Magnesium in Health and Disease

Laboratory Findings in 59 Epileptics on Prolonged Anticonvulsant Therapy

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INTRODUCTION

As early as 1900, Loeb (1900) studied the effect of metal ions on neuromuscular excitability. Since then the role of sodium (Na), potassium (K), and calcium (Ca) in neuromuscular excitation has been extensively studied. More recently magnesium (Mg) has been specifically investigated. Hyperexcitability of the peripheral or central nervous system constitutes the most frequent and prominent manifestation attributed to Mg deficiency states (Chutkow, this symposium). Some authors suggest that epileptical manifestations may be an expression of Mg deficiency (Wacker and Parisi, 1968; Hansson, 1971). Jain et al. (1970) reported hypomagnesemia in "idiopathic" epilepsy. Richens and Rowe (1970) were the first to report the occurrence of hypocalcemia and elevation of serum alkaline phosphatase (S-ALP) and Dent et al. (1970) reported the occurrence of osteomalacia in epileptics on prolonged anticonvulsant therapy. We therefore chose to study 1) serum magnesium (S-Mg) and serum calcium (S-Ca) concentration and S-ALP activity in patients with long-standing epileptic manifestations and 2) whether other biochemical changes might be found in patients receiving prolonged anticonvulsant therapy. A laboratory screening was carried out in a series of neurological cases with epileptic manifestations of long standing.

MATERIALS AND METHODS

Patients

In-patients of the Epilepsy Hospital, Erstagarden, Stockholm, 59 cases (4 men, 55 women), having an average age of 41.3 (S.E.M; 1.9) and an average duration of the neurological disease with epileptic manifestations of 29 .7 years (S.E.M; 2.1),were studied. The diagnoses are listed in Table 1.

Each patient received between one to six anticonvulsant drugs. Forty six of the 48 patients who were in the hospital throughout the period of the investigation, vide infra, had epileptic seizures despite intensive anticonvulsant medication. The principles of management were 1) not to allow the patients to lie in bed, except on medical indication,

2) to afford the patients as great a degree of freedom of movement as possible as well as an opportunity to work within the hospital (in the kitchen, laundry, workshops, or at the adjoining farmhouse), or outside the hospital area. The exact frequency of the patients' seizures, thus, could not be recorded.

The patients received a well-balanced diet, rich in protein, fruits, and vegetables, that contained between 10-20 mmol Mg daily.

Table 1. Patient Diagnoses

Diagnoses	No.
Epilepsy with minor and uncertain cerebral lesions	10
Moderate or massive cerebral lesions with epilepsy	15
Early cerebral lesions with mental retardation, or dementia with epilepsy	16
Epilepsy with psychiatric syndromes	12
Epilepsy with other diagnoses	6
Total	59

Controls

Intraindividual variation in S-Mg concentration of the epileptic patients was compared with that of 11 apparently healthy nonalcoholic men, 18-43 years old, whose blood was sampled in the morning in the postprandial state initially, and again after an interval of 10-14 days. As controls for comparing the mean S-Mg concentration, 95 nonalcoholic patients with a diagnosis of psychoneurosis and psychosis and no pathological laboratory findings, matched for age and sex with the epileptics and examined at the same laboratory, were studied. To compare mean S-Ca concentration, 135 patients of the same population, similarly matched, were used. For the remaining variables, the clinical chemistry laboratory's range of normal values was used as a basis for the estimation of the mean in order to compare it with the mean of the epileptic patients.

Magnesium Medication

Six patients with S-Mg concentration of < 0.75 mmol/liter, were given oral Mg (magnesium hydroxide); two patients received 36 mmol Mg daily for 1 week and four patients received Mg for 2 weeks; one of the latter inserted a daily dosage of 54 mmol. This patient (with hypomagnesemia, hypocalcemia, and low serum phosphate concentration) received, in addition to Mg (1.3 g daily), bone powder tablets, three times daily: each tablet contained 0.1 g Ca and 0.046 g phosphorus (P).

RESULTS

Serum Magnesium Concentration

No difference was found between the mean, standard error of the

mean ($\bar{x}$; S.E.M.) of the control group (0.839; 0.006) and that of the epileptic subjects (0.840; 0.009). On comparison of the distribution of controls and patients, with χ^2 analysis (or Mann-Whitney test), we found no significant difference, but a moderate negative skew could be noted in the epileptics, which could not be seen in the distribution of the controls. No correlation was found on multiple regression analysis between the S-Mg concentration and the age of the female epileptic patients, nor the duration of the illness. The incidence of hypomagnesemia ($\leq$0.73 mmol/liter was 9%, and of hypermagnesemia (>0.95 mmol/liter) was 2%.

Serum Calcium Concentration

The difference between the mean of the control material (2.400; 0.008) and the mean of the epileptics (2.348; 0.015) was statistically significant ($p<0.001$). On comparing the distribution, that of the epileptic patients shows a positive skew (on χ^2 analysis; $\chi^2 = 15.6$, df = 7; $p<0.05$ and on Mann-Whitney Test; $p<0.01$). Hypocalcemia ($\leq$2.20 mmol/liter) was found in 9%, and hypercalcemia in 2% of the noncontrols. On multiple regression analysis, no correlation was found between the S-Ca concentration in the female epileptics and the age of the patients, nor for the duration of the illness. In the controls on the other hand, one finds a slight, but statistically significant, rise ($p<0.001$) of the S-Ca concentration with increasing age: y (S-Ca concentration) = 2.355 + 0.002 x (age in years).

Alakaline Phosphatase

The mean S-ALP was significantly raised and the distribution differed significantly ($p<0.01$). In order to establish whether the increase in S-ALP was related to the duration of the illness or the age of the patients, a multiple regression analysis was carried out, followed by a partial regression analysis (Snedecor and Cochran, 1973). The rise of S-ALP was shown to be related to the age of the patient and to be independent of the duration of the disease. Rise of S-ALP was also found to be related to the presence of concomitant disease, e.g., hypothyroidism.

Other Laboratory Variables

The mean as well as the distribution of S-ALAT and of the erythrocyte sedimentation rate (S-ER) was significantly raised ($p<0.01$). The distribution of serum iron was significantly different ($p<0.01$). Hypersideremia was present in 11% of the female patients.

Blood Cell Count and Microscopy

There was no decrease in the total white cell count. The means of basophils, lymphocytes, and monocytes were significantly higher ($p<0.01$). The distribution of basophils differed significantly ($p<0.05$), as did that of lymphocytes, monocytes, and eosinophils ($p<0.01$). Twenty six percent of the patients had eosinopenia (total eosinophil count was not carried out). Only 10 patients had a normal white cell count, but

four of this latter group had red cell anisocytosis. Of the total subjects, 40% showed anisocytosis.

Phenobarbitone and Phenytoin

Phenobarbitone (mean value 3.91; 1.67, $\underline{n}$ = 36) ranged from 3-65 mg/liter. The phenytoin range was kept between 9-20 mg/liter.

Treatment Trial

The six patients with S-Mg concentration of < 0.75 mmol/liter, who received Mg treatment responded with a rise in S-Mg concentration. One patient, with hypomagnesemia, hypocalcemia, and low serum phosphate (PO_4) concentration who deteriorated steadily due to severe, prolonged, and frequent epileptic fits, showed no response to conventional treatment and prior to initiating Mg, Ca, and PO_4 supplementation was cyanotic and moribund. Epileptic seizures diminished in severity and frequency, and the patient made a striking gradual clinical recovery following treatment.

Intraindividual Variation in Serum Magnesium, Serum Calcium Concentration

In five patients with S-Ca of > 2.50 mmol/liter, serial sampling was undertaken to exclude hyperparathyroidism. Markedly oscillating S-Ca concentration was found, although the level was no longer near the upper border of the range of normal values. Serum Mg concentration also showed marked intraindividual variation on serial samplings in six patients not treated with Mg, as compared with healthy controls.

Effect of Medication on Laboratory Findings

The multiplicity of the drugs administered makes it impossible to isolate the possible specific effects of each drug on the laboratory findings, particularly since the age of the patients and the existence of concomitant diseases, other than epilepsy, were shown to affect the laboratory findings. As regards the long-term medication with phenobarbitone and/or primidone (metabolized to phenobarbitone (Bogan and Smith, 1968)) and its possible effect on the laboratory findings, no statistically significant correlation was found between S-Mg, S-Ca, nor S-ALP concentration levels and the levels of phenobarbitone in the blood of the 33 patients receiving either or both of these drugs, along with other anticonvulsant medication.

Lowering of Serum Magnesium and Serum Calcium Concentration

With regard to the incidence of lowering of either S-Mg or S-Ca concentration of <0.790 mmol/liter and <2.275 mmol/liter, respectively, in the diagnostic subgroups of epilepsy, the highest incidence of lowering of either cation was found in the group of epileptics with concomitant psychiatric diagnosis, 67% (8/12), and the lowest, 37% (6/15), in cases with massive or moderate cerebral organic lesions un-

derlying the epileptic seizures (Table 1).

DISCUSSION

The 9% incidence of hypocalcemia in our study is lower than that reported by Christiansen et al. (1973, 1974b), Hunter et al. (1971), and Richens and Rowe (1970), and the 9% incidence of hypomagnesemia is lower than that reported by Babel et al. (1973), Jain et al. (1970), and Christiansen et al. (1974a).

We could not confirm the finding of Christiansen et al. (1974a) of a signficiantly lowered mean S-Mg concentration, but found instead, a moderate negative skew not seen in the distribution of the controls, as well as a wider intraindividual variation than that of the healthy controls. We found no correlation between the S-Mg concentration of the female epileptics and the duration of the disease, nor with the age of the patient, whereas a correlation with age exists in a normal female population (Goldberg et al., 1973). No correlation was found between the S-Ca concentration and the duration of the illness, and no correlation with the age of the patient; the latter is in agreement with recent findings in normal population (Goldberg et al., 1973). In our control subjects, the S-Ca concentration was significantly correlated to age ($p<0.001$), contrary to recent findings in a normal population (Goldberg et al., 1973); the reason for this is not clear.

Jain et al. (1970) reported a 65% presence of hypomagnesemia and a low cerebrospinal fluid (CSF) Mg concentration in 52% of epileptics, selected so as to exclude cases with underlying organic lesion. Christiansen et al. (1974a) and Babel et al. (1973) do not differentiate their subjects diagnostically with regard to the extent of possible underlying organic damage. Our patients were screened diagnostically by means of electroencephalogram (EEC) examination and classified as outlined by Flodmark (1975) (cf. Table 1). The majority of our patients had severe long-standing epilepsy with underlying organic lesions. The lowest incidence of lowering of either divalent cation in our subjects was seen in patients with moderate or massive organic lesion underlying the epileptic manifestations. The difference in the incidence of hypomagnesemia, between the cited reports and our own, might, therefore, among other factors (e.g., diet) be due to heterogenity of the patients studied.

The intraindividual variation of S-Mg concentration studied in the epileptic patients, not treated with Mg, is marked. The S-Ca concentration shows marked oscillations, as well, but similar fluctuations are met with in nonepileptics with suspected hyperparathyroidism.

Normally, CSF-Mg concentration is 25-40% higher than that of the serum and CSF-Ca concentration is about 50% lower than that of the serum (Dawson, 1967). Hüber (1964) reported lowering of CSF-Mg levels in 3 out of 20 children examined during epileptic seizures and a return to normal during the nonconvulsive period. Babel et al. (1973), found significantly lowered serum and CSF-Mg levels within 24 hr of epileptic seizure in grand mal "idiopathic" epilepsy in adults. During the interseizure period the CSF-Mg rose and was no longer significantly lowered, but the S-Mg concentration remained low. Serum Ca concentration was high both in the postseizure and in the interseizure periods, whereas the CSF-Ca remained normal.

Seizures induced by electroconvulsive shock therapy in schizophrenics did not cause a fall of S-Mg concentration; on the contrary, a nonsignificant rise occurred, leading to the conculsion that the biochemical

changes constituted the cause and not the effect of epileptic seizures (Babel et al., 1973).

Our patients had seizures in spite of anticonvulsant therapy. This could be explained by the marked fluctuation of the intraindividual S-Mg and S-Ca concentration as compared with the controls; the instability of the divalent cations triggering off the epileptic seizure.

The question remaining to be clarified is whether the marked intraindividual variation in the level of the divalent cations might be caused by the anticonvulsant therapy. However, marked intraindividual variation in the S-Mg concentration was also noted in acute sequellae of alcohol abuse in the absence of anticonvulsant treatment (Stendig-Lindberg, 1974). It is noteworthy, that hypomagnesemia in alcoholics is well documented, hypocalcemia has been reported (Sullivan et al., 1969), and that chronic alcoholics are in addition, prone to epileptic seizures. The reported incidence of epileptic seizures in chronic alcoholism is 25% by Berglund, (1974), and 4-41% by Salum, (1972); in delerium tremens Nielsen (1965) reports 5%, Stendig-Lindberg (1977) 15%, and Salum (1972) 19%.

In another group of epileptic seizures, i.e., neonatal convulsions, hypocalcemia was reported as causal in 20-34% (Keen, 1969; McInerney and Schuberg, 1969; Rose and Lombroso, 1970). Hypomagnesemia and/or hypocalcemia are found in over 50% of the neonatal seizures reported and there is a significant lowering of both cations in the CSF (Brown 1970; Cockburn et al., 1973). In febrile convulsions in 100 children, Chhapparwal et al. (1969) found lowered S-Mg concentration in nearly 50% and lowered CSF-Mg in over 67%. The incidence of biochemical neonatal fits, is 7 per 1000 deliveries (Brown, 1970). A certain percentage of infants with convulsions, whether "idiopathic" or febrile, develop epilepsy later in life (Brown et al., 1972; Langslet, 1974).

In the patients we studied, epilepsy was preceded by neonatal convulsions in two cases and by febrile convulsions in three cases. The neonatal convulsions are believed to be caused by a primary disturbance of mineral metabolism (Rose and Lombroso, 1970; Hansson, 1971; Brown et al., 1972; Cockburn et al., 1973; Forfar, 1974). The hypomagnesemia and/or hypocalcemia reported in neonatal convulsions is seen prior to the initiation of anticonvulsant therapy.

Magnesium appears to have an important role in correcting not only hypomagnesemia but also hypocalcemia in neonatal convulsions (Cockburn et al., 1973). Paunier et al. (1968), Davis et al. (1965), and Salet et al. (1966) have reported neonatal hypocalcemia which responded to Mg treatment, but not to Ca therapy. Experimentally induced Mg deficiency in man can cause secondary hypocalcemia (Heaton, 1971).

The striking improvement of the moribund patient on Mg therapy, combined with Ca and PO_4, along with a decrease in the frequency of seizures, further, demonstrates the important role that mineral deficiency appears to play in the epileptic patient. Several authors interpreted the presence of hypocalcemia in epileptics as a possible result of anticonvulsant drug-mediated microsomal enzyme induction in the liver (Dent et al., 1970; Richens and Rowe, 1970; Hunter et al., 1971; Christiansen et al., 1972, 1974b). However, we found no significant correlation between the S-Ca or the S-Mg concentration and the blood level of phenobarbitone in the blood of 33 patients medicated by phenobarbitone and/or primidone, metabolized to phenobarbitone (Bogan and Smith, 1968), nor any other specific drug therapy.

Christiansen et al. (1973) reported raised S-ALP in 43%; in our patients we found a rise in 42%. It is of interest to note that of the 47 patients with raised S-ALP in the study by Richens and Rowe (1970),

hypocalcemia occurred more often in the group with an increase in the liver isoenzyme (28 patients) than in the group with an increase in the bone isoenzyme (18 patients). This finding was interpreted to be a result of drug-mediated microsomal enzyme induction in the liver, leading to increased breakdown of vitamin D to inactive products and subsequent osteomalacia (Dent et al., 1970; Richens and Rowe, 1970). However, we showed that S-ALP was not correlated to the blood levels of phenobarbitone, any other specific drug therapy, or to disease duration, but to the age of the patient and to concomitant disease, e.g., hypothyroidism. These findings in our view, imply that other factors are more important with regard to the elevation of alkaline phosphatase than the anticonvulsant drug-mediated induction of hepatic microsomal enzymes.

Anticonvulsants have been reported to give rise to folic acid deficiency (Neubauer, 1970; Maxwell et al., 1972) to suppress the insulin response of the glucose-stimulated cells of the pancreas (Malherbe et al., 1972; Segaard and Granfelt, 1973) and to give rise to a teratogenic effect (Fedrick, 1973) and tendency toward hemorrhage in the offspring of the epileptic mother (Seip, 1972), as well as to cause osteomalacia (Dent et al., 1970; Richens and Rowe, 1970; Hunter et al., 1971; Christiansen et al., 1972, 1973, 1974b).

We found, along with a low incidence of hypocalcemia and hypomagnesemia, a marked instability of S-Mg and S-Ca concentration, as well as a most unusual hypersidermia in 11% of the female patients and a raised mean S-ALAT and E-SR.

It is, nevertheless, noteworthy, that the differences between the biochemical parameters of these severely ill epileptics on prolonged anticonvulsant therapy and those of the controls or those estimated from the laboratory's range of normal values, although statistically significant, are quantitatively small. The feature of greatest interest in our findings is the suggested evidence of mineral metabolism disturbance in the epileptic.

SUMMARY

Laboratory screening was undertaken in 59 epileptics with an average duration of the illness of 29.7 years (SEM: 1.9). The incidence of hypomagnesemia and of hypocalcemia was 9% and of hypermagnesemia and hypercalcemia 2%. Marked intraindividual variation was noted in S-Mg and S-Ca concentration on serial sampling, as compared with healthy controls. The mean S-Mg concentration of the patients and the controls did not differ, the distribution showed a moderate, although statistically insignificant, negative skew, which could not be seen in the controls. The mean S-Ca concentration was significantly lower ($p<0.01$) and the distribution differed ($p<0.01$) in epileptics in comparison with controls. The mean S-ALP was significantly raised ($p<0.01$) and the distribution differed ($p<0.01$). However, S-ALP was positively correlated to the age of the patients ($p<0.05$) and to concomitant disease, other than epilepsy (e.g., hypothyroidism) and not to the duration of the epilepsy. Serum iron distribution differed significantly ($p<0.01$); it was noteworthy that 11% of the female patients had raised values. S-ALAT and E-SR means were significantly raised and the distribution differed ($p<0.01$). It is, nevertheless, noteworthy that the differences between the biochemical parameters of these severely ill epileptics, on prolonged anticonvulsant therapy, and those of the controls, or those calculated from the laboratory's range of normal values, although statistically

significant, are quantitatively small. No statistically significant correlation was found between S-Mg and S-Ca concentration, nor S-ALP level and the concentration of phenobarbitone in the blood of 33 patients receiving phenobarbitone medication and/or primidone--metabolized to phenobarbitone. Six patients treated with $Mg(OH)_2$, showed a resultant rise of S-Mg concentration. Remarkable clinical improvement was observed in one, moribund, epileptic with hypomagnesemia, hypocalcemia, and low serum PO_4 following treatment with Mg and a bone extract containing Ca and P. Our findings suggest the presence of mineral metabolism disturbance in the epileptic patient.

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