Early motor development, early visual attention and functional outcome in children
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CHAPTER 6

FAVORABLE OUTCOME IN A NEWBORN WITH MOLYBDENUM COFACTOR TYPE A DEFICIENCY TREATED WITH CPMP

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Abstract

Molybdenum cofactor deficiency (MoCD) is a lethal autosomal recessive inborn error of metabolism with devastating neurologic manifestations. Currently, experimental treatment with cyclic pyranopterin monophosphate (cPMP) is available for patients with MoCD type A caused by a mutation in the \textit{MOCS-1} gene. Here we report the first case of an infant, prenatally diagnosed with MoCD type A, whom we started on treatment with cPMP 4 hours after birth. The most reliable method to evaluate neurologic functioning in early infancy is to assess the quality of general movements (GMs) and fidgety movements (FMs). After a brief period of seizures and cramped-synchronized GMs on the first day, our patient showed no further clinical signs of neurologic deterioration. Her quality of GMs was normal by the end of the first week. Rapid improvement of GM quality together with normal FMs at 3 months is highly predictive of normal neurologic outcome. We demonstrated that a daily cPMP dose of even 80 $\mu$g/kg in the first 12 days reduced the effects of neurodegenerative damage even when seizures and cramped-synchronized GMs were already present. We strongly recommend starting cPMP treatment as soon as possible after birth in infants diagnosed with MoCD type A.
Introduction
Molybdenum cofactor deficiency (MoCD) is a rare inherited metabolic disorder leading to a combined deficiency of sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase, as well as amidoxime. The accumulation of sulfite due to lack of sulfite oxidase probably causes progressive neurologic damage and death in early infancy. Type A is most common (Figure 1) and occurs in approximately two-thirds of patients. Life-long intravenous administration of the missing substance, cyclic pyranopterin monophosphate (cPMP), is a potentially effective treatment strategy for these patients. In the first treated patient, cPMP substitution commenced 36 days after birth. Despite the initial promising results, the patient developed signs of quadriplegic cerebral palsy at 18 months. Therefore, starting treatment as soon as possible after birth is of utmost importance. Over the years, attention has been drawn increasingly to the need for early identification of infants at risk for neurologic impairment. The most reliable method to evaluate neurologic functioning up to 5 months after term is the assessment of the quality of general movements (GMs) from video recordings. Normal GMs are complex and variable, whereas abnormal GMs appear monotonous with reduced complexity and variability. At ~3 months, GMs acquire a fidgety character (i.e., continuous small movements of moderate speed in all directions). The quality of these fidgety movements (FMs), normally present between 9 and 20 weeks after term, is a particularly accurate marker for neurologic deficits: most infants (96%) with normal FMs have normal neurologic outcomes, whereas most infants (95%) in whom FMs are absent during this period develop cerebral palsy.

We report here on the neurodevelopmental outcome of a patient, diagnosed prenatally with MoCD type A, in whom experimental treatment with cPMP commenced 4 hours after birth.

Patient presentation
Clinical presentation
Our patient was the fifth child of healthy, white, nonconsanguineous parents. They had 2 healthy boys, but their 2 girls both presented with seizures on day 1 and died shortly afterwards. The first girl was thought to have had either sepsis or congenital heart disease, whereas in the second girl, urine levels of sulfite, sulfocysteine, xanthine, and hypoxanthine were elevated and compound Z (cPMP oxidation product) was absent without cPMP being detected. Subsequent DNA analysis revealed homozygosity for the 418+1G>a mutation in the MOC-1 gene, proving MoCD type A deficiency.

In the infant described here, prenatal diagnosis was based on DNA assessment. Birth was induced at 36 +3 weeks of gestation: the potential benefits of early treatment outweighing the risks of prematurity. After an uncomplicated delivery, a hypo-active girl was born revealing low muscle tone and hyperreflexia (birth weight: 3235 g; Apgar 8/8 at 1 and 5 minutes). Because of low pulse oxygen saturation and hypotension, she required continuous positive airway pressure, oxygen, and repeated saline infusions and dopamine up to 12 hours after birth.
Figure 1. Schematic presentation of molybdenum cofactor biosynthesis in humans. According to subsequent steps in the metabolic pathway, 3 subtypes of MoCD can be distinguished: type A, B, and C involving genetic mutations in MOSC-1, MOSC-2, and MOSC-3, respectively. cPMP, cyclic pyranopterin monophosphate; GTP, guanosine triphosphate; MPT, molybdopterin.

Dosing schedule and intravenous administration of cPMP

After parental consent and approval by the review board, experimental treatment with cPMP commenced 4 hours after birth (see dosing schedule in Table 1). In the absence of detailed dose finding and safety studies, cPMP was increased to 160 µg/kg per day on day 35 following the treatment schedule of the first patient. Given the excellent tolerability of 240 µg/kg per day in the initial patient (oral communication), cPMP was increased to 240 µg/kg per day to achieve lowest possible SSC levels. After discharge (10 weeks), cPMP infusion was continued once daily by the parents per central venous access.

Table 1. cPMP treatment protocol.

<table>
<thead>
<tr>
<th>Day of treatment</th>
<th>Total daily dose (µg/kg)</th>
<th>Number of infusions per day</th>
<th>cPMP dose (µg/kg)</th>
<th>Infusion time (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>1</td>
<td>8</td>
<td>30</td>
</tr>
<tr>
<td>1</td>
<td>80</td>
<td>2</td>
<td>8</td>
<td>30</td>
</tr>
<tr>
<td>1</td>
<td>80</td>
<td>3</td>
<td>8</td>
<td>30</td>
</tr>
<tr>
<td>1</td>
<td>80</td>
<td>4</td>
<td>56</td>
<td>120</td>
</tr>
<tr>
<td>2–4</td>
<td>80</td>
<td>1</td>
<td>8</td>
<td>30</td>
</tr>
<tr>
<td>2–4</td>
<td>80</td>
<td>2</td>
<td>72</td>
<td>180</td>
</tr>
<tr>
<td>5–6</td>
<td>80</td>
<td>1</td>
<td>80</td>
<td>180</td>
</tr>
<tr>
<td>7–12</td>
<td>80</td>
<td>1</td>
<td>80</td>
<td>180</td>
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<td>13–34</td>
<td>120</td>
<td>1</td>
<td>120</td>
<td>60</td>
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<td>≥35</td>
<td>160</td>
<td>1</td>
<td>160</td>
<td>60</td>
</tr>
<tr>
<td>100</td>
<td>240</td>
<td>1</td>
<td>240</td>
<td>60–20*</td>
</tr>
</tbody>
</table>

On day 1, 3 test doses were administered separated at 30-min intervals. From days 2 to 4, 1 test dose was given, again followed by a 30-min interval. *Decreasing in time of infusion.
Metabolic investigations
Within 2 days after birth, sulfite dipstick test results became negative and remained so. Within days 2 to 9, hypoxanthine and xanthine levels dropped from 325 and 824 µmol/mmol to normal levels of 11 and 33 µmol/mmol, respectively. Within days 2 to 16, SSC dropped from 77.7 µmol/mol creatinine to normal levels of 10.3 µmol/mol creatinine. Except for 3 central line infections, no serious drug-related adverse effects were seen.

Figure 2.
A, EEG (third row) and aEEG patterns registered with the CFM Olympic 6000 (Natus Medical Incorporated, San Carlos, CA) revealing 2 single seizures at 21 hours after birth. The scale on the y axis is semilogarithmical, ie, linear from 0 to 10 µV, and logarithmical from 10 to 100 µV. The x axis represents time, a 10-minute period on the aEEG and a 1-second period on the EEG indicated by the horizontal arrows. B, aEEG pattern revealing a continuous normal voltage pattern with sleep-wake cycling without any seizures at 14 hours after birth. The scale on the y axis is semilogarithmical, ie, linear from 0 to 10 µV, and logarithmical from 10 to 100 µV. The x axis represents time, a 10-minute period indicated by the horizontal arrows.
Within the first hour after birth, the infant showed myoclonic spasms accompanied by high-pitched crying, interpreted as clinical seizures lasting several minutes whereupon phenobarbital (20 mg/kg) treatment was given once. At 4 hours after birth, amplitude-integrated EEG (aEEG) demonstrated a burst suppression pattern without electrographic signs of epileptic activity. Experimental cPMP infusion was initiated simultaneously. After that, no clinical seizures were observed anymore. At 5.5 hours after birth, the aEEG background pattern changed to a continuous normal voltage pattern. Subclinically, at 6.5 and 21 hours, aEEG revealed 2 single seizures (Figure 2A). This was consistent with standard EEG that displayed multiform epileptiform discharges on day 1. Sleep-wake cycling was present from 14 hours after birth onwards (Figure 2B).

Assessment of GMs from birth until 18 weeks after term
Video recordings were made daily on days 1 to 8, days 10, 16, 23, and 28 (term age), and at days 118 (12 weeks postterm) and 153. The infant was recorded for 30 to 60 minutes. The recordings at days 118 and 153 were made during an outpatient visit and lasted 10 minutes, sufficiently long for reliable assessment of FMs. All recordings were assessed independently off-line by Ms Hitzert and Dr Bos by using Prechtl’s method.6 From birth until term age, GM quality was labeled normal, abnormal (poor repertoire, cramped-synchronized or chaotic), or hypokinetic (no GMs observed or brief GMs <3 seconds).9,10 We labeled the quality of FMs recorded at days 118 and 153 normal, abnormal (exaggerated speed, amplitude, and jerkiness), or absent (no FMs observed). Additionally, we determined a motor optimality score (MOS) by using the GM Optimality List for Preterm GMs and Writhing Movements.11 Until term age, the MOS is composed of GM quality (4 points if normal; 2 points if poor repertoire; and 1 point if cramped synchronized, chaotic, or hypokinetic) plus 7 other items including speed and presence of tremulous movements (2 points if normal; 1 point if abnormal). The MOS may range from 8 (low optimality) to 18 (high optimality). Approximately 3 months postterm age, the MOS is composed of FM quality (12 points if normal; 4 points if abnormal; and 1 point if absent) plus 4 other items including age-adequacy and quality of the concurrent motor repertoire (4 points if normal; 2 points if reduced; and 1 point if abnormal). The MOS at this age may range from 5 (low optimality) to 28 (high optimality).12

Figure 3 depicts the results on the quality of GMs. Two recordings were discarded due to crying (days 10 and 28). On the first day, just before cPMP infusion commenced, we observed cramped-synchronized GMs with an MOS of 8 points. Although GMs were still labeled abnormal (poor repertoire) on the second day, there was an improvement in MOS to 9 points after the fourth cPMP dose. The quality of GMs became normal after the 11th dose at day 6. At days 118 and 153, we observed normal FMs with an MOS of 26 points (not shown).
Figure 3.
A, Uric acid blood levels and B, urinary S-Sulfocysteine levels (SSC) in relation to the change in quality of GMs and MOS at postnatal days 1 to 8 (measurements 1–8), 16 (measurement 9) and 23 (measurement 10). Stars represent cramped-synchronized GMs, triangles poor repertoire GMs, and round symbols normal GMs.
Neurodevelopmental course up to 21 months’ corrected age

Follow-up at 26 weeks revealed dystonia (variable hypo- and hypertonia) with a continuously present tremor, which both improved during the next 6 months. At 21 months’ corrected age, we performed the Bayley Scales of Infant and Toddler Development, third edition. Data are shown in Table 2. At this age, no tremors were observed anymore. Behavioral outcome, evaluated by the Child Behavior Checklist 1.5 to 5 years, revealed no behavioral problems.

Table 2. Cognitive, fine, and gross motor outcome at 21 months’ corrected age measured with the Bayley Scales of Infant and Toddler Development, third edition.

<table>
<thead>
<tr>
<th></th>
<th>Scaled Score</th>
<th>Composite Score</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive</td>
<td>6</td>
<td>80</td>
<td>mildly delayed</td>
</tr>
<tr>
<td>Fine motor</td>
<td>8</td>
<td>90</td>
<td>normal</td>
</tr>
<tr>
<td>Gross motor</td>
<td>8</td>
<td>90</td>
<td>normal</td>
</tr>
<tr>
<td>Total motor</td>
<td>16</td>
<td>88</td>
<td>normal</td>
</tr>
</tbody>
</table>

Scaled scores for cognitive, gross, and fine motor outcome, as well as the cognitive and total motor composite scores were calculated corrected for preterm birth. Based on the scaled scores and the composite scores (mean: 10 [SD:3] and 100 [SD:15], respectively), the infant was classified as normal (<1 SD below the mean), mildly delayed (1–2 SD below the mean), or abnormal (>2 SD below the mean).

Discussion

This case report demonstrates favorable outcome, based on aEEG and GMs, in MoCD type A, in response to experimental cPMP treatment administered daily from the first day after birth.

Given the lack of drug-related adverse events at high cPMP doses (both in our and the previous case), the mild respiratory problems and hypotensive episodes during the first hours after birth might be related to transitional problems (due to elective late preterm birth) rather than to cPMP infusions.

Neurologic features of surviving MoCD type A children generally resemble those of ischemic brain injury and involve epilepsy, abnormal muscle tone, microcephaly, and lens dislocation. Accordingly, our patient presented with a brief period of clinical seizures before cPMP initiation. After commencing cPMP treatment, however, the aEEG background pattern normalized and clinical seizures dissolved. Sleep-wake cycling emerged as early as 14 hours after birth. In term asphyxiated infants, both improvement of aEEG patterns within 24 hours after birth and the onset of sleep-wake cycling within 36 hours are recognized as good prognostic indicators of normal outcome.

In accordance with previous preterm studies, we observed slight fluctuations in GM quality and MOS during the first week. The quality of GMs was already normal by the end of the first week, which indicates normal outcome. This expectation is substantiated by the normal FMIs shown at ~3 months after term, replicating previous observations in infants with inborn errors of metabolism.

MoCD may reveal phenotypic variability involving features of neonatal encephalopathy...
(diffuse brain swelling and diffuse cytotoxic edema) and late developmental delay. In our case, we observed both abnormal aEEG and abnormal motor repertoire immediately after birth. Neurologic improvement coincided with prompt neonatal treatment, in favorable contrast to her 2 older sisters. We hypothesize, therefore, that the advantageous clinical course is to be attributed to prompt initiation of treatment.

We demonstrated that experimental cPMP treatment markedly improved GM quality within the first week after birth in an infant with MoCD type A and that neurodevelopmental outcome at 21 months’ corrected age was normal with only a mild delay in cognitive skills function. Therefore, indirectly, cPMP may reduce the progression of neurodegenerative damage even when seizures and cramped-synchronized GMs are already present. Extended follow-up is urgently needed to reveal whether the beneficial effects of cPMP continue into childhood and beyond.

Conclusions
We strongly recommend starting cPMP treatment in infants with MoCD type A as soon as possible after birth.

Acknowledgements
We greatly acknowledge the help of H. J. ter Horst, MD, PhD, for evaluating aEEG patterns, Professor J. Reiss for DNA analysis, Dr. T. Brantsma-van Wulfften Palthe in Utrecht for correcting the English article, and A. M. Roescher, BSc, for performing the Bayley Scales of Infant and Toddler Development, third edition.
References


PART III

INTERRELATIONSHIP BETWEEN EARLY MOTOR DEVELOPMENT, EARLY VISUAL ATTENTION AND FUNCTIONAL OUTCOME

Chapter 7  Associations between developmental trajectories of movement variety and visual attention in fullterm and preterm infants during the first six months postterm

Chapter 8  Motor development in 3-month-old healthy term-born infants is associated with cognitive and behavioural outcomes at early school age

Chapter 9  Early visual attention in preterm and fullterm infants in relation to cognitive and motor outcomes at school age: an exploratory study