Pearls and Oysters: Reversible Postpartum Pseudo-Coma State Associated With Magnesium Therapy: A Report of 2 Cases

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Abstract
Magnesium (Mg) competes with calcium in normal synaptic transmission, inhibiting neurotransmitter release. As a drug, it is usually given as a treatment for eclampsia and pre-eclampsia. Two eclamptic pregnant women treated with Mg developed a pseudo-coma state immediately after emergency Caesarian Section. The clinical presentation was flaccid quadriparesis, areflexia, an absence of absent respiratory effort and vestibular-ocular reflexes, but with preserved pupillary responses. Decremental responses on repetitive nerve stimulation were found in both women. Recovery was obtained after cessation of the Mg. The persistence of pupillary reflexes in the absence of reflexes involving striated muscles was an important clinical clue, indicating neuromuscular junction dysfunction.

Pearls
• Neuromuscular junction (NMJ) dysfunction should be suspected when a patient treated with magnesium (Mg) develops flaccid paralysis with ophthalmoplegia.
• Pseudo-coma due to Mg is usually due to overdose.

Oysters
• Magnesium therapy, even at therapeutic doses, can result in a severe pseudo-comatose state in people with pre-existing NMJ dysfunction.
• When assessing brainstem function in the context of magnesium therapy, special attention must be given to assessing pupillary responses; their presence despite the absence of vestibulo-ocular reflexes is an important clinical clue, suggesting NMJ dysfunction.

Background:
Magnesium (Mg) competes with calcium in normal synaptic transmission, inhibiting neurotransmitter release. As a drug, it is usually given as a treatment for eclampsia and pre-eclampsia. We describe two women treated with Mg who developed a pseudo-coma state immediately after emergency Caesarian Section (CS).
Case presentations:

Case 1:

A 34-year old woman in her first pregnancy presented for delivery at term with hypertension and proteinuria, suggesting preeclampsia. She was given IV Mg and underwent emergency CS. Postoperative course was complicated by hemorrhage and hypovolemic shock, requiring surgical hemostasis and blood transfusion. Immediately after the second surgery she was found to be unresponsive with absent respiratory effort. The clinical suspicion was of severe hypoxic-ischemic encephalopathy and a neurological consultation was requested.

Examination revealed a GCS of 3 with absent vestibulo-ocular reflexes (VOR) and flaccid paralysis with absent tendon reflexes. Surprisingly, pupillary responses to light were present. The anesthesiologist reported absent respiratory effort and was unable to evoke a muscle twitch using a peripheral nerve stimulator. At this point, it was noted that her Mg infusion had accidentally been continued throughout the procedure—having been mistaken for saline—and had been given at a rapid rate during the hypovolemic state, resulting in overdose.

Mg was stopped and IV calcium gluconate was administered. Motor responses returned within 15 minutes and she fully recovered within 24 hours. A bedside repetitive nerve stimulation (RNS) test performed in ICU after the first calcium dose showed a decremental response at 3 Hz (figure 1A).

She later reported being fully conscious throughout the initial evaluation, even reporting that she had overheard discussion of posthumous organ donation. Unfortunately, serum Mg levels were not measured during the period of toxicity.

Case 2:

A 39-year-old woman in the 36th week of her ninth pregnancy. One month prior to admission, she complained of general weakness and dysphagia, however neurological examination was reported as normal. On the day of admission, she was found unresponsive and cyanotic. She received emergency intubation in the field and was transported to the ER. On arrival her BP was 170/68. She had proteinuria with impaired renal and hepatic function. A presumptive diagnosis of seizures as a manifestation of eclampsia was made, and she
underwent emergency CS. IV Mg was given peri-operatively and continued in the recovery room.

Eighteen hours post-surgery she was still unresponsive with no respiratory effort. Examination revealed ophthalmoplegia with absent VOR and corneal reflexes, and a flaccid quadriplegia with areflexia and absent plantar responses. However, pupils were round, mid-sized and responsive to light—a finding which reminded one of the authors of Case 1. As such, NMJ dysfunction due to Mg was suspected, and the Mg infusion was stopped. Nevertheless, she was sent for brain MRI, which was normal.

Mg levels at the time of Mg infusion cessation was 4.1mmol/L. An hour later, voluntary eye movements returned. Over the next few days, she regained limb movement but remained extremely weak. RNS test done at 3 HZ demonstrated a decremental response (figure 1B) and elevated serum anti-acetylcholine receptor (AChR) antibodies were found. She made a full recovery after treatment for MG with plasmapheresis, immunosuppressive treatment and thymectomy.

Discussion:

These two cases of NMJ dysfunction associated with peri-partum Mg treatment are strikingly similar. In both cases the presentation was of complete quadriplegia, respiratory muscle paralysis with ophthalmoplegia, but with preserved pupillary reflexes. The first woman had been erroneously given Mg at a dose expected to cause toxicity, presumably resulting in pure pre-synaptic failure, in the absence of additional post-synaptic dysfunction. In contrast, the second woman—who received Mg at therapeutic levels—developed complete NMJ block as a result of combined pre-synaptic and post-synaptic processes, due to magnesium and myasthenia gravis, respectively. To our knowledge this is the first case of undiagnosed MG becoming unmasked due to Mg therapy, in the form of pseudo-coma.

In both cases, the pupillary responses suggested a peripheral etiology rather than brainstem dysfunction. A pseudo-coma state caused by severe hypermagnesemia, has been reported before, with pupillary reflexes reported variably as either present\textsuperscript{2,5}, sluggish\textsuperscript{5,6}, or completely absent\textsuperscript{4} (table 1). The only case reported with a complete loss of the pupillary reflex was with Mg levels as high as 9.85mmol/L, about 2.5 times higher than the target level in eclampsia treatment\textsuperscript{4}; this suggests that parasympathetic ACh release is susceptible, but
less sensitive to high Mg levels when compared to somatic motor terminals. Interestingly, pupillary responses are often lost in other pre-synaptic NMJ disorders such as boutilism and Lambert-Eaton myasthenic syndrome. In case 2 the preserved pupillary responses were to be expected, given that Mg was given at therapeutic doses, and the additional effect of the ACh-receptor antibodies are limited to skeletal muscle.

NMJ dysfunction should be suspected in peri-partum women treated with Mg, who develop flaccid paralysis mimicking coma. Although extremely high Mg levels may abolish pupillary responses, their presence, even if somewhat reduced, in the absence of a VOR, is an important clinical clue.

Table 1
Pupillary responses previously reported at a range of serum magnesium levels

<table>
<thead>
<tr>
<th>Peak serum Mg Levels</th>
<th>Pupillary Response</th>
<th>Somatic Muscles</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.96 to 3.08 mmol/L (4.7 to 7.4 mg/dL)</td>
<td>Present (normal or slightly reduced, average reduction from 1.1 mm to 0.5 mm*)</td>
<td>Presumable normal but not mentioned explicitly (therapeutic dose)</td>
</tr>
<tr>
<td>4.1 mmol/L – (Case 2 presented here)</td>
<td>Present (magnitude not evaluated)</td>
<td>Complete paralysis including absent brainstem reflexes **</td>
</tr>
<tr>
<td>5.73 mmol/L</td>
<td>Present (magnitude not evaluated)</td>
<td>Failure to wake up, no explicit mention of somatic evaluation</td>
</tr>
<tr>
<td>9.5 mmol/L</td>
<td>Present, estimated as reduction from 5mm to 3mm</td>
<td>Complete paralysis including absent brainstem reflexes</td>
</tr>
<tr>
<td>9.85 mmol/L</td>
<td>Absent. No response - pupils fixed and dilated (6mm)</td>
<td>Complete paralysis including absent brainstem reflexes</td>
</tr>
</tbody>
</table>

* This is the only study where the response was measured by neuro-ophthalmologists. The others are bedside evaluations by neurologists.

** Combined effect of Mg with myasthenia gravis (Case 2 presented above)
References:


Figure 1- Repetitive nerve stimulation of the two patients showing decremental response at 3Hz:
Decremental response of 22% in patient 1 (A) and 48% in patient 2 (B) on repetitive nerve stimulation (RNS) during symptomatic weakness. RNS was performed on patient 1 after one dose of calcium gluconate and on patient 2 after resolution of magnesium toxicity, but before initiating treatment for myasthenia gravis. Testing was performed at 3 Hz in both cases and 1st and 4th responses were compared to obtain % decrement
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