REVIEW

Review and Hypothesis: Might Patients with the Chronic Fatigue Syndrome Have Latent Tetany of Magnesium Deficiency

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ABSTRACT. The latent tetany syndrome (LTS) parallels CFS in its neuromuscular and psychiatric manifestations, as well as in inner ear disturbances: vestibular in CFS and FM, as well as in LTS, and increased vulnerability to noise-induced deafness in LTS. Microvascular damage to the cochlea is seen in Mg deficiency, noise-induced deafness, and might be a

factor in migraine and other severe headaches in both LTS and in CFS and FM. Abnormal sleep patterns occur in both LTS and CFS; impaired cognition more in CFS than in LTS. However, some brain and neurotransmitter dysfunctions seen with Mg deficiency might be contributory to cognitive disorders of CFS. Mg loss caused by enhanced catecholamine release produced by stress may well be contributory to stress-induced acute episodes of CFS. Malfunctions of the cellular and humoral immunological systems are caused by experimental Mg deficiency. Whether allergies in CFS patients and abnormal response to antigenic challenge are results of low Mg remains to be proven. Mitral valve prolapse is seen in many LTS and CFS patients; whether a putative Mg deficiency predisposes to this abnormality is not known. Clinical improvement with Mg treatment has been proven in LTS, and seemed helpful in the rare cases of CFS and FM in whom it has been tried. The Mg status should be determined in patient with CFS and FM, but methodology is a handicap. Serum Mg is an inaccurate index. Three methods show promise. Percentage retention of a Mg load is accurate but requires patient's cooperation. Free ionic Mg measurement requires ion-selective electrodes. Blood cell Mg is reliable in a little more than half the patients; sublingual cell Mg seems more accurate. More intensive, and controlled studies of the Mg status of CFS and FM patients, and of their response to Mg therapy is desirable. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: getinfo@haworthpressinc.com]*

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INTRODUCTION

Chronic fatigue syndrome (CFS) is widely recognized, is of uncertain etiology (1), and has created diagnostic confusion for centuries (2,3). Numerous environmental, metabolic, infectious, immunologic, and psychiatric disturbances have been implicated in the many complaints. When the syndrome was found to be associated with abnormal immunologic responses to infection, it was termed postinfectious neuromyasthenia, chronic virus infection, myalgic encephalomyelitis, "chronic fatigue immune dysfunction syndrome" (CFIDS), and fibromyalgia (FM) (1-9). Possibly pertinent to such disturbances are the abnormal immunologic findings in Mg deficiency (10- 13). There are many parallels in clinical manifestations and

dysfunctions in the latent tetany syndrome (LTS) of marginal magnesium (Mg) deficiency, and those of CFS, an observation made in 1992 (14), following publication of a small study that reported low erythrocyte Mg levels in patients with CFS and their favorable response to a six-week trial of weekly intramuscular Mg injections in most of them (15). Chronic fatigue, weakness, depression and anxiety, sleep disturbances, paresthesias and sensorineural hearing loss, as well as neuromuscular irritability and myalgias have long been known to respond to long-term Mg supplementation (16-21). That stress commonly precedes acute CFS events is another indication that Mg inadequacy might be a factor, because stress hormones cause Mg loss, and low Mg levels increase secretion of catecholamines (22,23). A few reports of CFS and FM improvement with Mg administration support the premise that low Mg or abnormality in its utilization might be contributory to their pathogenesis. Thus, it is important to determine the Mg status in CFS and FM, a need which has created difficulties because of methodological problems. Diagnostic tests to determine whether Mg deficiency exists, should allow for documentation of the possible value of Mg treatment in these conditions. Serum Mg levels, the easiest to measure, are least reliable (unless an ion-selective electrode is used to measure physiologically active free ionic Mg) since most Mg is intracellular. Mg levels in blood cells or sublingual cells have provided better results, and percentage retention of a Mg load has been accurate, but cumbersome. Carefully controlled, large clinical trials, with measurement of the Mg status before, during and after Mg supplementation, might clarify the pathogenesis, as well as providing a new therapeutic approach to those patients with CFS who have low Mg levels.

NEUROMUSCULAR AND PSYCHIATRIC CLINICAL SIGNS OF LTS, CFS, AND FM, AND RESPONSE TO MAGNESIUM THERAPY: MUSCLE SYMPTOMS AND SIGNS

LTS: Muscle weakness, fatigue, and pain (aching and/or cramps with spasms or tetany) characterize LTS patients, in whom Mg deficiency has been identified. Abnormal electrical activity of muscles, elicited by electromyographic (EMG) recordings under conditions of ischemia (induced with a blood pressure cuff), has long been recognized as a diagnostic finding in LTS, in which marginally low serum Mg, but more consistently, low red blood cell (rbc) levels are seen. First identified in Belgium and France almost forty years ago, it was termed "cryptotetany" or "spasmophilia" (24-

26). This condition has since been widely reported in continental Europe (16, 27-32). This test has not been applied in patients with CFS or FM.

The first published American case of latent tetany in which marginal Mg deficiency but normal calcium levels was associated with serum Mg levels at the low limit (1.65 mEq/L) of the accepted normal range, was reported in 1971 (33). Her long-standing complaints--including weakness, chronic fatigue, depression, insomnia, and generalized pruritus (requiring very large doses of anti-histamine drug for control) had led the patient to a cardiologist after an internist, an allergist, and a psychiatrist had failed to diagnose her condition, or to institute therapy that alleviated symptoms, other than transitory relief of pruritus with anti-histamines. Because she had manifestations similar to those of LTS, we undertook a Mg-load/retention test. She retained a high percentage of a Mg (intramuscular) load. An EMG study run before the test injection of Mg disclosed repetitive muscle twitches, that substantially diminished several hours after an intramuscular injection of Mg. The predisposing condition in this patient was then found to be renal Mg wasting. It was speculated that this might have been contributory to co-existing decreased tubular chloride reabsorption, with increased intracellular and interstitial fluid volume (clinically expressed by slight edema) and normotensive aldosteronism. (34). Daily oral $MgCl_2$ supplements and weekly intramuscular $MgSO_4$ injections maintained her essentially free of complaints for more than five years, following which she was lost to follow-up.

In an American clinic that treated patients with neuropsychiatric disorders often brought on by stress (18), among 50 such patients who had serum Mg levels within that laboratory's range of normal (1.4-2.1 mEq/L, mean = 1.69 ± 0.41), low rbc Mg (mean 4.65 ± 0.31 mEq/L, range 2.72-5.80) was found in half. These disparate findings suggest that the rbc Mg is a better determinant of Mg but also suggest that the low limit of the "normal" serum Mg might actually be subnormal. The parenteral Mg load test, to determine tissue Mg deficiency, confirmed Mg deficiency in 80% of those with low rbc Mg. Of these, 64% had high urinary Mg output before the Mg load (suggestive of renal Mg wasting). Chvostek's sign (ChvS) was present in 36 (72%). In an extension of this study, all 75 patients with ChvS had ischemic EMG tracings indicative of LTS. As a guide to prevalence of LTS in those populations, the frequency of ChvS was, therefore, assessed in 100 women seeking routine gynecologic care and in 24 patients with agoraphobia. ChvS was present in 26% of gynecologic patients and in 74% of the agoraphobic.

The presence of ChvS was positively correlated with myospastic symptomatology in both groups.

It is not surprising that in LTS, where demonstration of subnormal Mg levels is part of the diagnosis, prolonged Mg therapy has been reported to relieve symptoms, and to restore the patients to normal activities of life (14,16-21,24-34). Nor should it be surprising that in CFS/FM clinics where Mg deficiency is not suspected, the Mg status is rarely investigated, and its possible therapeutic utility has rarely been explored.

CFS: Several early papers, in which Mg and potassium aspartate treatment of chronic fatigue was reported to be effective, had not elicited the more recently identified CFS characteristics, and thus might not have been true CFS (35-39). Experimental evidence that these salts improved energy metabolism (41,42) justified their oral administration to patients suffering from depressive anxiety and fatigue, even on awakening, that increased during the day, as well as headaches, that were often preceded by illness or stress.

The first study to test the hypothesis that CFS patients have low tissue levels of Mg and that Mg treatment would improve their well-being, was reported in England in 1991(15). Determination of rbc Mg of 20 CFS patients and of 20 healthy controls matched for age, sex, and social class disclosed that CFS patients had lower rbc Mg than did controls. In a double-blind, placebo-controlled clinical trial, 32 CFS patients were randomly allocated to an intramuscular injection of MgSO4 (I g 50%) weekly for six weeks (#15) or to placebo (#17). Twelve of those receiving the Mg claimed better energy levels, and improved emotional state, and less myalgic pain than did patients given placebo. The rbc Mg became normal in all Mg-treated patients, but in only one of the control patients given placebo. That brief paper evoked several letters to the editor (42-48). Two suggested that the favorable effect of Mg in muscle fatigue might be a consequence of the role of Mg in energy metabolism in the mitochondria (42,43); one wondered how such a small amount of Mg could be beneficial (44); one pointed out limitations of laboratory Mg determinations (45) and several failed to confirm low rbc Mg findings in CFS patients (8), or in either CFS or FM (45-48). To evaluate the role of Mg in CFS or Mg there was need for more extensive studies, of longer duration (49). A letter reporting on a study of several hundred CFS patients whose rbc Mg was analyzed commented that normal Mg values were never found in 12 consecutive patients (50). Another paper reported

only slightly low rbc Mg in FM patients (51), one failed to confirm lower than control rbc Mg values in CFS patients (52), and one has recently reported lower than control mean rbc Mg levels in CFS patients: 2.05 and 2.43 mmol/L rbc, respectively, but no difference in serum values (53). Referring to the weekly Mg injections that were found beneficial in CFS (15), a letter (48) and a brief report of trial of Mg in CFS (52) commented on failure to confirm demonstration of Mg retention after a Mg load, that did not yield clinical improvement a week after the single injection. However, it should not be expected that a single intramuscular Mg injection would produce detectable clinical improvement in a chronic disorder. This was cautioned by the pioneer in LTS studies, who recommended that after laboratory evidence of Mg deficiency is sought, sustained oral Mg administration (5 mg of Mg daily) should be provided, with clinical evaluation repeated monthly (14).

Long-term Mg treatment induced substantial improvement of a young Japanese woman with chronic general malaise, low grade fever, swelling of lymph nodes, myalgias and arthralgias, as well as headache and insomnia, that was diagnosed as CFS (54). Additional findings were eosinophilia, high serum immunoglobulin E, and low natural killer cell (NK) activity. After failure of treatment with non-steroidal anti-inflammatory drugs, minor tranquilizers and anti-depressant drugs, intravenous MgSO4 was given once a week. After six weekly Mg infusions, the patient noticed less vulnerability to fatigue and improvement in her impaired daily activities. After six months of sustained Mg treatment she was able to leave the hospital. A Japanese review (55) reported that measures to restore NK cell activity and other immunologic abnormalities seemed promising, unlike antidepressants which relieved only depressive anxiety. They cited trials with Mg treatment of CFS patients, that were reported to improve CFS patients' sense of well-being. (See below for discussion of Mg and immunology.)

FM: Low tissue levels of Mg have been reported in FM, with and without eosinophilia (56). That the above CFS patient and some FM patients exhibit eosinophilia is intriguing in drawing parallels between FM and LTS, in view of the long-known eosinophilia of experimental Mg deficiency (57). A FM patient (56) had persistent myalgias, cramping, and weakness not responsive to therapy. Despite normal serum Mg, the Mg load/retention test suggested low tissue Mg. Parenteral Mg produced dramatic improvement in symptoms and raised intracellular Mg. After cessation of Mg treatment, his symptoms

recurred. Reinstitution of Mg treatment again led to symptomatic improvement.

Sleep Patterns and Electroencephalography

LTS: EEG and clinical analysis of sleep in 100 cases of LTS disclosed shortened sleep cycles and frequent pseudoawakenings, with quick shifts from one sleep stage to another (58). It was postulated that the sleep disorder of Mg deficiency in humans, as well as in rats, might be related to catecholamine excess, abnormal cerebral monoamines, histamine, and other neurotransmitters. A Romanian team of investigators (59) demonstrated that in a study of 397 hypomagnesemic patients 107, who were selected for LTS, had no sign of organic cerebral lesion. In those cases, EEG and EMG changes were studied before, during and after hyperpnea. Analysis of computerized EEG maps disclosed temporo-spatial cortical distribution of the sinusoidal slow waves generated by the reticulate neuronal hypersynchrony. In a further study of ten such patients who had the restless leg syndrome without other neuropsychiatric conditions that could generate restless legs findings, EEG recordings demonstrated reticular neuronal hypersynchrony generated by hyperpnea (sinusoidal slow waves) (60). Classical EEG studies indicated neuromuscular hyperexcitability. Continuous 8-hour polysomnography disclosed sleep disorders: agitated sleep with frequent nocturnal awakenings, increased percentage and duration of light slow-wave sleep, and rapid, frequent changes of various stages of light slow wave sleep and of rapid eye movement (REM) sleep (as in other parasomnias caused by Mg deficiency).

Another team of investigators showed that Mg supplementation normalized the disturbed sleep of rats that had been fed a Mg deficient diet for 40 days (61). They then found that Mg-deficient rats sleep less than normal, but unlike sleep-deprived rats fed full diets, which have elevated brain serotonin, their dopamine content had risen, but brain serotonin level was normal (62). Since serotonin uptake is Mg-dependent, the authors suggest that the failure to exhibit increased brain serotonin might be due to depressed serotonin accumulation. Electropolygraphic (EPG) tracings, recorded at regular intervals, showed that Mg repletion restored to normal both monoamine metabolites (brain dopamine levels and 5-hydroxy-indoleacetic acid) and the EEG, as well as decreasing vigilance wakefulness and increasing sleep (63,64). Further studies disclosed that the cerebral monoamines, including norepinephrine and serotonin, homovanillic acid, and 5-hydroxy-

indoleacetic acid, are affected by Mg deficiency. The structures most affected are hypothalamus, brain stem, and corpus striatum, structures that have important roles in maintenance of vigilance, as well as in various regulatory functions: neuroendocrine (hypothalamus), autonomic (brain stem) and motor (corpus striatum) (64).

CFS and FM: Sleep disturbances characterized by polysomnography as showing a prominent alpha EEG nonrapid eye movement sleep anomaly have been accepted as part of the syndrome in CFS and FM patients (65-75) that accompanies increased nocturnal vigilance and light, unrefreshing sleep (70). The degree of sleep impairment, which leads to overwhelming daytime weariness, has been proposed as a contributory factor to the fatigue component of CFS and FM. It has been suggested that agents that affect central nervous system neurotransmitters, particularly those that affect serotonin, may have potential in management of this condition; and should be evaluated in large controlled clinical trials (7 1).

Experimental studies have linked immune-neuroendocrine-thermal systems and the sleepwake cycle (70,75). Whether alterations, either by drug therapy or by Mg supplementation in appropriate cases, of aspects of the systems that accompany disordered sleep physiology might correct the nonrestorative sleep, pain, fatigue, cognitive and mood symptoms in patients with FM or CFS remains to be ascertained.

Cognitive Disorders

LTS: Apart from subjective reports of diminished ability. to concentrate by LTS patients (20), no data on cognitive impairment in LTS has been found, even though the abnormal sleep found in LTS (58) might be expected to lead to transient diminished cognitive capacity. On the other hand, severe human Mg deficiency causes brain dysfunction that can include apathy, poor memory, confusion, disorientation and hallucinations, before coma or convulsions ensue (76). Alcoholism, which has long been known to be one of the important causes of Mg deficiency (76-79), has more recently been implicated in the learning defects of infants borne to alcoholic mothers, via the resultant Mg loss-induced abnormality in regulation of the NMDA receptor (80, 81), which has been proposed to be important in learning (81,82). Additionally, Mg administration has been shown to lessen cognitive dysfunction caused by experimental trauma (83) or directly by perinatal NMDA-induced brain damage in rats (84), mice (85) or piglets (86).

CFS: Cognitive dysfunction that includes impaired attention, loss of ability to concentrate, and memory loss is not uncommon in CFS (65,70,87-97). It is not often detectable by magnetic resonance imaging and single-photon emission computed tomography that indicate cortical lesions (95,96). These changes may appear abruptly, and are often associated with mood changes (90). Response-related processes (91) and tasks requiring conceptually driven encoding and retrieval processes and conceptualization (92) are the findings in CFS that differ most from controls. The overall pattern indicates a significant memory deficit, which is consistent with temporal-limbic dysfunction and differs from that of depressed patients and control subjects (94). Patients have been found to be impaired on tests of spatial span, spatial working memory, and selective reminding condition of pattern-location associated learning, but not in executive test of planning (97). In an attentional test, eight patients were unable to learn a response set; the remainder exhibited no impairment in the executive set shifting phase of the test. CFS patients were also impaired on verbal tests of unrelated word association learning and letter fluency. Better performance on cognitive measures occurred with improvement in fatigue and depression (97).

Inner Ear Disturbances

LTS: Vestibular disorders and occult nystagmus are often seen in patients with US (20,98-100). Additionally, sensorineural hearing loss that may be sudden in onset and that improves with Mg supplementation has occurred in LTS (22,98,101). Since experimental Mg deficiency in rats intensifies hearing loss caused by sound, and Mg supplementation is protective (102-108), Mg-supplementation trials were undertaken in soldiers exposed to loud noise (of gunshots) during training, and in pilots (107). In noise-exposed pilots, the effect of oral Mg-supplement prophylaxis was tested in a placebo-controlled double blind study involving 320 volunteers with normal hearing during a two-month period for its effect on noise-induced hearing loss. Audiograms of all test subjects were compared with pre-entry values and permanent threshold shifts were determined. Loss of hearing after exposure to noise was twice as high in the placebo group as in those receiving supplemental Mg. Prophylactic and Mg dosage effects were tested in humans occupationally exposed to repeated hazardous noise in a placebo-controlled double-blind study with 540 volunteers, who were instructed to use ear plugs when exposed to noise (108). Hearing acuity and Mg levels in serum, rbc, lymphocytes and urine were determined before, during, and after 3-6 months of noise exposure. Subjects received a daily drink containing 3,

5, or 6.7 mmoles Mg as the aspartate or placebo. Significantly greater bilateral hearing damage, that was negatively correlated with rbc: Mg and particularly with lymphocyte Mg. Significantly positive effects were seen at 5 and 6.7 mmole Mg dosages, in that that was less hearing loss, that correlated with elevated intracellular Mg values.

CFS and FM: My survey of the literature has not disclosed reports of deafness in CFS patients, but abnormalities of vestibular function have been found (109). Among patients with FM, more than a quarter have low frequency sensorineural hearing loss and almost three quarters have low painful sound threshold (110), and they often complain of nonspecific dysequilibrium. verified by objective tests (110- 112).

Migraine and Other Severe Headaches

LTS: Migraine headaches are prevalent in US patients (20-22,113,114), as well as in women with eclampsia and other complicated pregnancies, conditions that are also commonly associated with low Mg levels (113,115-119). The greater frequency of migraine in women, particularly between 20 and 50 years of age than in men (115,119) and in those with LTS before menopause (p. 90 in ref 20), suggests that estrogen might play a role, possibly in those with marginal Mg intakes, by shifting blood Mg to bone (120). Migraine headaches have been shown to be associated with subnormal Mg levels: in brain (by nonmagnetic resonance (12 1), in blood-serum, red and white blood cells (122-127), and by ionized serum Mg determination (128), as have tension-, persistent, and cluster-headaches (129,130). Several mechanisms, entailing interaction with or presence of low levels of Mg, have been considered in the pathogenesis of migraine (115,117120,131,132). Mg has been reported effective prophylactically and therapeutically against migraine attacks (123,128-130,133,134). Determination of free ionic serum Mg by ion-selective electrode technic has been shown to differentiate between headaches that respond to Mg therapy and those that do not (128-130).

CFS and FM.- As with LTS, there is a greater incidence of headaches, especially migraine, but also tension-, persistent, and cluster-headaches among patients with CFS or FM than among subjects not prone to such headaches (21,90,95,110,145,146). Another similarity with LTS is the greater frequency of migraine in women than in men that is seen also in CFS and FM (1,137,138).

Mitral Valve Prolapse

LTS: A cardiac abnormality that has been reported to occur commonly in LTS is mitral valve prolapse (MVP) (17,20,139-148) and hypomagnesemia has been reported in as many as 85% of MVP patients (149). It has been proposed that LTS patients are vulnerable to development of MVP if their Mg deficiency has not been repaired (20,139,140). A suggested mechanism by which Mg deficiency might predispose to MVP might be by interfering with the mechanism by which fibroblasts degrade defective collagen (141,146).

CFS and FM. Echocardiograms disclosed a 75% incidence of MVP in FM (110). In a series of 115 patients with symptoms of fatigue and, activity impairment, atypical precordial pain, and cardiac arrhythmia, that preceded by years development of congestive heart failure, 27 were diagnosed as having MVP, and 28 had CFS; of 60 patients with hypertension, 36% had combined MVP and fatigue (150).

IMMUNOLOGIC DYSFUNCTIONS OF LTS AND CFS AND FM

LTS: The occurrence of urticaria and extraordinarily high requirement

for and tolerance of anti-histaminic drugs in a patient with LTS, and the reduction in need for pruritus-controlling treatment with elevation of serum Mg to the normal range, was first noted in the United States in 1975 (33). The same year, a review was published in France, that reported that more than half the patients with allergies associated with urticaria, and/or rhinitis, conjunctivitis, or asthma had Mg deficiency, usually associated with latent tetany (15 1). An analysis of 405 cases of non-infectious rhinopathy showed Mg deficiency in 52%; 17% with allergy and 35% with pseudo-allergic vasomotor rhinitis, a clinical form of LTS. Allergic rhinitis is familial and is associated with elevated IgE (98). The pseudo-allergic rhinitis form is provoked by stress, and positive skin tests involve histamine, acetylcholine or compound 48-80 (152,153). The role of Mg in immediate 15 allergic reactions, associated with histamine release and eosinophilia has been reported in patients with bronchial asthma, whose rbc Mg decreases during an acute attack (154). Low levels of Mg in polymorphonuclear cells, but normal serum and rbc Mg have been documented in 50 patients with bronchial asthma between attacks (155). Asthmatic patients in clinical remission could tolerate larger amounts of administered histamine (in a

histamine-bronchoprovocation test) after inhalation of aerosolized Mg sulfate, in a randomized double-blind test (156). The relevance of this observation to acute treatment of severe attacks of asthma has been demonstrated, but only with use of intravenously administered pharmacologic doses of MgSO4 (157-162). At the high therapeutic levels, Mg inhibits histamine-induced bronchial constriction. That high dietary Mg is associated with better lung function and decreased risk of airway hyper-reactivity and wheezing has been demonstrated in a random sample of adults 18 to 70 years of age (163). With ranges of 182-654 mg of dietary Mg in men and 160-527 mg in women, 100 mg higher intake of Mg was associated with significantly better pulmonary function and decreased odds of self-reported wheeze in 12 months of follow-up.

Also seen in the American patient detailed in 1975 (33) was chronic mucocutaneous and paronychial candidiasis, which suggests impaired cell-mediated immunity and abnormal T-lymphocyte function. The frequency with which this form of *Candida* infection occurs in patients with LTS was determined in 50 patients (164). Recurrent or chronic infections with C *albicans* was reported by 34% of that group, either in the past or at time of examination, and 48% had type I hypersensitivity to *C albicans* extract intradermal testing.

CFS and FM: Both humoral and cellular immunologic dysfunctions have been reported in CFS (5-9,165-170). The abnormalities are in accord with evidence suggesting chronic, low-level activation of the immune system (165,166). There is high prevalence of allergic manifestations--from cutaneous allergies to eosinophilia and eosinophil activation, detectable by measurement in serum of eosinophil cationic protein in CFS patients (168,169). Although there are low levels of circulating immune complexes and of several autoantibodies (particularly antinuclear and antithyroid and several monoclonal antibodies to T- and B-lymphocytes [1661), there are modestly elevated levels of Epstein-Barr virus-related antibodies, immunoglobulin G to viral capsid antigen and to early antigen (5). Extensively investigated as possibly playing an etiologic role in CFS and FM are viral infections. Epstein-Barr and herpes viruses, enteroviruses, influenza viruses, and parvovirus have been suspected (171-178). However, the premise that persistent virus or other infections cause these diseases is being questioned (180-184).

Among cytokines tested, serum transforming growth factor beta (TGF- beta) levels were elevated in CFS patients (167). Release of interleukin 1 beta (IL-1 beta), stimulated by lipopolysaccharide, release of IL-6 stimulated by phytohemagglutinin, and tumor necrosis factor-alpha were significantly increased in peripheral blood mononuclear cell cultures from CFS patients as compared to controls. Enhanced release of inflammatory cytokines by such cell cultures from CFS patients suggests that these cells are primed for increased response to immune stimuli, indicating association between abnormal regulation of these humoral factors with the immunologic consequence of CFS and FM (110, 167).

Reduction of numbers of natural killer (NK) cells, and in their activity, is also found in CFS patients (5-9,110,170). It has been proposed that this might increase susceptibility to cancer, particularly non-Hodgkin's lymphoma and brain cancer; clusters of CFS preceded cancer in an epidemiologic study (90,184,185). Restoration of NK activity by biological response modifiers, has been reported to produce improvement in CFS patients (55).

POSSIBLE MAGNESIUM-DEFICIENCY MEDIATED MECHANISMS IN CFS AND FM

Immunologic Aberrations

Activation of viruses in CFS patients, observed by investigators into viral factors, is analagous to the evidence that among subjects vaccinated with influenza vaccine. Those exhibiting increased antibody levels for all strains have significantly lower rbc Mg than do those with lower titers (186,187). The difference in immune response, that was related to the rbc Mg level was found to be linked to the major histocompatability complex (HLA type). BW35 subjects had both increased antibody response and low rbc Mg levels (187). This genetic variable suggests a reason for individual differences in reactions to marginal Mg deficiencies. Familial differences in absorption and excretion of Mg and the high heritability of tissue Mg levels that has been associated with the major histocompatability complex, may influence individual and familial variability in susceptibility to immunologic disorders.

There are many facets of humoral and cellular immunology that are affected by Mg. Early studies of the effects of Mg deficiency in rats provided the first clues that Mg inadequacy can cause histamine release, as manifested by

cutaneous hyperemia and inflammation (57,188,189). As much as ten-fold increase in eosinophilia caused by Mg deficiency (57) preceded release of histamine and serotonin (190). Experimental Mg deficiency depresses cell-mediated immunity, it impairs phagocytic activity, as well as lymphocytic function (11). Mg participates in the T-cell mediated immunity that requires cooperation of the mononuclear phagocyte system and is involved in production of cytokines, interleukins, interferons, transforming growth factor, and tumor necrosis factor. In severely Mg deficient rodents, it was found that there were greatly increased plasma concentrations of inflammatory cytokines such as tumor necrosis factor, of IL-I, IL-6, and the inflammatory neuropeptide, substance P (63,191).

A final immunologic parallel in CFS and Mg deficiency is the decreased numbers and activity of natural killer (NK) or cytotoxic T-cells *(supra vide* and 192), which might contribute to the postulated increased predilection to lymphoid and other cancers in CFS patients (90,184,185), and to the development of thymic lymphomas and leukemias in Mg deficient rats (193,194). Also, immunosurveillance against implanted neoplastic cells seems to be diminished by Mg deficiency (195). Higher frequencies of lymphomas and both lympholeukemias and granuloleukemias of cattle and humans have been associated with areas in Poland with mineral (e.g., Mg) deficiencies (196).

STRESS

Acute episodes of CFS and FM are often precipitated by exposure to stress, whether emotional or physical. The resultant increased catecholamine release, which increases Mg loss, can be a factor in CFS and FM. Paradoxically, low levels of Mg intensify the secretion of the catecholamines (reviewed elsewhere [23]), thus increasing the risk of adverse effects of stress.

Noise, Inner Ear, Migraine and Sex Difference

The inner ear disturbances (vestibular and auditory) seen in CFS and FM have also been seen in LTS and in the case of patients with LTS have been protected against by Mg therapy. The stress of loud noise causes Mg loss and intensifies the need for Mg. Increased catecholamines have been implicated in constriction of cochlear arteries with reduction of cochlear blood flow and of Mg levels in fluid around hair cells, with increased influx

of sodium and calcium and disturbance of energy metabolism of the inner ear (103-106). Possibly the mechanism might also entail Mg deficiency-induced release of substance P, which induces expression of the endothelium-leukocyte adhesion molecule of the cochlear microvasculature (63), further reducing cochlear blood flow. In Mg deficient guinea- pigs and rats that had hearing loss after noise exposure for four weeks, the loss of hearing correlated negatively with perilymph and rbc Mg levels (103,105). The deafness was induced both from the direct auditory trauma, and from the Mg deficit. The stria is the metabolic energy source of the cochlea. The apex of the cochlea is where the low frequency sounds are transduced; since that is where the blood supply is most distal, it is the area most vulnerable to impairment of blood flow (197).

The foregoing studies of Mg and deafness were all with men. Low frequency deafness occurs more frequently in post-menopausal women with cardiovascular disease than in young women and men (197,198). Estrogen allows for better Mg utilization when on a marginal Mg intake (120) such as is characteristic of the Western diet (198-201), an observation that led to speculation that this advantage might be a factor in the lesser cardiovascular disease rates in young women than in young men (198). Mg protects against development of cardiovascular disease (202-204), especially that associated with microangiopathy that gives rise to cardiomyopathy (204). Thus, it is plausible that the microvascular lesions of the inner ear might similarly be contributed to by Mg deficiency, that occurs with loss of the metabolic advantage conferred by estrogen. In fact, the vascular damage that has been implicated in the low frequency hearing loss seen more in elderly women with cardiovascular disease than in the same age men with such disease affects the capillaries and arterioles of the stria vascularis (197).

Whether Mg deficiency is contributory to deafness that is not precipitated by loud noise, or that is sex-linked, is speculative. The finding that acutely Mg deficient weanling litter-mate rats that did not die in convulsions on exposure to blasts of noise exhibited markedly decreased response to sound (205) is a provocative preliminary observations.

Another condition that occurs with greater frequency in women, between the ages of 20 and 50 years than in men (115,119), in US before the menopause (p. 20 in ref 20), and CFS and FM (1,137,138) is migraine. In this instance, estrogen shifts blood Mg to bone, resulting in lowering of circulating Mg, particularly in those with marginal Mg intakes (120). Among the

mechanisms considered in the pathogenesis of migraine are several in which low serum or brain Mg might play a role. As serum Mg falls, the counteraction by Mg of the procoagulative effect of calcium cannot take effect (120). This constitutes a serious problem, especially in LTS women on high estrogen oral contraceptives, whose tendency to develop thromboembolic events is reduced by Mg supplements (206). Additional Mg-influenced substances that affect platelet aggregation, blood coagulation and vasoconstriction include those increased by Mg deficiency: thromboxane, endothelin, and endothelial-derived contracting factor: EDCF which increased risk, and those that are increased by optimal Mg levels and that decrease risk: prostacycline and endothelial-derived relaxing factor: EDRF (207-209).

Counteraction by Mg of blood coagulation and vasoconstriction might be mechanisms by which Mg limits brain hypoxia. In addition, Mg reduces serotonin-induced spasms of (canine) cerebral arteries (210), and excess serotonin has been found to be released from platelets of migraineurs (211). Regional cortical oligemia, that outlasts electrical depression of cortical neurons during a migraine attack (212,213) precedes an attack of migraine. Central neuronal hyperexcitability involves overactivity of the excitatory amino acids (214). Stimuli that activate the migraine attack evoke neuronal depolarization, slow depolarization shifts, and spreading suppression of spontaneous neuronal activity, possibly by glutamate and K' dependent mechanisms. Low brain Mg2+, which has been identified in migraineurs (12 1) and consequent reduced gating of glutamatergic receptors may provide the link between the physiologic threshold for a migraine attack and the mechanisms of the attack itself by promoting glutamate hyperactivity, neuronal hyperexcitability, and susceptibility to glutamate-dependent spreading depression.

Neurologic; Neurotransmitter Effects of Magnesium

It has long been known that Mg deficiency causes neuromuscular excitability that occurs early (20). Experimental Mg deficiency-induced sustained release of histamine-which it has been suggested might function as a central neurotransmitter (216), which might contribute to increased neurologic irritability of severe Mg deficiency. Recent resurgence of interest in the neurologic consequences of Mg deficiency has stemmed from the finding that Mg, at physiologic levels, blocks neuronal N-methyl-D-aspartate:NMDA (218). NMDA-receptors are normally activated by

glutamate and/or aspartate which are the principal neurotransmitters for excitatory synaptic transmission. This knowledge provides a mechanistic explanation for the anticonvulsive activity of Mg, since the epileptiform activity of Mg deficiency is blocked by other NMDA receptor antagonists. Excitatory amino acids have been shown to be highly sensitive to extracellular free ionic Mg (219). Mg also decreases motor neurone responses evoked by norepinephrine, and by the inflammatory neuropeptide (substance P*), in isolated rat spinal cord. But these effects were not as marked as the Mg decrease of NMDA-induced responses. In addition, Mg deficiency increases production of substance P-which is found in central nervous system neurons. Through its proinflammatory and free radical-releasing effects, substance P might be contributory to the irritability caused by Mg deficiency (220).

PROBLEMS IN DETERMINING CLINICAL MAGNESIUM STATUS

Interpretation of measured Mg levels is difficult. Serum levels are the easiest to obtain but provide the least reliable index, since less than 1% of the total body Mg is in the serum (221,222). Determination of free ionic Mg in serum by an ion-selective electrode (IS) has promise, since it seems to reflect the Mg that is physiologically active (128-130,223-225). Red blood cells or mononuclear blood cells might be utilized, but there has been some questions as to methodology, applicability, and sensitivity,(221,226). Study of percentage retention of a parenteral load of Mg f227,228), or if that is inconvenient, by retention of an oral loading test be evaluated (229), is a reliable index of total body Mg. A non-invasive technic of measuring whole cell Mg content in sublingual cells has become commercially available (230). (For information on sublingual cell test: Intracellular Diagnostics, Inc., 1-800-874-4804) It has provided data from the sublingual cells that correlate well with cardiac tissue levels (230,23 1), with severe depression (232) and with chronic disorders with characteristics of CFS, termed electromagnetic dysthymia (233). In a recent study of 100 patients with significant depression with and without chronic pain, who were tested for Mg deficiency by both parenteral load and white blood cell (wbc) Mg, all retained over 50% of the Mg load, but only 60% had low wbc Mg (232). The sublingual test for Mg was as reliable as the parenteral Mg load test (232,234). In seven patients shown to be Mg deficient by this test, administration of intravenous $MgSO_4$ (2 grams daily for 10 days), then exhibited normal sublingual cell Mg. In a personal communication, CN Shealy has informed me that of 25 consecutive CFS patients, 72% exhibited

Mg deficiency by the sublingual cell test. Controlled clinical trial of Mg supplementation, with monthly clinical evaluation has been suggested as a means to ascertain whether Mg deficiency is a factor in CFS (14).

CONCLUDING COMMENTS

Since there is no satisfactory therapy for CFS, and there is a Mg-responsive condition: LTS-which resembles CFS and FM, the Mg status of CFS patients should be evaluated. But it is the determination of Mg deficiency that has constituted the major handicap in understanding its significance in clinical medicine. Comparison of the manifestations of the Mg dependent LTS, and those in which the possible role of Mg in the pathogenesis of the disease is rarely considered (CFS and FM), and the mechanisms by which Mg inadequacy might cause the manifestations, suggest that the relationships are more than coincidental. Muscle weakness and pain, chronic fatigue, depression, insomnia and other sleep disorders are the neuromuscular findings common to both. Cognitive impairment is definite in CFS. Although brain dysfunction and actual damage has been noted only in severe Mg deficiency (in rodents or in alcoholics), objective tests of cognition in LTS patients are necessary to confirm subjective complaints of impaired ability to concentrate. Effects of Mg on neurotransmitters and on inflammatory substance release, might explain symptomatic benefit achieved by Mg supplements in LTS. It seems worth determining whether Mg supplements are applicable also to those disorders when part of the CFS.

Noise-associated deafness in adults that is protected against by Mg supplementation, and the evidence that deafness and vestibular disorders can be associated with Mg deficiency in weanling rodents may well reflect cochlear microvascular damage in humans with ear disorders. An additional disorder that is associated with (cerebral) microangiopathy is migraine-that is frequent both in CFS and LTS. Diagnosis of mitral valve prolapse is more common both in the disorder that is clearly associated with Mg deficiency and in CFS and FM.

The evidence that Mg deficiency causes a variety of both humoral and cellular defense disturbances, among which are several that have been identified in CFS and FM, is a reason to suspect that either Mg deficiency or its abnormal utilization might be a pathogenic factor in CFS. It has been suggested that the immunologic response to infection that often precedes CFS may be linked to the nervous system and to catecholamine release and

to that of pituitary hormones (235). An intriguing hypothesis: "neurogenic switching" ties together allergies (e.g., of "sick building syndrome" or multiple chemical sensitivity syndrome) with immunogenic inflammation and neurogenic inflammation, mediated by substance P or other neuropeptides (236). Neurogenic switching is proposed as a mechanism by which a stimulus at one site can result in distant inflammation, that is hypothesized to play a role in food allergy-inducing asthma, urticaria, arthritis, and provides a mechanism to explain how allergens, infectious agents, irritants and emotional stress can exacerbate such conditions, including migraine and FM (236). Release of histamine, which binds to sensory nerves to produce an afferent signal, is rerouted via the central nervous system to another site. Since Mg deficiency results both in early release of substance P and in subsequent histamine release, it might be appropriate to add Mg deficiency to the neurogenic switching hypothesis.

Another postulate, stemming from work with severely Mg deficient rodents, sheds light on the mechanism of the immunopathology resulting from inflammatory damage induced (via neuropeptides: substance P and calcitonin gene-related peptide) (220,237). The resultant excessive T lymphocyte cytokine production is important in the free radical production seen in Mg deficiency (191,220,237,23 8). Although patients with CFS, or even LTS, have nowhere near the degree of Mg deficiency that was produced experimentally in mice, rats and guinea pigs to produce immunopathology (that mimics in part that seen in CFS and LTS), it is possible that at fault in the human syndromes might be Mg transport mechanisms, perhaps genetically controlled.

The use of Mg, as one of the down-regulators of NMDA firing, has been suggested to control the immune disease manifestations of CFS, and the evidence of free radical injury to the brain in CFS (239) supports the rationale for combined Mg and antioxidant therapy in CFS. The finding that Mg deficiency is associated with free radical production, (as well as having direct effects on immunologic mechanisms) suggests that the Mg effect might be enhanced by adding antioxidants to Mg treatment also of LTS. It is provocative that magnesium and taurine (an antioxidant amino acid) has been proposed as therapy for migraine (132) and for the complex of complaints termed electromagnetic dysthymia, which includes CFS as an extreme case (233).

A final personal observation is that the similarities of complaints that lead to diagnoses of CFS or LTS, and the evidence as to Mg-dependent mechanisms involved that explain the benefit of Mg in LTS, when given for long enough to correct a presumed long-term deficiency, suggest that the parallels between these two syndromes exist because they may actually be one syndrome. Might it be that in clinics where Mg status is investigated, the diagnosis is LTS; where it is not, the diagnosis is CFS or FM?

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