Favorable Outcome in a Newborn With Molybdenum Cofactor Type A Deficiency Treated With cPMP

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 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 μg/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. Pediatrics 2012;130:e1005–e1010
Molybdenum cofactor deficiency (MoCD) is a rare inherited metabolic disorder leading to a combined deficiency of sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase. 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 (Fig 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 MOCS-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 after birth. 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 MOCS-1 gene, proving MoCD type A deficiency.

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**Treatment**

**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.

**Metabolic Investigations**

Within 2 days after birth, sulfite dipstick test results became negative and remained so. Within days 2 to 9, the cortical EEG completely normalized.

**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>
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<tr>
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<td>9</td>
<td>80</td>
<td>1</td>
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</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.
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.

Amplitude-Integrated EEG
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

![Amplitude-Integrated EEG](image-url)

**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 semilogarithmic, i.e., linear from 0 to 10 μV, and logarithmic 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 semilogarithmic, i.e., linear from 0 to 10 μV, and logarithmic from 10 to 100 μV. The x-axis represents time, a 10-minute period indicated by the horizontal arrows.
seizures (Fig 2A). This was consistent with standard EEG that displayed multiformal epileptiform discharges on day 1. Sleep-wake cycling was present from 14 hours after birth onwards (Fig 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 post-term) 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. 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). 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. 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 post-term 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).

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
At 21 months both improved during the next 6 months. A continuously present tremor, which variable hypo- and hypertonia) with follow-up at 26 weeks revealed dystonia (not shown). 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).

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.

### 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 hypertensive 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 FMs 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.

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### REFERENCES


(Continued from first page)

Ms Hitzert collected and analyzed the video recordings of general movements and drafted the first version of the manuscript; Dr Bos analyzed the general movements and co-wrote the manuscript; Dr Bergman performed the treatment at the Division of Neonatology and performed the first period of monitoring; Dr Veldman developed the treatment plan and was principal investigator of the study; Dr Schwarz developed cPMP purification, production and characterization, and proposed treatment strategy; Dr Santamaria-Araujo characterized cPMP, developed cPMP production and purification, performed cPMP stability analysis, performed metabolite analysis and determined compound Z content; Dr Heiner performed metabolite analysis; Dr Sival and Dr Lunsing were responsible for follow-up and neurodevelopmental assessment in the first and second girl; Ms Arjune contributed to the cPMP formulation and metabolite analysis; Dr Kosterink supervised endotoxin assays, preparation of cPMP for infusion and supervised quality control of cPMP on intravenous medication standards; and Dr van Sprosen was responsible for the diagnosis of MoCD, performed the treatment and monitoring, and co-wrote the manuscript.

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