HYPOMAGNESEMIA AND HYPERMAGNESEMIA

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The body of the adult human contains about 2000 mEq of magnesium with half of it in the skeleton and the other half in soft tissues (1). The concentration of magnesium is highest (15 to 20 mEq/kg wet weight) in the cells of the liver and striated muscles. The normal concentration of magnesium in plasma ranges between 1.5 and 2.0 mEq/1; about 20 to 30% of magnesium in blood is bound to protein and the rest (75 ± 9%) (SD) is present in a diffusible form (2, 3). The kidney appears to play a paramount role in maintaining the plasma levels of magnesium within a narrow limit (4). Indeed, oral or intravenous loads of magnesium are rapidly excreted (5, 6) and in the magnesium deficient state or with rigid dietary restriction, magnesium almost disappears from the urine (7, 8).

HYPOMAGNESEMIA

By definition, magnesium deficiency indicates a decrease in the total content of body magnesium. Because of the remarkable ability of the normal kidney to conserve magnesium, poor dietary intake of this ion is usually not associated with a deficient state. However, prolonged and severe dietary restriction of magnesium (<1 mEq/day) can cause symptomatic magnesium deficiency in humans (9); this is produced by the renal and fecal obligatory losses that slightly exceed the low intake. In disease states, the major factors underlying the pathogenesis of magnesium deficiency are excessive magnesium losses in the urine, feces and other body fluids and lack of intestinal absorption. The disease states and clinical entities that may be associated with hypomagnesemia and magnesium deficiency are listed in Table 1.

Although marked hypomagnesemia is usually present in states of magnesium deficiency, changes in the concentration of magnesium in the plasma do not always reflect alterations in body magnesium. Metabolic studies in human fed a diet deficient in magnesium for more than 20 days maintained normal plasma magnesium despite a negative balance of 42 to 72 mEq of magnesium (8). Furthermore, after the administration of large doses of vitamin D, hypomagnesemia may appear without detectable decrease in intracellular magnesium. Finally, a diminished magnesium content in muscle has been reported in patients with advanced uremia, despite normal or elevated levels of magnesium in blood (10).

It appears, therefore, that the diagnosis of magnesium deficiency could not always be made by measuring plasma levels of magnesium. Other measures have been used to assist in the diagnosis of magnesium deficiency. These include the concentration of magnesium in erythrocytes, magnesium content of muscle, body-exchangeable magnesium and magnesium balance (11). However, these methods are either difficult to perform or do not provide a good index of the state of body magnesium. The fate of an intravenous load of magnesium may help in the diagnosis of magnesium depletion (8). Normal subjects excrete almost all the parenterally administered magnesium within 24–48 hours, while subjects with magnesium deficiency may retain more

Table 1. Clinical states associated with hypomagnesemia and/or magnesium depletion.

1. Decreased intake
   - Protein-calorie malnutrition
   - Starvation
   - Prolonged intravenous therapy

2. Decreased intestinal absorption
   - Malabsorption syndromes including nontropical sprue
   - Massive surgical resection of small intestine
   - Neonatal hypomagnesemia with selective malabsorption of magnesium

3. Excessive losses of body fluids
   - Prolonged nasogastric suction
   - Excessive use of purgatives
   - Intestinal and biliary fistulas
   - Severe and chronic diarrhea as in ulcerative colitis and infantile gastroenteritis
   - Rarely, prolonged lactation

4. Excessive urinary losses
   - Diuretic therapy
   - Diuretic phase of acute renal failure
   - Chronic alcoholism
   - Primary aldosteronism
   - Hyperparathyroidism
   - Malignancy, hyperparathyroidism, or vitamin D intoxication
   - Renal tubular acidosis
   - Diabetes mellitus, especially during and following treatment of ketoacidosis
   - Hyperthyroidism
   - Chronic renal failure with magnesium wasting
   - Aminoglycoside toxicity
   - Administration of Ca-platinum

5. Miscellaneous
   - Idiopathic hypomagnesemia
   - Acute pancreatitis
   - Porphyria with inappropriate secretion of antidiuretic hormone
   - Multiple transfusions or exchange transfusion with citrated blood

than 20% of the intravenous load of magnesium. Thus, the retention of intravenously administered magnesium is consistent with magnesium deficiency (12) even in the presence of normal plasma concentration of magnesium. This test is valid only when renal function is normal and when magnesium depletion is not due to inability of the kidney to conserve magnesium.

Symptomatic hypomagnesemia or magnesium depletion requires therapy. Thus, the recognition of the manifestations of this entity is important for the institution of the proper treatment. The signs and symptoms of magnesium depletion are usually mixed with, and sometimes masked by, the clinical manifestations of the basic disorders which caused the magnesium deficient state. The main clinical manifestations of magnesium depletion include neuromuscular disturbances and behavioral abnormalities. These, as well as, the laboratory findings are listed in Table 2.

Table 2. Clinical manifestations and laboratory findings of magnesium deficiency.

1. Clinical manifestations
   - Anorexia, nausea, weakness and apathy
   - Muscular fibrillation
   - Tremors
   - Ataxia
   - Vertigo
   - Carpopedal spasms
   - Frank tetany
   - Hyperreflexia, occasionally hyporeflexia
   - Depression
   - Irritability
   - Psychotic behavior

2. Laboratory findings
   - Hypomagnesemia, hypocalcemia, hypokalemia
   - Hypophosphatemia, occasionally hyperphosphatemia
   - Low magnesium in cerebrospinal fluid
   - Electrocardiogram may show:
     - Prolonged QT
     - Broadening and decreased amplitude of T waves
     - Occasional shortening of ST segment
   - Electromyogram may show myopathic-like potentials

Magnesium deficiency is managed by replacement with magnesium salts. Since the magnitude of the deficit is not easy to estimate, the planning of the replacement therapy is usually empirical. A deficit of 1 to 2 mEq/kg body weight may exist in the presence of marked hypomagnesemia (plasma level of <1.0 mEq/l). The amount of magnesium required will be twice the estimated deficit, since about 50% of the administered magnesium will be lost in the urine even when marked deficiency of this ion exists. Magnesium sulfate (MgSO4. 7 H2O) is usually used for the parenteral therapy. The molecular weight for this hydrated compound is 246.5 and each gram of the salt contains 8.12 mEq of magnesium. Usually about 40–50% of the deficit is given in the first day of therapy and the rest in divided doses during the following 2 to 4 days. In patients with normal renal function, 50 mEq of magnesium may be given intramuscularly over 4 to 6 h and the intravenous dose should not exceed 100 mEq/12 h, or 16 mEq of magnesium intravenously every 2–4 h during the first day of treatment. Frequent measurement of plasma magnesium concentration during the administration of this ion is advised. The dosage of magnesium should be substantially reduced in patients with renal failure and serial monitoring of serum magnesium is mandatory in these patients. A clinical finding that may help recognize the development of hypermagnesemia during such therapy is the loss of deep tendon reflexes which usually occurs when plasma magnesium concentrations exceed 6.0 mEq/l.

An attempt should be made to identify the disease state which has led to the magnesium deficient states and if possible, to treat the underlying cause. Also, an effort should be made to prevent magnesium depletion in any clinical setting which may predispose to its development. For example, in patients who require prolonged gastric suction, or in those who need prolonged intravenous fluid therapy, daily supplement of 10 to 15 mEq of magnesium could prevent magnesium depletion. Magnesium supplement should also be considered in patients undergoing marked diuresis following the relief of urinary tract obstruction.

HYPERMAGNESEMIA

Elevated plasma levels of magnesium are encountered in patients with acute (13, 14) and chronic renal failure (3, 15), during the administration of pharmacologic doses of magnesium, in some infants born to mothers who had been treated with magnesium for eclampsia (16) and during the use of oral purgatives or rectal enemas containing magnesium (17, 18). Mild hypermagnesemia may be seen in patients with adrenal insufficiency (19), and in those with familial hypocalciuric hypercalcemia (20). Since the kidney is the main organ responsible for the maintenance of plasma magnesium level within the normal range, extreme caution should be exercised with the use of magnesium-containing medications to patients with impaired renal function. In clinical practice, acute or chronic renal failure is the clinical setting in which hazardous hypermagnesemia may be encountered.

The signs and symptoms of hypermagnesemia are the results of the pharmacological effect of this ion on the nervous and cardiovascular systems. Deep tendon reflexes are usually lost when plasma magnesium level exceeds 6.0 mEq/l. Respiratory paralysis, narcosis, hypotension, and abnormal cardiac conduction may develop as plasma levels of magnesium approach 10 mEq/l.

The initial mandatory steps in the management of symptomatic hypermagnesemia include cessation of magnesium administration and intravenous injection of calcium salts. The administration of 5 to 10 mEq (100–200 mg) of calcium ion may be adequate to reverse the manifestations of hypermagnesemia, although greater amounts may be needed. On occasion, peritoneal or even hemodialysis with magnesium free dialysate may be needed to control severe hypermagnesemia. In patients who develop respiratory paralysis, artificial respiration should be used until the plasma concentration of magnesium in lowered.