UNUSUAL CAUSE OF SEIZURES
5 yr old child presented with
- h/o spasm of arms and legs-3 mths
- h/o one episode of up rolling of eyes with carpopedal spasm one month back
- Child was evaluated and treated for hypocalcemia
- 3rd born to 3rd degree consanguineous parents
- Evaluated for IEM-reported normal
- h/o 2 sibling deaths due to seizures-unknown etiology
  - NO significant neonatal event
One year of age - 3 episodes of seizures and tetany

Development-normal

EEG abnormal, phenobarbitone till 2 yrs

Calcium and magnesium continued. Magnesium stopped 1 mth ago and now child developed seizures.
O/E:
- Conscious, obeying commands
- Chvostek sign+
- Carpopedal spasm+
- Wt-14kg(<3rd centile)
- Ht-110 cm(50th centile)
- Systemic examination normal
<table>
<thead>
<tr>
<th></th>
<th>15/1/13</th>
<th>17/1/13</th>
<th>18/1/13</th>
<th>19/1/13</th>
<th>20/1/13</th>
<th>22/1/13</th>
<th>24/1/13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca</td>
<td>5.9(ionised 0.658)</td>
<td>4.8(ionised 0.411)</td>
<td>7.6</td>
<td>8.4</td>
<td>9.4</td>
<td>8.7</td>
<td>8.4</td>
</tr>
<tr>
<td>Mg</td>
<td>0.4</td>
<td>0.8</td>
<td>1.3</td>
<td>1.1</td>
<td>1.5</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>PTH</td>
<td>5.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td>116.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALP</td>
<td>89</td>
<td>91</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphorus</td>
<td>5.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.4</td>
</tr>
</tbody>
</table>
Following IV calcium gluconate and magnesium supplementation, carpopedal spasms resolved after 6 hrs.
- FeMg < 2% (<1% pre renal, >2% - ATN)
- 24 hrs urine calcium - 35 mg/day
- Spot urine Mg/creat - 0.3 (N)
- Spot urine calcium/creat - 1 (N)
Child was treated for low calcium with Inj calcium gluconate and magnesium sulphate for hypomagnesemia

- Inspite of correction his magnesium levels continued to be low
- Genetic analysis of the child is being planned.
DISCUSSION
Hypomagnesemia

- Hypomagnesemia is defined as serum magnesium level less than 1.8 mg/dl (0.74 mmol/litre).
- Hypomagnesemia can be due to:
  - Increased gastrointestinal or renal losses
  - Redistribution from extracellular to intracellular space
CAUSES

- Transient
- Transient neonatal hypomagnesemia
- PEM particularly with diarrhea

- Permanent:
  - Usually deficient intake alone does not lead to apparent clinical symptoms. Renal magnesium wasting and/or intestinal magnesium malabsorption
HYPOMAGNESEMIA

- Whenever a child with tetany does not improve with IV calcium, consider hypomagnesemia as the cause

Cause:
- Nutritional inadequacy (PEM particularly with diarrhea)
- GI diseases
- Excessive renal wasting

Ca, P, MG
Three elements
PERMANENT:

- Usually deficient intake alone does not lead to apparent clinical symptoms, because of efficient renal conservation
- Renal magnesium wasting and/or intestinal magnesium malabsorption are the causes. Mostly familial

1. Isolated Recessive Hypomagnesemia With Normocalciuria
2. Autosomal Dominant Hypomagnesemia With Hypocalciuria
3. Hypomagnesemia With Secondary Hypocalcemia
4. Gitelman syndrome
5. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) - autosomal recessive disorder
• 30 to 50% of dietary magnesium is absorbed
• Small intestine is the major site of magnesium absorption
• There is passive absorption which is directly proportional to the intake
• Absorption is decreased in the presence of substances which complex with magnesium (phytates, phosphates, oxalates, free fatty acids). Calcium decreases Mg absorption.
- Calcium decreases magnesium absorption
- Vitamin D and PTH are said to increase magnesium absorption
• Renal excretion is the principal regulator of magnesium balance
• 15% of absorption occurs in the proximal tubule and 70% occurs in the ascending limb of loop of Henle
• High magnesium levels inhibit resorption in TAL
• 5-10% of filtered magnesium is resorbed in the distal tubule
SYMPTOMS

- Neuromuscular manifestations
- Tremors
- Chvostek sign and Trousseau sign
- Seizures
- Tetany
CARDIOVASCULAR MANIFESTATION

- Widening of QRS complex
- Prolonged PR interval
- Ventricular arrhythmias
- Enhanced digitalis toxicity
- Peaked T waves (moderate Mg deficiency)
METABOLIC

- Hypokalemia
- Hypocalcemia
- Reversible respiratory muscle failure in severe cases
**HYPOMAGNESESEMIA**

- Transient neonatal hypomagnesemia is common due to IUGR, IDM, following exchange transfusion.
- Permanent – defective intestinal absorption
- Requirement: 35 mg/ day upto 6 mo
- 75 mg/ day beyond 6 mo
- Because of efficient renal conservation, low intake alone does not cause clinically apparent Mg deficiency.
- Source: whole grains, beans, legumes, all green leafy vegetables (component of chlorophyll) milk, egg and meat.
<table>
<thead>
<tr>
<th>CAUSES</th>
<th>Renal</th>
<th>Endocrine</th>
<th>Metabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>inherited</td>
<td>acquired</td>
<td>Hyperaldosteronism</td>
</tr>
<tr>
<td></td>
<td>Gitelmans diuresis</td>
<td>Postobstructive</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td></td>
<td>Bartters</td>
<td>SIADH</td>
<td>Hypoparathyroidism</td>
</tr>
<tr>
<td></td>
<td>Familial Hypomagnesiemia With Hypercalciuria</td>
<td>Loop and thiazide diuretics</td>
<td>Excess vit D</td>
</tr>
</tbody>
</table>
GENETIC CAUSES

- Hypomagnesemia with secondary hypocalcemia
- Autosomal recessive disorder
- Usually manifests in the newborn period with restlessness, tetany, tremors
- Hypokalemia is occasionally present, corrected on Mg correction.
- Double intestinal and renal transport defect
- Genetic linkage to chromosome 9q22
- Mutations in a new gene TRPM6, highly expressed in intestinal epithelia and kidney tubules
- Isolated Familial hypomagnesemia
- Congenital impairment of renal tubular absorption
- Varying spectrum of presentation
- Absence of hypokalemia or nephrocalcinosis
- Autosomal dominant or autosomal recessive inheritance
Autosomal recessive form is a distinct entity
Autosomal dominant form may manifest with hypocalciuria and mild hypomagnesemia
Dominant negative mutations in FXDY2 gene
This encodes Na k ATPase subunit
HYPOMAGNESEMA WITH HYPERCALCIURIA

- Autosomal recessive disorder
- Nephrocalcinosis is a cardinal feature
- Ocular abnormalities like horizontal nystagmus, chorioretinal abnormalities present
- In contrast to Gitelmans syndrome metabolic acidosis is present
- Defective tubular reabsorption of Ca and Mg in TAL
- Mutations in CLDN16 gene identified
First step is to measure fractional excretion of magnesium and calcium creatinine ratio

\[ \text{FeMg} = \frac{\text{urine mg} \times \text{serum creatinine}}{0.7 \times (\text{serum magnesium} \times \text{urine creatinine})} \times 100 \]

- \( \text{FeMg} < 2 \) indicates poor intake, gastrointestinal losses or intracellular shift
- \( \text{FeMg} > 4 \) indicates renal magnesium wasting
Demonstration of reduced excretion of infused Mg load (2.4 mg/kg of lean body wt over 4 hrs)

- Reduced excretion is less than 80% of infused load excreted over 24 hrs
- Patients with malnutrition, cirrhosis or long term diuretic use typically have a positive test
The route of magnesium supplementation varies with the clinical manifestations. Children with severe manifestations should receive 50 meq of MgSO₄ over 8 to 24 hours. This dose can be repeated to maintain plasma magnesium above 1 mg/dL. Oral replacement in an asymptomatic patient is also possible.
Urinary magnesium wasting is initially associated with excretion exceeding intake. As plasma magnesium concentration falls, Mg excretion is gradually lowered. Correcting hypomagnesemia with Mg supplements will partial remove the stimulus to Mg retention. Addition of a potassium sparing diuretic will lower Mg excretion.
- Oral replacement in an asymptomatic patient preferably a sustained release preparation
- Tablets containing MgCl and MgSO4 provide 5-7 meq of magnesium per tablet
- Six to eight tablets should be taken daily in divided doses for severe Mg depletion
- Two to four tablets sufficient for mild asymptomatic disease
mutations in the CLDN16 gene have been identified in patients with familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC), a disease of excessive renal Mg2+ and Ca2+ excretion.
Calcitriol is needed because hypomagnesemia results in decreased production and resistance to the actions of active vitamin D, which leads to the disturbance of intracellular signal transmission. Although high-dose oral Mg is reported as a sufficient therapy in most of the patients with primary familial hypomagnesemia, addition of active vitamin D to the usual oral Mg and Ca therapy seems very useful, as in this patient.
- GI malabsorption
- Renal wasting
CALCIMAX SUSP oral susp: calcium carbonate 625 mg, magnesium hydroxide 180 mg, zinc gluconate 14 mg, vitamin E 200 IU.
- GI causes
  - Inadequate intake
  - Refeeding syndrome
  - Hungry bone syndrome
  - Chronic diarrhea