later outcome in neonates presenting with severe inborn errors of metabolism (IEM) is difficult. The assessment of the early motor repertoire is a reliable method of evaluating the integrity of the central nervous system in young infants. This method is based on an age-specific qualitative assessment of general movements (GMs, 0-8 weeks of age), fidgety movements (FMs) and the concurrent motor repertoire (9-20 weeks of age).

**Aim:** To determine the quality of the early motor repertoire (at 0-20 weeks post-term age) in relation to later neurological outcome in infants with severe IEM.

**Study design:** Prospective cohort study. The quality of the motor repertoire was assessed from serial videotape recordings.

**Subjects:** Five infants with IEM. Four presented with a severe IEM in the neonatal period: an undefined gluconeogenesis defect, propionic acidemia, arginosuccinate synthetase and arginosuccinate lyase deficiency. One neonate was antenatally diagnosed with arginosuccinate synthetase deficiency.

**Outcome measures:** Outcome at the age of at least 18m was determined by neurological examination and developmental tests.

**Results:** All infants initially had abnormal GMs: hypokinesia, followed by GMS of a poor repertoire. The quality of the early motor repertoire normalised in 3 infants, and remained abnormal in 2. The more severe and persistent abnormalities of the motor repertoire were considered with the more abnormal neurological and developmental scores, later on.

**Conclusions:** The quality of the early motor repertoire might be related to later neurological outcome in infants with inborn errors of metabolism.

Introduction

General knowledge about inborn errors of metabolism (IEM) has improved in the last decade. Many IEM, including urea cycle disorders and organic acidemias may lead to the accumulation of ammonia, a toxic product of amino acid metabolism. Other IEM that may compromise brain function include defects in the mitochondrial respiratory chain and disorders in gluconeogenesis. Hyperammonaemia may present at any age and leads to neurodevelopmental sequelae of varying severity. In general, the age of onset, duration and degree of hyperammonaemia predict the prognosis and the extent to which the neurological changes may be reversible. In urea cycle defects, the duration and peak levels of ammonia are reported to be directly related to neurological outcome, while the onset and duration of symptoms are considered clues as to the severity of the neurodevelopmental sequelae. There remains a large degree of variability in the neurological outcome of infants presenting with severe IEM in the neonatal period.

A method which suitably predicts neurological outcome in young infants without IEM is Prechtl's method based on the qualitative assessment of the early motor repertoire. This method is based on visual Gestalt perception of the quality of GMs in infants up to the age of 5 months post-term. GMs are movements that involve the whole body in a variable sequence of arm, leg, neck and trunk movements. They arise during early fetal life and persist until 3 to 4 months post-term age. Normal GMs wax and wane in intensity, force and speed, are complex and variable, and have a
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gradual beginning and end. There are several types of abnormal GMs: Poor-repertoire GMs are abnormal GMs with a monotonous component, and movements of different parts of the body do not occur in the complex way as seen in normal GMs. Cramped-synchronised and chaotic GMs are also abnormal GMs. Cramped-synchronised GMs appear rigid and lack a normal smooth, fluent character. All limb and trunk muscles contract and relax almost simultaneously. Chaotic GMs are rare; they are characterised by movements of all limbs with a large amplitude, and occur in a chaotic order without any fluency or smoothness.

Around 6 to 9 weeks post-term age, GMs gradually disappear and fidgety movements (FMs) emerge which remain until 16 to 20 weeks’ post-term. FMs are movements of small amplitude, moderate speed and variable acceleration of the neck, trunk and limbs in all directions. FMs are intermittently or continually present in the awake infant, except during periods of fussing or crying. The quality of FMs can be judged as normal, or abnormal (amplitude, speed and jerkiness are exaggerated) and there may even be a complete absence of FMs (no FMs observed between 6 and 20 weeks’ post-term). During this period, the motor repertoire also consists of a large variety of other movement and postural patterns, the so-called concurrent motor repertoire. Previous studies have shown that the quality of FMs and the concurrent motor repertoire is a powerful tool for the early and specific prediction of cerebral palsy (CP) and complex minor neurological dysfunction (MND) in several populations at risk.

It is not known whether the quality of GMs, FMs and concurrent repertoire is affected in infants with IEM. It is also not known if, by using this technique, the neurological outcome in patients presenting with an IEM in the neonatal period could be predicted in the first few months of life. Therefore, the aim of our study was to investigate (1) the course of the spontaneous motor repertoire during the first months of age, and (2) its relationship to the later neurological and developmental findings in infants presenting with a severe IEM in the neonatal period.

Patients and methods

Infants

Five infants were included in our study after acquiring informed consent. All infants were treated at the University Medical Center Groningen between June 1999 and December 2002 and had an IEM causing hyperammonaemia or lactic acidemia. One infant was antenatally diagnosed with an IEM, the other infants were all diagnosed with an IEM around the 3rd postnatal day. Patient characteristics are listed in Table 1. The ethical committee of our hospital approved the study.

Recording and evaluation of the spontaneous motor repertoire during the first 5 months of age

Serial video recordings, approximately 30 minutes long, were made of the infants in the first or second week after birth up to the age of 20 weeks. The first video recording was made as soon as the diagnosis of an IEM was considered. Further recordings were made every 2 weeks until discharge and
### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Case</th>
<th>Inborn error type</th>
<th>Clinical presentation</th>
<th>Highest value(^1) toxic metabolite</th>
<th>Acute treatment</th>
<th>Complications</th>
<th>Admissions for metabolic derangement beyond neonatal period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ASS (prenatally diagnosed)</td>
<td>39 wk / 3775 grams; Apgar 8-9 No symptoms</td>
<td>NH(_3), 74 μmol/l day 9</td>
<td>Only diet, benzoate and phenylbutyrate</td>
<td>Septicaemia S. Aureus, day 5</td>
<td>Once, gastro-enteritis, max NH(_3), 274 μmol/l</td>
</tr>
<tr>
<td>2</td>
<td>ASS</td>
<td>38 wk / 3000 grams; no perinatal problems. day 3 lethargic, convulsions, coma, hypothermia, respiratory insufficiency. Diagnosis urea cycle defect same day (day 3)</td>
<td>NH(_3), 2051 μmol/l day 3</td>
<td>Peritoneal dialysis, during 5d</td>
<td>Small subdural hemorrhage</td>
<td>3 times, gastro-enteritis and viral infections, max NH(_3), 129 μmol/l</td>
</tr>
<tr>
<td>3</td>
<td>ASL</td>
<td>40 wk / 3820 grams / no perinatal problems. day 2-3 lethargic, convulsions, hypertonia, respiratory insufficiency. Diagnosis urea cycle defect day 3</td>
<td>NH(_3), 847 μmol/l day 3</td>
<td>Peritoneal dialysis, during 2d</td>
<td>None</td>
<td>1 time, gastro-enteritis and viral respiratory infection. Max NH(_3), 217 μmol/l</td>
</tr>
<tr>
<td>4</td>
<td>PPA</td>
<td>37 wk / 3300 grams; no perinatal problems. day 3 expiratory grunting, hypothermia, lethargic, bulging fontanel, persistent metabolic acidemia. Diagnosis PPA day 4</td>
<td>pH 7.16; BE-12 NH(_3), 566 μmol/l, day 3</td>
<td>Veno-venous haemodialysis during 2d</td>
<td>None</td>
<td>2 times, gastro-enteritis, complicated by convulsions Max NH(_3), 181 μmol/l, pH always normal</td>
</tr>
<tr>
<td>5</td>
<td>Suspected GGD</td>
<td>39 wk / 2680 grams; Apgar 3-9, slightly asphyctic, after 3 days lactic acidosis with hypoglycemia. So far no diagnosis</td>
<td>Lactate 23 mmol/l day 4</td>
<td>High glucose resulting in normal lactate levels</td>
<td>Icterus (bili max 386 μmol/l) MRI 9m: Abnormal myelin staining in subcortical white matter</td>
<td>None. Especially during first year lactate usually between 2 and 3 mmol/l, with higher levels when frequency of food intake was decreased</td>
</tr>
</tbody>
</table>

\(^1\)Reference value lactate 0.5-2.2 mmol/l Reference value NH\(_3\), 15-45 μmol/l
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at 6 to 10 weeks, at 11 to 16 weeks and at 16 to 22 weeks post-term age at the outpatient clinic. They were made during periods of active wakefulness between feeds, with the partially dressed infants lying in supine position. The recordings were later evaluated off-line by JLMB and AFB according to Einspieler et al.10 Both observers were unaware of the infant’s clinical history and neurological status. Previous studies have shown that this method has a high inter-observer reliability.10,17 The longitudinal trajectories of the quality of the motor repertoire were assessed from the serial measurements, in an age-specific way. From birth until around 8 weeks’ post-term, we judged the motor repertoire as normal, abnormal (poor repertoire, cramped synchronised or chaotic) or hypokinetic (no GM observed during a recording of at least 45 minutes).21,22 From the recordings made after the 9th week of life, we assessed the quality of FMs as normal, abnormal (amplitude, speed and jerkiness were exaggerated) or the absence of FMs (no FMs observed between 9 and 20 weeks post-term). The same recordings were used to judge the quality of the concurrent motor repertoire as normal if it was smooth, variable, fluent and complex. Reduced complexity (monotony), jerkiness and/or stiffness were considered to be signs of abnormality.15,17,23,24

Neurological and developmental follow-up assessment at 2-3 years of age
At around 2 to 3 years of age, neurological and developmental follow-up was performed. It contained a neurological examination in accordance with Touwen.25 The children were classified as being neurologically normal, having mild neurological deficits (e.g. coordination or gross motor problems) or abnormal. The Bayley Scales of Infant Development (BSID)-II26 or Snijders-Oomen non verbal intelligence test (SON-R 2½-7)27 was performed to evaluate the mental and psychomotor status.

Neurological and developmental follow-up assessment at 4 to 8 years of age
Between 4 and 8 years of age, neuropsychological follow-up was determined by using the Wechsler Intelligence Scale for Children-Revised (WISC-R)28 or the Snijders-Oomen non verbal intelligence test (SON-R 5½-7).27 Test results, which were two standard deviations below the mean, were considered to be abnormal.

Clinical characteristics:
Clinical characteristics and parameters of all infants in the neonatal period like: birth weight, gender, presentation of IEM, maximum value of toxic metabolites and complications were registered. Furthermore, clinical characteristics beyond the neonatal period, such as admissions for metabolic derangement and maximum values of toxic metabolites, were retrieved.

Results
Five infants (n=5) were included in the study. Two infants (case 1 and 2) had arginosuccinate
synthetase deficiency (ASS). Case 3 was diagnosed with arginosuccinate lyase deficiency (ASL). Case 4 had propionic academia (PPA) and one infant (case 5) had a further undefined gluconeogenesis defect (GGD). Neonatal characteristics and metabolic derangements after the neonatal period are summarised in Table 1.

**Individual GM trajectories up to 5 months post-term age**

Individual trajectories of the quality of the early motor repertoire are shown in Table 2. Except for case 1 no GMs with a normal quality were observed before the fidgety age. In 4 out of 16 GM-observations before fidgety age (25%) the early motor repertoire was judged as hypokinetic. Between 6 and 8 weeks postnatal age, poor repertoire GMs with a cramped character but not synchronised, were observed in 3 infants (case 2, 3 and 5).

Between 9 and 16 week post-term age (fidgety age), normal FMs were observed in 3 infants (case 1, 2 and 3). Abnormal FMs were observed in one infant (case 4), and in one infant (case 5) no FMs were observed during the recordings and therefore classified as absence of FMs. In the infants with normal FMs, two infants (case 1 and 2) showed a normal concurrent motor repertoire, the other infant (case 3) had a monotonous and jerky concurrent motor repertoire.

**Neurological and developmental findings during follow-up at 2-3 years of age**

Around 2 to 3 years of age (range 18-37 months) all infants were tested. Details on neurological and developmental follow-up data are provided in Table 2. Neurological assessment according to Touwen showed that one infant (case 1) developed normally, 3 infants developed mild neurological deficits (case 2, 3, and 4) and one infant developed dyskinetic spasticity combined with West syndrome (case 5). Developmental follow-up data showed abnormal scores in four infants (case 1, 2, 3 and 4). One infant did not meet criteria for a basal score because of severe neurological and behavioural impairments (case 5).

**Comparison between quality of the early motor repertoire and neurological and developmental findings at 2-3 years of age**

The quality of the early motor repertoire before fidgety age correlated well with neurological outcome at 2 years of age. The only infant with a normal quality of the early motor repertoire (case 1) had a normal neurological outcome around 2 years of age. In all children with poor repertoire GMs before fidgety age (case 2, 3, 4 and 5), abnormalities in neurological outcome were observed at about 2 to 3 years of age.

The quality of the early motor repertoire during fidgety age showed an even better correlation with the neurological and developmental follow-up assessment at 2 to 3 years of age. The absence of FMs was observed in case 5 who developed a dyskinetic CP. In the patients with normal FMs, combined with a normal concurrent motor repertoire, one infant developed normally (case 1), and one infant developed mild neurological deficits (case 2). One infant with normal FMs combined with
Table 2: Quality of general movements (GMs) during the first 5 months, in relation to neurological and developmental findings at follow-up.

<table>
<thead>
<tr>
<th>Case (defect)</th>
<th>Postnatal age</th>
<th>Follow-up data about 2-3 years of age</th>
<th>Follow-up data 4-8 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1-4</td>
<td>Day 5-13</td>
<td>Week 2-5</td>
</tr>
<tr>
<td>1 (ASS)</td>
<td>PR-Sy</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (ASS)</td>
<td>H</td>
<td>H</td>
<td>PR-Sy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (ASL)</td>
<td>H</td>
<td>H / PR-Sy</td>
<td>PR -crammed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (PPA)</td>
<td>-</td>
<td>PR</td>
<td>PR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 (GGD)</td>
<td>-</td>
<td>PR</td>
<td>-</td>
</tr>
</tbody>
</table>

ASS, Arginosuccinate synthetase deficiency; ASL, Arginosuccinate lyase deficiency; PPA, Propionic acidemia; GGD, gluconeogenesis defect (defined). H, Hypokinesia; PR, poor repertoire of GMs; Sy, synchronised GMs; N, Normal GMs; NF, Normal fidgety movements; Rep, repertoire of movement patterns; AF, abnormal fidgety movements; No F, absence of fidgety movements. MDI, mental developmental index; PDI, psychomotor developmental index; SON-R 2.5-7, Snijders Oomen Nonverbal Intelligence test, age range 2.5 – 7 years.
a monotonous concurrent motor repertoire (case 3), and one infant with abnormal FMs and a jerky concurrent motor repertoire (case 4) developed minor neurological deficits at 2 years of age.

**Neurological and developmental findings during follow-up at 4 to 8 years of age**

Between 4 to 8 years of age, all infants, except one who died (case 5), were tested. Neurological assessment showed that none of the infants developed normally, 3 infants had MND (case 1, 2 and 4) and one infant had developed severe neurological deficits combined with epilepsy (case 3). Developmental follow-up data was not obtained on one infant (case 4) because of severe neurological and behavioural problems. The other infants showed abnormal scores on developmental tests (Table 2).

Confounding by metabolic derangements was also investigated. These data showed that one child (case 4) had no metabolic derangements and three infants (case 1, 2 and 3) had at least once a metabolic derangement between 4 and 8 years.

**Discussion**

The present study indicates that in infants with a neonatal presentation of an IEM, the quality of the early motor repertoire could be affected in the same way as infants not having an IEM. Furthermore, our data indicated that the quality of the early motor repertoire, particularly the quality of FMs and the concurrent motor repertoire at 9 to 16 weeks’ post-term is associated with the neurological outcome at the age of 2 to 3 years. Studies in non-IEM populations showed that absence of FMs between 9 and 16 weeks’ post-term predicts CP in 95% of cases, whereas FMs of a normal character in this specific age period predicts normal outcome in 98%. This is in line with our data in the present study in which the one infant with absence of FMs developed dyskinetic CP, whereas all infants with normal FMs did not develop CP. Our data also showed that the quality of the concurrent motor repertoire could further differentiate the degree of neurological dysfunction in infants with a neonatal presentation of an IEM. Those infants with normal FMs, but an abnormal quality of the concurrent motor repertoire, developed mild neurological deficits at 2 to 3 years of age. In contrast, those with a normal quality of the concurrent motor repertoire showed normal neurological development. In infants not having IEM, we recently reported that the quality of the FMs combined with the quality of the concurrent motor repertoire is also predictive, to a considerable extent, of minor neurological dysfunction at school age.

The early motor repertoire of infants with IEM had some specific characteristics. Most infants with IEM had hypokinesia at first, followed by abnormal or poor repertoire GMs lasting for several days to weeks. The quality of the early motor repertoire before fidgety age was also, albeit less strongly, associated with the neurological and developmental findings at 2 to 3 years of age. This is in line with previous studies on the predictive value of the quality of the early motor repertoire. These studies showed that normal GMs had good predictive value for a normal neurological outcome,
but poor repertoire GMs have low predictive value for an abnormal outcome.\textsuperscript{10,13,29} The longitudinal trajectory was shown to be most predictive in both infants with and without IEM. The more severe and persistent the motor repertoire abnormalities, the more abnormal the scores in later neurological and developmental tests.

Our findings may have implications for children with IEM. Our data showed that the qualitative assessment of FMs and the concurrent motor repertoire is an appropriate method to evaluate treatment options in infants with IEM, from a very early age onwards. Because the liver is responsible for the metabolism of the precursors that result in the accumulation of ammonia, orthotopic liver transplantation (OLT) has been proposed as a treatment option. Several papers reported the effect of OLT on the neurological outcome in infants with hyperammonaemia due to IEM.\textsuperscript{30,31} In some diseases with hyperammonaemia, OLT is reported to induce a nearly complete metabolic correction and cessation of progression, but not reversal, of neurological deficits.\textsuperscript{30,31} Furthermore the time of transplantation remains controversial. Mc Bride et al. suggest that early OLT improves neurological outcome compared with later transplantation.\textsuperscript{32} Others did not show any difference in neurological outcome timing of OLT in any of these diseases.\textsuperscript{8,30}

A limitation of this study can first be found in the small number of infants included. This is due to the relative low prevalence of IEM and the risk of early mortality in infants with an IEM. A second limitation can be found in the possibility of deterioration of neurological status due to metabolic derangements between early infancy and 2 to 3 years of age. All but one of the infants had metabolic derangements after the neonatal period, although they were rather mild (ammonia levels not being >300 umol/l in the acute phases). Nevertheless, the data could be biased by the direct effect of slightly elevated ammonia levels on brain development, in infants with IEM, even without clinically evident metabolic derangements. Previous studies showed that also slightly elevated ammonia levels could cause irreversible effects on the developing brain.\textsuperscript{33} Furthermore, although our results suggest that the quality of the early motor repertoire is related to neurological outcome in infants with IEM, the numbers are obviously too small to draw any conclusions regarding the predictive value of the early motor repertoire.

In conclusion, this study showed that the assessment of the quality of the early motor repertoire might be helpful to assess neurological outcome at 2 to 3 years of age in infants with a neonatal presentation of an IEM. Specifically the quality of FMs and concurrent motor repertoire between 11 and 16 weeks post-term age were associated with neurological outcome. The clinical significance of our findings is that the qualitative assessment of the early motor repertoire may be helpful in evaluating interventions and treatment options in children diagnosed with IEM. Further investigations in multicenter trials, with a larger patient cohort, are necessary to confirm our findings.
Chapter 6

References


