Magnesium, Stress and Neuropsychiatric Disorders

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Abstract

Magnesium has a profound effect on neural excitability; the most characteristic signs and symptoms of Mg deficiency are produced by neural and neuromuscular hyperexcitability. These create a constellation of clinical findings termed tetany syndrome (TS). TS symptoms include muscle spasms, cramps and hyperarousal, hyperventilation and asthenia. Physical signs (Chvostek's, Trousseau's or von Bonsdorff's) and abnormalities of the electromyogram or electroencephalogram can usually be elicited. Signs and symptoms of TS are frequently encountered in clinical practice, especially among patients with functional or stress-related disorders. The role of Mg deficit in TS is suggested by relatively low levels of serum or erythrocyte Mg and by the clinical response to oral Mg salts, which has been demonstrated in controlled studies. Among the more serious neurologic sequelae of TS are migraine attacks, transient ischemic attacks, sensorineural hearing loss and convulsions. Mg deficiency may predispose to hyperventilation and may sensitize the cerebral vasculature to the effects of hypocarbia. Mg deficiency increases susceptibility to the physiologic damage produced by stress, and Mg administration has a protective effect; studies on noise stress and noise-induced hearing loss are taken as an example. In addition, the adrenergic effects of psychological stress induce a shift of Mg from the intracellular to the extracellular space, increasing urinary excretion and eventually depleting body stores. Drugs used in neurology and psychiatry may affect Mg levels in blood and may diminish signs of tetany, making assessment of Mg status more difficult. Pharmacologic use of Mg can decrease neurologic deficit in experimental head trauma, possibly by blockade of N-methyl-D-aspartate receptors. In conjunction with high doses of pyridoxine, Mg salts benefit 40% of patients with autism, possibly by an effect on doparnine metabolism.

Text

Magnesium ions have a well-established depressant effect on the central nervous system [1] and on neuromuscular transmission [2]. The cardinal symptoms of severe Mg deficiency in humans are neuropsychiatric: asthenia, tremor, convulsions, irritability, tetanic spasms, muscle cramps and confusion [3-9]. These symptoms are largely produced by heightened neural and neuromuscular excitability [3, 7], a condition called tetany. In experimental human Mg deficiency, asthenia and tetany are usually accompanied by hypocalcemia and hypokalemia, leading some authors to speculate that the symptoms of Mg deficiency result from ionic interactions and are not Mg specific [9]. In most clinical studies [3-7], however, asthenia and tetany occur when serum calcium and potassium are normal, suggesting that Mg deficit may produce neuromuscular symptoms without altering circulating levels of other ions. Furthermore, when mild hypocalcemia occurs in Mg-deficient tetany, administration of intravenous Ca does not improve symptoms or signs, whereas intravenous Mg improves clinical status and raises both Mg and Ca in blood, substantiating the ability of Mg deficiency alone to cause tetany [6, 7, 9]. Although mild hypomagnesemia is quite common in hospitalized patients [10, 11], the identification of tetany caused by mild Mg deficiency is so uncommon in the US that individual case reports are published [12]. One explanation for this discrepancy is that hypomagnesemia can occur without alteration of cerebrospinal fluid (CSF) Mg concentration [13]. Another explanation is that the signs and symptoms of tetany are usually so subtle or nonspecific that they go unrecognized.

Tetany Syndrome and Mg Deficiency

Tetanic seizures were treated with mineral salts as early as the seventeenth century [14]. The naming and description of the tetany syndrome (TS), with manifestations that varied from emotional lability and paresthesias to carpal-pedal spasm and epileptiform convulsions, occurred during the second half of the nineteenth century [15]. The recognition of physical signs (Trousseau's, Chvostek's and von Bonsdorff's) led to an understanding that tetany could occur in a latent form with symptoms occurring only intermittently or not at all [15]. Interest in the diagnosis of latent tetany in English-speaking countries was primarily related to tetany as a sign of Ca deficiency [16, 17]. Once accurate measurements of serum Ca and ionized Ca became commonplace, interest in the phenomenon of tetany waned. On the European continent, in contrast, research and speculation concerning the phenomena of tetany continued [15]. Electromyography (EMG) [18] and electroencephalography [19] characteristics of tetany were described. The syndrome of latent tetany or Ispasmophilia' was recognized as a common, multifaceted disorder [15]; its researchers recognized that it was very similar to the condition described in the English literature by the names neurocirculatory asthenia and hyperventilation syndrome [20, 21]. Physicians treating TS identified subtle abnormalities in Ca or electrolyte transport in the disorder [22, 23]. Kugelberg studied the mechanisms of Chvostek's sign [24] and Trousseau's

and von Bondorff s signs [25]. He concluded that tetany is primarily a disorder of accomodation of nerves which adapt to a gradual decline in transmembrane electrical potential by altering the voltage requirements for generating an action potential [26]. This process protects nerves from discharging inappropriately in response to changes in their physical or chemical milieu. It is impaired, he found, by Ca deficiency and by ischemia; he did not study the effects of Mg.

In 1959, Roselle and de Doncker [27] described the EMG in TS associated with chronic Mg deficiency. Since 1960, Durlach [20] has maintained that chronic Mg deficit is the commonest cause of TS. He divides the symptoms into five categories: (1) central manifestations of emotional lability, breathlessness and hyperventilation, tremor, headache, dizziness, insomnia and asthenia; (2) peripheral manifestations of paresthesia, formication, fasciculation, cramps, radicular pain and poor exercise tolerance; (3) organ-specific functional disorders producing palpitation, chest pain, pallor, diaphoresis, Raynaud's phenomenon, biliary dyskinesia or spastic colon; (4) 'trophic' phenomena with fragility of nails, hair and teeth; (5) acute crises characterized by hyperventilation, syncope, convulsion, carpal-pedal spasm. TS due to chronic Mg deficiency may be separated from other neuropsychiatric disorders with similar symptoms by the presence of Chvostek's sign (found in 8 5 %), midsystolic cardiac clicks (found in 3 5 %) or Trousseau's sign (found only in the severer cases). EMG of the intrinsic muscles of the hand during or after ischernia or hyperventilation shows repetitive spontaneous discharges in most cases; electroencephalography often manifests 'diffuse irritative' abnormalities with spikes and sharp waves; an echocardiogram may confirm the presence of mitral valve prolapse, which is found in over a third of cases. The number of signs present is generally proportional to the severity of the Mg deficit. Serum and erythrocyte Mg concentrations are generally lower in a population with TS than in control populations, but in any individual case, the serum and/or erythrocyte Mg may be normal when symptoms occur. Indeed, the central hyperexcitability symptoms tend to be greater when either serum or red cell Mg is reduced than when both blood compartments show low Mg levels [28]. Difficulty in precisely differentiating TS caused by Mg dificit from other conditions can be anticipated from Durlach's [20] own observation that central symptoms may occur in the absence of peripheral symptoms, Chvostek's sign or EMG abnormalities, especially in men. Furthermore, Chvostek's sign can be elicited in 4.5-36 % of 'normal subjects' [17, 29, 30], and the EMG abnormalities of tetany occur in 17-45% of normal subjects under certain experimental conditions [29, 31]. These tetanic manifestations in healthy subjects, called 'spasmorhythmia', are thought to represent a constitutional susceptibility to the development of TS, which becomes manifest under conditions of Mg or Ca deficiency, alkalosis or emotional distress [29].

A Belgian team studied the correlates of tourniquet-induced repetitive EMG activity and Chvostek's sign in 39 healthy females and 39 healthy males, defining spasmorhythmia as 2 min or more of repetitive activity induced by 10 min of forearm ischernia. Individuals with spasmorhythmia differed from individuals without spasmorhythmia in having a slightly lower plasma Mg concentration (0.79 vs. 0.82 mmol/l, p < 0.005) and a greater tendency to emotional lability, anxiety, depression, crying spells, mental anguish and

phobias elicited on blinded psychiatric interview by two different observers [32].

Duc et al. [33] reported results on 5,645 patients examined for TS over a 10-year period. Their principal symptoms were insomnia, headache, back pain, paresthesia, fasciculation, muscle cramps, chest pain, palpitation, palpebral fluttering, dizziness, dyspepsia and constipation. Chvostek's sign was present in 60%, and tetanic crises occurred in 25%; EMG signs of latent tetany could be elicited in 89% of patients not taking psychotropic drugs. There was no significant difference in plasma Mg between patients with TS and a control group, but erythrocyte Mg was 10% lower in the tetanic patients ($p < 0.001$). In the subgroup subject to tetanic crises, erythrocyte Mg was 7.5% lower than in the subgroup without tetanic crises ($p < 0.005$).

The reader may well wonder whether TS is commonly a manifestation of Mg deficiency, as advocated by Durlach [20], or anxiety neurosis, or the result of habitual hyperventilation and hypocapnia, as advocated by Lum [34]. Fehlinger and Seidel [35] concluded that 'so-called genuine tetany' and hyperventilation syndrome were indistinguishable by history, physical examination, psychological testing or electrodiagnostic testing. They considered some psychometric parameters, such as impaired concentration and increased reaction time, to indicate an organic component to the disorder. When compared to control patients, serum Ca and Mg were both significantly reduced. When they separated tetanic patients with attacks of hyperventilation from patients without hyperventilation attacks, they found that hyperventilators had significantly lower Mg levels than nonhyperventilators and concluded that Mg deficiency was a probable cause of hyperventilation. They postulate that Mg deficiency, by impairing mitochondrial function, increases the relative amount of anaerobic glycolysis in the brain, creating a local metabolic acidosis which stimulates hyperpnea [36]. Fehlinger et al. [37] performed a double-blind, placebo-controlled study of a pyrrolidone carboxylic acid salt of Mg in 64 patients with TS and found a significant improvement in overall symptoms and in hyperventilation attacks associated with the active drug. The therapeutic effect was accompanied by a small but significant increase in plasma Mg and K concentrations. It is of interest that muscle cramps, paresthesias and changes in the EMG were similarly affected by active and placebo therapy, without significant difference. In another study, comparing Mg citrate with placebo, the authors found significant improvement in muscle strength and mental concentration and a decrease in hypocapniainduced cerebral vasoconstriction with active drug [38].

Although these studies do not prove that TS is a distinct disorder commonly caused by a primary Mg deficiency, they do demonstrate that tetanic phenomena are common occurrences associated with symptoms generally regarded as functional or anxious, and are usually accompanied by low levels of Mg in one blood compartment or another.

Fehlinger [21] attributes some neurologic disorders which accompany TS, such as migraine headaches, to the combined vasospastic effects of Mg deficiency and secondary hypocapnia. Support for this notion comes from

studies showing a high prevalence of migraine symptoms (28%) in patients with mitral valve prolapse P9], a condition which shows a strong correlation with TS [20]. Although serum Mg is no different between migraine patients and controls, CSF Mg is significantly lower in migraine patients than in controls (p < 0.001) [40]. A group at Henry Ford Hospital measured intracellular Mg in brains of migraine patients using $31p$ nuclear magnetic resonance spectroscopy [41]; levels were 19% lower in migraine patients studied during an attack than in controls (p < 0.02). The small number of patients studied between attacks prevented adequate analysis to determine whether low brain Mg occurs interictally as well. Dexter [42] reported that rebreathing aborted migraine attacks in 6 migraine patients; this would suggest that the cerebral vasculature in migraine patients is very sensitive to pCO_2, a possible effect of Mg deficit [38].

Fehlinger [21] has also attributed some of the infrequent neurologic disorders encountered in TS patients to vasoconstriction induced by Mg deficit. The Alturas were the first to suggest and demonstrate that Mg deficits can induce cerebrovasospasm [43]. Transient ischemic attacks (TIA) and specific prolonged reversible ischemic neurologic deficits occur in about 10 % of TS patients evaluated in Fehlinger's Berlin clinic [36]. Over 90% of neurologic events in these patients are rapidly reversible; the remainder are prolonged. The nature of neurologic deficits is described in Table 1.

No deaths have occurred in any of the 103 patients reported, nor has there been any evidence of myocardial infarction or of extracranial cerebrovasular obstruction. The median age for the first TIA was 34 years; 88.3% of patients were female. This is in marked contrast to the epidemiology of TIA associated with arteriosclerotic cardiovascular diseases. In 19.4%, the first TIA was associated with the onset of a more generalized TS, in 5.6% TS developed some time after the TIA and in 75 % TS had been present for several years prior to the first TIA. Convulsions were reported by 10.7% of TS patients with TIA, compared to 5 % of TS patients without TIA. Hyperventilation attacks were equally present in TS patients with or without TIA (75% vs. 69%); serum Mg was nonsignificantly lower in the presence of TIA. Hypomagnesemia (<0.7mmol/1) was present in 22.9% of TS/TIA+ patients, 15.8% of TS/TIA- patients and 4.2 % of controls (p<0.01).

Fehlinger et al. [44] also evaluated patients with idiopathic sudden deafness for the presence of TS. Signs and symptoms of latent or manifest tetany were present in 93% of females and 38 % of males. There were no significant differences in serum or erythrocyte Mg between sudden deafness patients and controls. Among women whose hearing loss had improved spontaneously after the initial episode of deafness, however,

Table 1.
Neurologic deficits of patients with TIA and TS

Nature of deficit	*n*
Aphasia	34
Hemiparesis	29
Diplopia	15
Sudden deafness	13
Monoparesis	11
Hemianopsia	7
Amaurosis fugax	7
Visual paresis	4
Quadrantanopsia	3
Central scotomata	2

From Fehlinger et al. [36].

erythrocyte Mg was 15.7% higher than among women whose hearing loss remained constant or worsened (p = 0.01). These data do not establish a clear relationship between sudden deafness and Mg or a role for TS in the pathogenesis of sensorineural hearing loss; they do suggest a protective role for erythrocyte Mg in women with sudden deafness.

Mg, Noise and Sensorineural Hearing Loss

Experimental support for a relationship between Mg status and sensorineural hearing loss comes from the work of Ising et al. [45]. They first studied auditory-evoked potentials in guinea pigs fed an Mg-deficient diet and then variably repleted with Mg-enriched drinking water. There was a significant negative correlation between the Mg content of perilymph and the degree of hearing loss induced by chronic noise stress (r = -0.86) [45]. Next, they studied auditory-evoked potentials in rats on Mg-enriched and Mg-poor diets exposed to noise stress for 16 h a day [46]. The relatively mild Mg deficiency sustained over a period of 3 months produced a 20-35% decrease in Mg concentrations of plasma, erythrocytes and perilymph, yielded none of the pathological effects associated with severe Mg deficiency in rats and had no effect on auditory threshold. Noise stress produced low levels of hearing loss (7-14 dB) in rats fed Mg-enriched food and much greater hearing loss (24 dB) in Mg-deficient rats. The degree of hearing loss was negatively correlated with plasma and erythrocyte Mg levels. In a subsequent study [47] they found that gentamycin-induced hearing loss was markedly increased by mild Mg deficiency. Administration of gentamycin for 5 days to normal rats caused an elevation of hearing threshold of 11 dB at 10 kHz and 13 dB at 20 kHz, which had decreased to 2 and 6 dB, respectively, a week later. In Mg deficiency, the hearing loss was 42 dB at 10 kHz and 43 dB at 20 kHz; I week later, despite a normal diet, hearing loss had not improved in the Mg-deficient group. Complete irreparable deafness occurred in 36% of Mg-deficient rats and in none of the normal rats given gentamycin. In a human study, fighter pilots occupationally exposed to noise stress underwent evaluation of hearing thresholds at 3, 4 and 6 kHz and serum Mg concentrations [48]. The correlation between age-adjusted hearing loss and serum Mg was -0.61 (n = 24, p < 0.001). The authors speculate that alterations in K, Na and Ca transport induced by mild Mg deficiency are responsible for impaired function of cochlear hair bundles [49].

Stress/Mg Interactions

The effect of Mg status on hearing loss is complicated by the effect of noise stress on Mg metabolism; this well-studied interaction has yielded considerable support for clinical theories concerning the relationship between stress and Mg in diverse situations. Consequently, it is reviewed here in detail. Two hours of noise stress in guinea pigs causes a mean reduction in erythrocyte Mg of 2 mmol/g dry weight and a simultaneous increase in serum Mg by 0.8 mmol/l, suggesting a shift of Mg from the intracellular to the extracellular compartment [50]. In rats, chronic noise stress causes an increase in serum Mg and a decrease in erythrocyte and

myocardial Mg [46, 50]. When Mg intake is normal, 20 days of noise stress raises the mean serum Mg from 0. 9 5 to 1. 15 mmol/l and lowers mean erythrocyte Mg from about 5.8 to 4.8 mmol/kg dry weight. After 24 h of silence, the serum Mg drops below the control level to 0.90 mmol/l, and the erythrocyte Mg increases but does not reach control levels, failing to rise above 5.4 mmol/kg dry weight, even with a fourfold increase in dietary Mg. Myocardial Mg decreases in parallel with erythrocyte Mg [50]. The implication is that a net excretion of Mg occurs in response to noise stress, leaving the animal depleted. In fact, Mg excretion increases from a control value of 6 to 16 mmol/g creatinine under noise stress [50]. Similar results occur in humans. Ising et al. [51] exposed 57 human volunteers to work under 7 h of traffic noise or 7 h of quiet. Under noise stress, the serum Mg increased by 2.4% (p 0.01), the urine Mg increased by 15 % (p 0.01) and the erythrocyte Mg decreased by 1.5% (p = 0.05). The degree of increase in serum Mg correlated with a decrease in work performance (r = 0.37, p = 0.05). Brewery workers laboring for I week in a noisy hall (95 dB) lost 5% of their blood cell Mg content compared to a similar group using ear protectors [52].

The metabolic effects of noise stress in humans and animals are accompanied by changes in catecholamine metabolism. Brewery workers working for 1 day with ear protection and 1 day without excrete significantly more norepinephrine (NE) and its metabolite vanilly1mandelic acid in urine under the noise stress condition [52]. In a similar study of male volunteers exposed to traffic noise, urinary NE increased 8.5% (NS) and urinary epinephrine increased 27 % (p = 0.01) during the 7-hour period of noise stress [51]. Pronounced increases in catecholamine excretion also occur in rats exposed to noise [53, 54], although it appears that preexisting Mg deficiency is necessary for this effect to occur [53]. The effect of Mg status on the behavioral and biochemical response to noise completes the cycle. Urinary catecholarnine excretion increases progressively with increasing dietary Mg deprivation in rats without noise stress. The addition of noise further increases NE but not epinephrine excretion; the more pronounced the noise and the greater the Mg deficit, the higher the catecholamine excretion, with epinephrine and NE excretion reaching 5 and 10 times control levels under extreme but nonlethal conditions [48]. Noise stress in Mg-deficient rats causes a decrease in myocardial Mg and an increase in cardiac Ca concentration that is independently proportional to the degree of Mg deficiency and the duration of noise [55]. The decrease in myocardial Mg displayed a negative linear correlation with the excretion of NE [50].

Erythrocyte Mg levels are inversely proportional to some effects of noise stress in humans and animals. Erythrocyte Mg is negatively correlated with self-reported noise sensitivity (r = -0.27, p = 0.05), with noiseinduced emotional lability (r = 0.37, p = 0.01) and with noise-induced feelings of tenseness (r = -0.29, p = 0.05) in human volunteers [46]. The hypertensive effect of injected NE in noise-stressed rats was negatively correlated with erythrocyte Mg (r = -0.70, p < 0.01) [47]. Deposition of collagen in the rat heart, a sign of physiologic aging, is synergistically accelerated by noise stress and Mg deficiency [56]. Mg supplementation prevents this effect; caffeine feeding increases it [57]. In summary, noise exposure causes an increased excretion of catecholamines and a shift of Mg

from the intracellular to extracellular space with a resulting increase in Mg excretion. This effect on Mg metabolism is initially protective; the relatively high serum Mg level of acute stress is thought to buffer the physiologic response to stress. Prolonged noise exposure causes a gradual Mg depletion associated with accelerated physiologic aging. Dietary Mg deficiency aggravates in a synergistic fashion all the effects of noise stress, including ototoxicity, adrenergic hyperactivity, Mg depletion, psychological and physiologic deterioration. Mg supplementation appears to protect against some of the effects of noise. Humans with relatively high intracellular Mg as measured by the erythrocyte level are less adversely affected by noise than are humans with relatively low erythrocyte Mg.

The extra-aural effects of noise can be produced by a wide variety of stressors, including overcrowding and prolonged handling of animals [39,45]. Guinea pigs are so sensitive to the effects of handling that serum Mg changes induced by noise and diet can be obscured by experimental design that does not control for handling stress [39]. Rats injected with direct- and indirect-acting sympathornimetic amines similarly develop intracellular Mg depletion, which is associated with an increase in intracellular Ca and Na; adrenergic activity appears to mediate the impact of stress on Mg metabolism [58]. Dietary Mg depletion accelerates these electrolyte shifts; Mg supplementation reduces them [53, 59]. The type A or 'coronary prone 'behavior pattern in humans is characterized by time urgency, impatience, extreme competitiveness and hostility when compared to its opposite or type B pattern [60]. When stressed psychologically, type A individuals show significantly greater increases in plasma and urinary catecholamines and cortisol than type B individuals [61], and correspondingly greater changes in heart rate, blood pressure and vascular resistance [62]. In 1980, Altura [63] first suggested that the type A behavior pattern may be associated with Mg deficiency. Henrotte et al. [64] studied the effect of a signal detection task on Mg metabolism of 20 type A and 19 type B French university students. Mental stress increased the urinary catecholamines and serum free fatty acids of both groups; the effects were significantly greater in type A than in type B individuals. Plasma Mg increased by 1.5% (p < 0.05), and erythrocyte Mg decreased by 0.5% (p < 0.01) in type A subjects; there was no change in these levels for the type B subjects. The high degree of statistical significance for these small changes was due to the homogeneity of response in type A subjects, producing a very low standard deviation. Henrotte [65] attributes the flux of Mg from erythrocyte to plasma to the stimulation of 0-adrenergic receptors on the erythrocyte membrane.

The experimental observations of the effects of various types of stress on electrolyte and catecholamine levels are consistent with clinical observations of patients with TS. Excretion of catecholamines is 89% greater (p < 0.001), and excretion of vanillylmandelic acid is 53% greater (p < 0.01) in TS patients than in controls; this increase in adrenergic activity correlates with lower serum K and serum and erythrocyte Mg and higher venous blood pH [66]. Ca and Na content of erythrocytes from TS patients is greater in patients with TS than in controls [67]. Administration of Mg salts produces a small increase in serum K and serun and erythrocyte Mg in these patients but does not affect erythrocyte Ca or Na levels [68]. There are no data to indicate that Mg therapy by itself lowers

catecholamine excretion in these patients and most clinicians favor the use of P-blockers in addition to Mg [20, 21, 29]. In reviewing his experience treating nervous children with TS, Ducroix [69] concluded that the pathogenesis of the syndrome is still unclear, particularly with regard to the interaction of psychogenic and metabolic factors, and that the best test of Mg deficiency was a trial of oral Mg therapy. This is the ultimate position of Durlach [20] and Fehlinger [21] also. Both authors recommend the use of acidic salts of Mg, believing that they have superior absorption and do not aggravate the alkalosis manifested by some TS patients. Durlach recommends 5 mg/kg/day, and Fehlinger prefers 6-7 mg/kg/day. Ducroix prefers 10 mg/kg/day for children because of their low body weight and increased requirements for growth. Fehlinger has described a group of patients with a continuous requirement for oral Mg at doses of 400-1,400 mg/day. When hospitalized and given placebo instead of Mg, these patients drop their plasma Mg from a mean of 0.85 to 0.74 mmol/1 within 1 week and become acutely symptomatic [21].

In summary, there are groups of individuals among whom asthenia and dysphoria are common complaints, who show elevated urinary catecholarnines and mildly depressed circulating Mg levels. When properly examined, almost all these patients show sings of latent tetany. Their symptoms generally improve with oral Mg supplementation. It is not clear why these individuals are so sensitive to the effects of mild Mg deficit or whether their deficiencies are primarily caused by diet or metabolism. The biological and psychological profiles of these patients can be predicted from studies of humans and animals subjected to prolonged noise; it is likely that an interaction between the effect of chronic stress and inadequate Mg intake can explain the appearance of this syndrome and also the variability of serum Mg levels, which are raised by stress and lowered by deficient diet.

Interest in this phenomenon in the English-speaking world is likely to be stimulated by a recent, highly publicized British study of patients with chronic fatigue 'syndrome [70]. Their mean erythrocyte Mg was 0.1 mmol/1 lower than that of a carefully selected control group (p < 0.001). Thirty-two patients were randomly treated with weekly injections of $MgSO_4$, 1 g, or placebo, for 6 weeks. Erythrocyte Mg increased significantly in the active treatment group and did not change in the placebo group. Fatigue, muscle pain and emotional lability were significantly improved by Mg injections. This study is important because of the correlation between biochemical and symptom response and the use of a randomized double-blind placebo-controlled design, which is rarely used in European studies of Mg therapy.

Mg and Epilepsy

Although epileptic fits occasionally occur in TS and were reported in 5-10 % of Fehlinger's cases, the prevalence of TS or Mg deficiency in idiopathic epilepsy has not been established. A Brazilian study found lower serum Mg in epileptic patients than in controls (1.868 vs. 2.087 mEq/1, p < 0.001),

but all levels were within the normal range [71]. Immediately following a seizure, both serum and CSF Mg increased. Others have found CSF Mg to increase after a seizure [72], but serum Mg does not increase consistently [73]. Epilepsy itself does not cause Mg depletion, but anticonvulsant drug therapy may [74-77]. Steidl et al. [78] studied serum and erythrocyte Mg in relationship to drug use, serum drug concentrations and Mg therapy in epileptics. No significant effects on serum Mg were found; erythrocyte Mg was significantly lowered ($p < 0.05$) in patients with phenobarbital levels > 20 gg/ml or with diphenylhydantoin levels > 10 gg/ml. Mg lactate 3 g/day produced an increase of 25.6% (NS) in erythrocyte Mg when administered to patients taking both phenobarbital and diphenylhydantoin; in patients taking phenobarbital, diphenylhydantoin and primidone, the same dose of Mg lactate raised erythrocyte Mg by 46.7% ($p < 0.05$). The clinical significance of Mg depletion and repletion in these patients was not clear in that most patients had been free of seizures for 1 year before the study commenced.

The Major Psychoses and Mg Status

Kirov [79] has recently reviewed the literature on Mg status of patients with schizophrenia or bipolar affective disorder. There was no consistent effect of schizophrenia, mania or depression on serum Mg across 40 studies or on CSF Mg across 12 studies. Neuroleptic therapy in chronically ill patients consistently lowered serum Mg in 8 studies reviewed by Kirov. Decrease in stress hypermagnesernia may explain the effect [80]. Lithium, on the other hand, does not alter serum Mg when administered over several months [81, 82]. In that a single dose of Li given to patients and healthy volunteers acutely raises serum [83] and plasma [84] Mg, it is likely that Li has direct and indirect effects that alter extracellular Mg in opposite directions. The effect of imipramine with or without electroconvulsive therapy on Mg metabolism appears to be variable [85]. Although disorders in Mg metabolism do not play a primary role in the major affective disorders or psychoses, Kirov [79] has proposed a secondary role for Mg deficiency in some acutely ill psychiatric patients. He speculates that the higher than normal variability of serum or plasma Mg in psychiatric patients may represent the combined effects of stress, medication and deficiency and may produce clinically significant depletion. He has observed an association between severity of anxiety or depression and low plasma Mg. Pliszka and Rogeness [86] measured serum Mg in 165 boys admitted to a psychiatric hospital and found low Mg levels to be associated with dysphoric mood and sleep disorders. A French team has recently demonstrated that Mg aspartate-HCI was as effective as Li in stabilizing the mood swings of rapid-cycling bipolar depressives [87].

Mg/Pyridoxine Responsiveness of Childhood Autism

The combined effect of oral Mg (5 mg/kg/day) and high-dose vitamin B6 (15 mg/kg/day) has been studied repeatedly in infantile autism. In the initial uncontrolled trials conducted by Rimland [88], pyridoxine alone produced impressive improvement in speech and behavior of some

children; side effects of enuresis, sound sensitivity and irritability were common with high-dose pyridoxine, but addition of Mg 300-500 mg/day alleviated them. A subsequent placebo-controlled, double-blind study of the subgroup of pyridoxine responders found that pyridoxine 300-500 mg/day plus Mg 200400 mg/day produced significant improvement in behavior: better eye contact, less self-stimulation, fewer tantrums, more interest in the world, more frequent speech; in no case did complete remission occur, however [89]. Subsequent studies in France confirmed the value of combined Mg/vitamin B6 therapy in a large subgroup of autistic patients but failed to demonstrate any effect of Mg or vitamin B_6 alone [90-92]. In these studies, the combination therapy lowered the abnormally high urinary excretion of the doparnine metabolite homovanillic acid of some autistic children but did not affect its excretion of normal children. Mg/vitamin B6 also corrected the abnormal amplitude and morphology of cortical evoked potentials in autistic individuals. LeLord et al. [93] report that 47% of autistic patients respond positively to Mg/vitamin B_6 therapy. Rimland [94] asked the parents of more than 1,000 autistic children to evaluate the effects of various treatments on their children. He found that 43% of 318 patients who had tried the Mg/vitamin B6 regimen experienced benefit compared to an improvement in 20-40% of autistics who had taken various neuroleptics, tranquilizers and stimulants. Adverse side effects occurred in only 5% of children receiving Mg/vitamin B_6 and in 19-49% of children on drug therapy [94].

The mechanism of action of Mg/vitamin B_6 in autism is unknown. Rats rendered moderately Mg deficient have a selective doubling of cerebral doparnine, which is restored to normal with Mg feeding [95]. Mg, therefore, seems to have a unique relationship to dopamine; the therapy may partially correct an error in dopamine metabolism in some autistic people.

Mg Effects in Cerebral Trauma

Vink and McIntosh [96] recently reviewed the relationship between Mg and traumatic brain injury, the major cause of death in individuals under the age of 44 living in industrialized countries. Brain-injured rats develop a marked decline in intracellular free Mg as demonstrated by 31p magnetic resonance imaging. Rats rendered Mg deficient by diet show a significantly worse outcome with brain injury than do normal rats.

Intravenous infusion of Mg sulfate prior to trauma attenuates the decline in free Mg and improves neurologic outcome. Mg chloride infusion 30 min after trauma at doses of 12.5 or 125 umol produces a significant improvement in motor function at 4 weeks after the injury when compared to saline infusion. They found that other pharmacologic agents which reduce the neurologic deficits of head trauma, such as opiate and N-methylD-aspartate antagonists, improve the outcome to the extent that they restore cerebral free Mg levels toward normal. Mg ion protects neurons in vitro from anoxic damage [97]; excitatory neurotransmitters which activate N-methyl-D-aspartate receptors amplify such damage [98]. Rats injected with the N-methyl-D-aspartate agonist quinolinate experience hippocampal degeneration and convulsive seizures; rats given subcutaneous injections of Mg sulfate (600 mg/kg) up to 3 h after the

quinolinate injection showed significant protection against neurotoxicity [99].

Conclusions

Mg ions have nutritional and pharmacologic actions that protect against the neurotoxicity of agents as diverse as environmental noise, sympathornimetic amines and physical trauma. Mg deficiency, even when mild, increases susceptibility to various types of neurologic and psychological stressors in rodents, healthy human subjects and diverse groups of patients. Repletion of deficiency reverses this increased stress sensitivity, and pharmacologic loading of Mg salts orally or parenterally induces resistance to neuropsychologic stressors. Mild Mg deficiency appears to be common among patients with disorders considered functional or neurotic and appears to contribute to a symptom complex that includes asthenia, sleep disorders, irritability, hyperarousal, spasm of striated and smooth muscle and hyperventilation. By increasing the sensitivity of cerebral arteries to the regulatory effects of CO_2, Mg deficiency may contribute to the cerebral vasospasm of some patients with migraine headache or TIA [100, 101]. The application of increasingly sensitive methods for measuring intracellular Mg levels is likely to clarify the nature of Mg deficit in such patients; when physical and electrodiagnostic evidence of neuromuscular hyperexcitability accompanies such symptoms, the therapeutic administration of Mg salts is warranted, whether blood Mg levels are low or normal.

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