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Latent Tetany And Anxiety, Marginal Magnesium Deficit, And Normocalcemia

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Abstract

The identification of marginal magnesium deficit, such as we have detected in a patient with anxiety, depression, and psychomatic complaints, is a difficult diagnostic problem. Electromyography of a limb, rendered acutely ischemic either just before or after hyperventilation, can elicit latent tetany in this condition, as well as in calcium deficiency. We have demonstrated iterative electrical activity in our patient, whose magnesium deficit is attributable to renal wasting of magnesium. We have elicited similar patterns in several other patients, who had marginally low serum magnesium and who also exhibited weakness, anxiety, and psychosomatic disorders. This preliminary report suggests the need for further consideration of the possibility that chronic magnesium-deficit may contribute to the syndrome of latent tetany, psychosomatic complaints, and weakness.

Electromyographic evidence of latent tetany has been observed in some patients with marginal magnesium deficit, whose multiple ill-defined complaints may be mistaken for psychoneurosis.[1-7] Deficiency of magnesium, which is predominantly an intracellular cation, is not often diagnosed in this country unless the depletion is so severe as to cause symptoms referable to overt tetany, or metabolic encephalopathy, or both. This form of encephalopathy has been clearly related to lowered brain and cerebrospinal levels of magnesium in magnesium-derived rats by Chutkow and his colleagues.[8,9,10]

Since 1958, however, lesser degrees of magnesium deficit (associated with a neuromuscular syndrome) have been reported by Rosselle[1,2] as "cryptotetany", and by Durlach[3-7] as "spasmophilia." Although some patients with this syndrome exhibit slightly depressed levels of serum magnesium, low erythrocyte levels have been reported to occur more consistently.[5,6,7] This syndrome, which occurs more frequently in women than in men, is accompanied by many psychosomatic complaints. The physical examination is usually normal (or non-contributory). The electrocardiogram sometimes exhibits ventricular premature contraction or mildly abnormal final deflections. The conventional electromyogram is normal. However, hyperventilation, and ischemia of the tested muscle, produce iterative electrical activity. We have not found reference to this syndrome in the English language literature since Rosselle's and Durlach's monographs,[1-7] although there have been numerous publications in French and Italian language journals (over 30 citations by Durlach in his 1969 monograph[7]). Recently we diagnosed this condition in a postmenopausal woman.[11]

Case Report and Methods

SLB, a 57-year-old woman of Italian ancestry, was hospitalized because of weakness, depression, anxiety, "spots before the eyes", generalized pruritus, swelling of the lower extremities and puffiness around her eyes and mouth. This clinical picture, which also included occasional dyspnea and precordial pain, gastrointestinal complaints, without detectable organic cause, had persisted for over two years. Cardiologic examination was normal, psychiatric evaluation indicated only depressive anxiety, which yielded partially and temporarily to treatment, with diazepam and amitryptoline. Although skin testing showed no specific allergy, use of antihistamine therapy has been necessary for control of pruritus. The similarity of her clinical picture to that described as "cryptotetany" or "spasmophilia"[1-7] led to investigation of her magnesium status (details described elsewhere[11]). Her initial serum magnesium level was found to be marginally low (1.67 mEq/L), by the range accepted as normal in the hospital laboratory (1.9-2.5).[13] Conventional nerve conduction tests and EMGs had been found normal, but EMG studies (by a technique modified from that employed by Rosselle[1,2] and Durlach[3-7]) elicited iterative activity.* After about three minutes (two minutes of hyperventilation, followed by one minute of ischemia) single motor unit of discharges appeared, firing at a relatively slow rate (two to three per second). At this time, there were no visible muscle twitchings or spasms. Within the next 15-30 seconds, motor unit activity increased in frequency, and the sounds characteristic of visually recorded

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*The typical patterns of increased electrical activity are described[1] as (1) repetitive potentials of one or more motor units, with repetitive discharges (2-8 times) at frequency of 125 to 250 per second, termed doublets, triplets, quadriplets or multiplets, (2) spontaneous discharges of a motor unit of high frequency (4-12 per second) during slight involuntary contraction. Rosselle[1] interprets the EMG as positive if regular repetitive activity persists for at least two minutes during the post-ischemic phase or after hyperpnea.[1] If the modification is used, the patient hyperventilates before ischemia is induced (See Appendix).

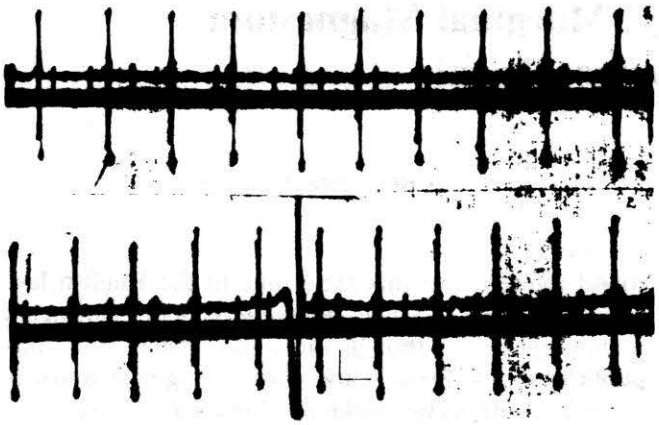

Figure 1: Doublets from abductor pollicis brevis after two minutes of hyperventilation followed by 1.5 minutes of ischemia. Calibration signifies 100 ms and 100 uV.

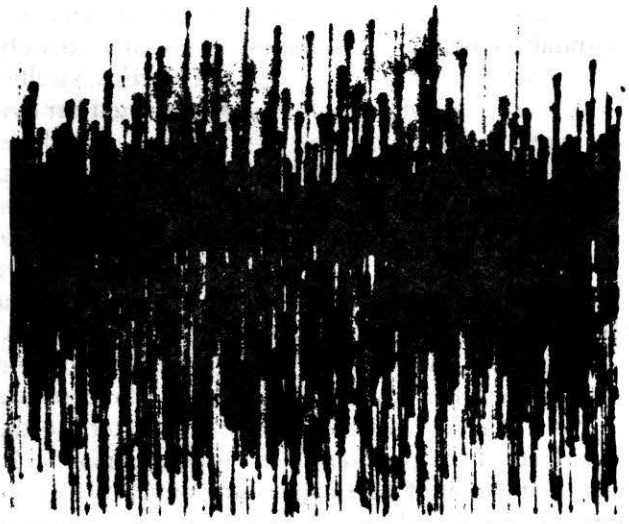

Figure 2: Complete interference patterns recorded simultaneously from abductor pollicis brevis and abductor digiti quinti after 2.5 minutes of ischemia.

doublets and triplets could be heard. (Fig. 1).

During the following 60 seconds, the activity increased to such an extent that a complete interference pattern was recorded (Fig. 2) and at the same time marked wrist and finger spasm were evident. These contractions were completely involuntary. With release of the cuff after only two and a half minutes of ischemia, all electrical activity disappeared within 30 seconds.

The next day, to test for magnesium deficit, the patient was given an intramuscular injection of 2 ml of a 50% of solution of magnesium sulphate (to test for percentage retention of magnesium).[11,12] She retained over 60% of the parenterally administered magnesium, in contrast to the normal retention of 15-20%.[11,12]

Within two hours of the injection she experienced marked relief of all of her symptoms. In the course of her hospitalization the patient had received many other injections, none of which had evoked the clinical improvement experienced following the injection of magnesium. The EMG, taken shortly thereafter, was normal and repetitive firing and spasm could not be provoked by hyperventilation, followed by ischemia for 10 minutes.

For several weeks, thereafter, she received oral magnesium supplements, and it was possible to decrease the use of antihistamine and diazepam. However, a month later, the intensity of her complaints completely returned, and she obtained brief (1-2 day) periods of relief only after intramuscular injections of magnesium. Placebo injections produced no clinical change. Rehospitalization, on several occasions, for metabolic and hormone studies, revealed that she was a renal magnesium waster, and that she had intermittent normotensive aldosteronism, with peripheral edema and sodium retention.[11] Her serum magnesium level usually remained below 1.7 mEq/L, serum calcium was normal (9.5-9.7 mg%). Serum magnesium values of 2.1 mEq were reached after repeated intravenous or intramuscular injections of magnesium. On one such occasion, her hyperventilation/ischemia EMG did not revert to normal, even when tested while she was receiving an intravenous infusion of 200 ml of dextrose and water, to which 2 ml of magnesium sulphate had been added. Her symptoms improved the next day, after a second magnesium-infusion. Two hours after completion of the second infusion, her EMG was normal.

Discussion

Our patient with the abnormal hyperventilation/ischemic EMG pattern and carpal spasm, and those described in Europe,[1-7] all had marginal magnesium deficit.* Similar signs are also seen with hypocalcemic latent tetany.[14,15,16] However, Roselle[1,2] and Durlach[3-7] have reported that their patients had similar clinical and electrical phenomena with magnesium deficit, in the absence of hypocalcemia. Similarly, our patient showed these findings with marginally low serum magnesium levels, but normal serum calcium levels.

*We have subsequently obtained similar electrical findings on three additional patients without neuromuscular disease. In two, the hyperventilation/ischemia EMG was found abnormal after the diagnosis of magnesium deficit had been made on the basis of serum magnesium levels of 1.1-1.4 mEq/L and multiple psychosomatic and neuromuscular complaints. In another, the hyperventilation/ischemia test was employed because of the patient's bizarre neuromuscular complaints. When strongly positive EMG results were elicited, his serum electrolytes were analyzed. He was normocalcemic, but his serum Mg was 1.5 mEq/L. To evaluate the significance of these patients' neuromuscular irritability, as demonstrated by electromyography following hyperventilation and ischemia, we tested ten normal volunteers, who did not have neuromuscular or psychiatric abnormalities. Magnesium serum levels, which were done only in five, were within normal limits. None exhibited the EMG pattern described here, even when the post-hyperventilation ischemia was maintained for ten minutes.

Although hypocalcemia and hypomagnesemia each causes clinically manifest neuromuscular irritability and electromyographic abnormalities, such as are reported here, nerve physiology studies indicate that the mechanisms are not the same. Chutkow[17] has reviewed the evidence and points out that, although magnesium depletion has electrophysiologic effects on nerve axons similar to those of calcium depletion, the calcium effect far outweighs the magnesium effect at this site. Calcium is principally involved in nerve membrane potential and stability; depressive effect of hypercalcemia is caused by nerve membrane hyperpolarization, decreased sodium conductance, and resultant elevation of the depolarization threshold. With hypocalcemia there is an increase in depolarization that allows for response to slow depolarization and loss of accommodation,[21,22] as a result of which peripheral nerves discharge independently.[23]

When a nerve impulse reaches the skeletal myoneural junction, the resultant depolarization of the nerve endings releases acetyl choline (ACh) into the synaptic space.[24,25] ACh molecules then diffuse across the synaptic cleft and attach to specific receptors of the specialized area in the postsynaptic sarcolemma, which results in non-specific increased ionic permeability, flow of an ionic current, and depolarization (the end plate potential). When this depolarization reaches the excitation threshold of the adjacent sarcolemma, a muscle action potential develops, that ultimately initiates the muscle contraction. Magnesium exerts its major neuromuscular effects at the myoneural junction.[17,24-30] At this site, calcium and magnesium are antagonistic.[25,28,29,30,31]

Calcium enhances, and magnesium inhibits, the release of ACh. Additionally, the sensitivity of the motor end plate is diminished by high magnesium concentrations,[25] such high concentrations also having cholinesterase-activating effects.[32,33] Thus, hypocalcemia exerts two paradoxical effects: it increases peripheral nerve excitability, but it decreases release of the neurotransmitter (ACh) into the myoneural synaptic space. We postulate that the hypocalcemia-induced suppression of neuromuscular transmission may be overcome by the increased presence of ACh resulting from magnesium deficit. Increased transmitter augments the tendency towards repetitive sarcolemmal depolarization and muscle contraction.*

Since either hypocalcemia or hypomagnesemia can elicit similar abnormal hyperventilation/ischemia EMG patterns, both cautions must be measured to elucidate the specific deficit. The patients described here, and those reported earlier,[1-7] all had marginally low serum magnesium and normal serum calcium levels. In our group, we rarely saw serum magnesium levels below 1.5 mEq/L.

In view of our patient's latent tetany and neuropsychiatric manifestations, the findings of Chutkow et al[8,9,10] may have special relevance. They demonstrated that rats with acute, subacute or chronic magnesium-deficiency exhibit decreased brain and cerebrospinal fluid magnesium levels, not necessarily closely related with changes in blood levels of magnesium. They found that even small decreases in brain magnesium are accompanied by marked alterations in brain excitability.[10] Whether the slight electroencephalographic abnormalities of our patient, elicited only during hyperventilation, reflect a magnesium-deficit encephalopathy, remains to be proved.

Chutkow and Grabow[10] also commented on the histamine-release of magnesium-deprivation,[36,37] an important point in terms of the evidence that histamine may be a central neurotransmitter.[10] Note should be made, here, that one of our patient's most distressing complaints is generalized pruritus, and that her requirement for antihistamine therapy exceeds the amount tolerated by most subjects.

Worth mentioning, also, is the fact that 75% of Roselle's patients with latent tetany of magnesium-deficiency improved on treatment with thyroxine.[1] This is a provocative finding, since thyroid hormone affects protein-binding of magnesium; its influence on the ratio of free to bound magnesium is not definitely established.[38] Before instituting this therapeutic approach in our patient, who has thyroid function at the low limit of the normal range, we considered the similarity of some of her findings to those of some patients with periodic paralysis or weakness, who also have intermittent aldosteronism, and who exhibit exacerbations in response to administration of salt.[39,40] In this context, we must recall that some patients with periodic paralysis have responded favorably to thyroid administration or stimulation, and have experienced recurrence of weakness or withdrawal of thyroid therapy,[41] whereas others have periodic paralysis in association with hyperthyroidism.[41,42] Whether our patient, who also suffers from marked weakness, presents another facet of hypokalemic periodic paralysis (magnesium deficit being known to predispose to loss of muscle potassium, and to prevent its repletion)[43,44] requires further elucidation.

Remaining to be explored is the relationship of such patients' multiple neuropsychiatric complaints with a possible metabolic encephalopathy, that may be caused by chronic magnesium deficit.[8,9,10] Study of cerebrospinal fluid levels of magnesium, during phases of exacerbation and remission, possibly in association with metabolic balance data obtained during magnesium

*Combined deficits give rise to severe forms of neuromuscular irritability. Whether the convulsions of infantile hypomagnesemic hypocalcemia, that are refractory to treatment until both deficits are corrected,[34,35] are relevant to the clinical tetany that is the subject of this paper is moot. What happens at the myoneural junction in response to calcium and magnesium may differ from what happens in the central synapses.

supplementation and restriction, may provide valuable insight into the syndrome described here.

APPENDIX

1. The subject, lying completely relaxed on a comfortable couch, is instructed not to move the hand or arm (to eliminate voluntary contraction of the muscles of the limb being tested) throughout the entire test procedure. A blood-pressure cuff is wrapped around the upper arm.
2. A teflon-coated monopolar needle electrode is inserted into the abductor digiti quinti being tested and a surface electrode is taped over the insertion of this muscle. A similar pair of electrodes is employed to record from the ipsilateral abductor pollicis brevis muscle. The electrical activity from both muscles is displayed simultaneously on two channels of a Teca TE-4, with constant monitoring on fiberoptic readout.
3. After determining whether there is electrical activity at rest, the patient is asked to hyperventilate for two minutes. Then the cuff is inflated to about 20 mm Hg above the pressure which obliterates the radial pulse. If spontaneous discharge occurs early, pressure is maintained for two minutes, to allow for development of the interference pattern. (A pattern of electrical activity produced when numerous motor units are active so that their action potential can no longer be identified individually). Pressure should not be maintained longer than ten minutes.

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