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Plasma Calcium, Copper, Magnesium, and Zinc Concentrations in Patients with the Alcohol Withdrawal Syndrome

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We determined zinc, copper, magnesium, and calcium concentrations by atomic absorption spectrophotometry in the plasma of 30 patients hospitalized for treatment of seizures during a period of alcohol withdrawal. Those patients who developed delirium tremens or a prolonged hallucinatory state had significantly higher plasma copper concentrations ($P = 0.026$), significantly lower zinc concentrations ($P = 0.004$), and significantly higher copper/zinc ratios ($P = 0.001$) than the patients who recovered uneventfully. Zinc deficiency may be one of the factors that contribute to the neurologic complications of alcoholism. A determination of the plasma copper/zinc ratio early in the course of alcohol withdrawal could be of value in indicating which patients have the most substantial underlying disease or metabolic imbalance and therefore may be at greatest risk of developing delirium tremens or prolonged hallucinosis.

Additional Keyphrases: *trace elements · alcoholism · prognostic aid · atomic absorption spectroscopy · toxicology · normal values*

The syndrome of tremulousness, irritability, seizures, delirium, hallucinations, and autonomic over-flow in various combinations may become manifest during a period of withdrawal from alcohol. These signs and symptoms are similar to those seen during withdrawal from other central nervous system depressant drugs. However, the exact pathophysiology involved in the genesis of this syndrome during alcohol withdrawal is poorly understood. Some patients develop delirium tremens; others have only isolated seizures or hallucinosis. Respiratory alkalosis, lactic acidosis, and low serum magnesium concentrations have been noted as fairly consistent features of these cases (*1*). However, no other laboratory test results correlate well with the onset of clinical signs (*2*).

It has been documented that plasma zinc is depressed and plasma copper concentration is increased as a nonspecific reaction pattern during the active phase of various diseases involving several organ systems, including alcoholic cirrhosis (*3–7*).

In an attempt further to define the pathophysiology of the neurologic complications of alcoholism, we determined plasma zinc, copper, magnesium, and calcium concentrations in a group of patients hospitalized for the management of seizures that occurred during a period of alcohol withdrawal.

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Materials and Methods

Patient Sample

In all, we studied 30 cases, all of them patients hospitalized for treatment of seizures that occurred during a period of relative or absolute alcohol withdrawal. All patients were known to be severe chronic alcoholics who had been drinking excessively for prolonged periods of time before the onset of seizures. Subsequently, after admission, the patients were further subdivided into groups comprised of cases with seizures only with uneventful recovery (16 cases) and cases developing delirium tremens (nine cases). A third group consisted of those patients who remained in a prolonged hallucinatory state after the seizures but did not develop frank delirium tremens (five cases).

The 30 patients studied had no history of other conditions that may cause changes in plasma copper and (or) zinc concentrations, including diabetes, recent surgery, myocardial infarction, cerebral infarction, osteosarcoma, lymphoma, lung cancer, Hodgkin's disease, rheumatoid arthritis, sickle cell anemia, uremia, or pernicious anemia. None of the women were pregnant nor were any currently using oral contraceptives.

Apparatus

The analyses were conducted with a Perkin-Elmer Model 403 atomic absorption spectrophotometer.

Procedures

All plasma samples were obtained as soon as possible after the occurrence of seizures (usually within 48 h). In four of the patients who developed delirium tremens, the plasma was obtained before onset of this syndrome. The methods used for obtaining and analyzing the plasma have been detailed elsewhere (*3, 8, 9*). The techniques described by Reimold and Besch (*10*) were used to prevent sample contamination.

The mean concentrations of the metals were compared by use of the Mann–Whitney U-test. Laboratory tests were conducted without prior knowledge of the clinical status of the patients, and patients were evaluated without knowledge of the results of the trace-metal determinations.

Results

Normal values for plasma zinc and copper concentrations for our laboratory were established as part of a separate study by determining these metals in the plasma of a group of 20 laboratory workers and secretaries at this institution (*8*). Pregnant women, those taking oral contraceptives or any other medication other than vitamins or aspirin, or any subjects with chronic or recent illness were excluded from this group. Our normal ranges (*3*) are similar to those of other investigators

Table 1. Normal Range of Concentrations of Some Metals in Plasma

Metal	Range
Calcium	85–105 mg/liter
Copper	650–1450 μg/liter
Magnesium	18–30 mg/liter
Zinc	650–1200 μg/liter
Copper/zinc ratio	0.80–2.00

using the same or other comparable laboratory techniques (Table 1).

The patient groups are described in Table 2. Group I had seizures followed by an uneventful recovery. Nine had seizures followed by delirium tremens (Group II). Five patients had seizures followed by a prolonged hallucinatory state without delirium tremens (Group III). The age, sex, and racial composition of the Group I vs. Groups II and III patients was quite similar (Table 2). Every patient had at least one seizure; some had two or three. Prolonged status epilepticus was not seen in any of the patients in this study.

For the patients with seizures only, the mean (±SD) plasma copper concentration, 1210 (±250) μg/liter, was within the normal range. The mean (±SD) plasma zinc concentration (730 ± 140) μg/liter was in the low normal range. The copper /zinc ratio was 1.72 ± 0.52. The copper/zinc ratio for our normals was 0.8–2.0. The mean (±SD) plasma magnesium concentration, 16.6 ± 4.4 mg/liter, was slightly below our normal range. The mean plasma calcium, 86.2 ± 17.6 mg/liter, is within the normal range.

For the group of nine patients developing delirium tremens, the mean plasma copper was increased, 1450 ± 400 μg/liter. The plasma zinc was depressed, 540 ± 140 μg/liter. The copper/zinc ratio was above normal, 2.79 ± 0.92. In the delirium tremens group, the plasma magnesium was relatively low, 14.4 ± 3.6 mg/liter. The mean plasma calcium was within the normal range, 91.0 ± 10.7 mg/liter.

The plasma metal concentrations in Group III were similar to those of the group that developed delirium tremens. The mean plasma copper concentration was above normal, 1520 ± 230 μg/liter, and the zinc was depressed, 610 ± 120 μg/liter. The Cu/Zn ratio was increased (2.56 ± 0.70). The mean plasma magnesium was also substantially depressed in Group III, 13.8 ± 4.1 mg/liter. Mean plasma calcium (89.8 ± 11.2 mg/liter) was within the normal range.

Table 3 summarizes the statistical comparisons between Group I and the combination of Groups II and III. Significant differences ($P < 0.05$) were found for copper and zinc, and for the copper/zinc ratio.

Because plasma copper was increased and plasma zinc depressed in Groups II and III, the ratio may be a more sensitive biochemical indicator than are copper and zinc concentrations separately. Plasma copper/zinc ratios have previously been reported to be more useful than data on the individual concentrations for the evaluation of acute lymphoblastic leukemia (*11*) and pulmonary tuberculosis patients (*9*). Because plasma magnesium was also depressed, although not significantly, in Groups II and III, another ratio, Cu/Zn·Mg, incorporating the magnesium concentration into the denominator, was also calculated and found to differ significantly in Group I vs. the combined Groups II and III. In the calculation of this ratio, copper and zinc concentrations were expressed in micrograms per liter, magnesium concentrations in milligrams per deciliter. Plasma calcium and magnesium were not significantly different.

Only three of 16 patients with seizures only had Cu/Zn ratios exceeding 2.00. Four of five patients with hallucinosis and seven of nine in the delirium tremens group had Cu/Zn ratios exceeding 2.00 (Figure 1). Similar data for Cu/Zn·Mg ratios are illustrated in Figure 2. Four of the nine cases in the delirium tremens group had blood samples withdrawn before onset of frank delirium tremens. In these four cases the Cu/Zn ratios were 2.14, 3.17, 3.44, and 4.75.

Discussion

Our results indicate that patients who develop hallucinosis or delirium tremens after seizures during a period of alcohol withdrawal tend to have depressed plasma zinc and magnesium concentrations and increased plasma copper, copper/zinc ratios, and copper/zinc·magnesium ratios. In addition, the increase in the Cu/Zn and Cu/Zn·Mg ratios is of significantly greater magnitude in those patients who develop hallucinosis or delirium tremens after their seizures as compared to those who have an uneventful recovery in the postictal period. Furthermore, in four of the nine cases of delirium tremens, the

Table 2. Patient Sample Studied

Group	Description	No. cases	Age		Race		Sex	
			Mean	Range	Negro	Caucasian	Male	Female
I	Alcohol withdrawal seizures only	16	41.2	26–61	15	1	15	1
II and III	Alcohol withdrawal seizures and delirium tremens or a prolonged hallucinatory state	14	41.5	21–63	12	2	12	2

Table 3. Metal Concentrations in Plasma of Patients with Alcohol-Withdrawal Syndrome

Metal or ratio	Seizures (16 patients) Group I		Seizures & DT'S or prolonged hallucinosis (14 patients) Groups II and III		Significance[a] (*P*) Group I vs. Groups II and III
	Mean	SD	Mean	SD	
Copper, μg/l	1210	250	1470	340	0.026
Zinc, μg/l	730	140	570	130	0.004
Calcium, mg/l	86.2	17.6	90.6	10.2	n.s.[b]
Magnesium, mg/l	16.6	4.4	14.2	3.6	n.s.
Copper/zinc	1.72	0.52	2.71	0.83	0.001
Copper/zinc·magnesium	1.17	0.67	2.00	0.83	0.004

[a] Mann–Whitney U-Test. [b] n.s., not significant at $P < 0.05$.

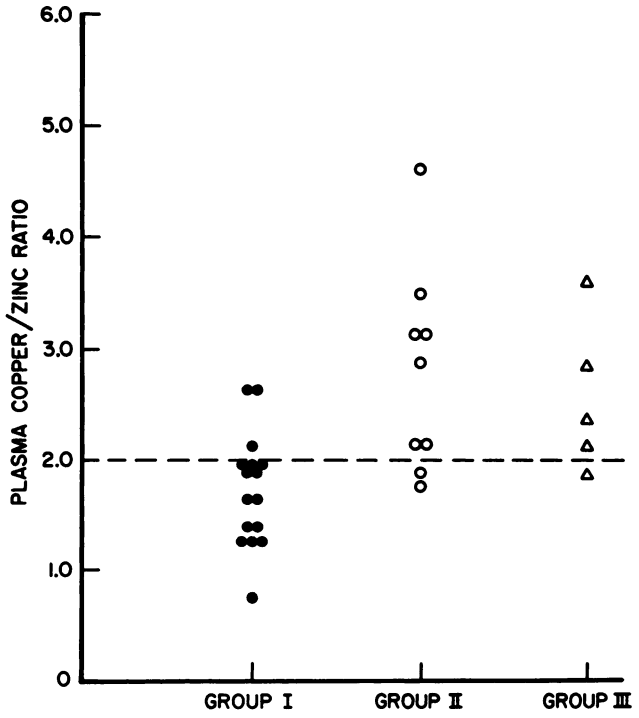

Fig. 1. Plasma Cu/Zn ratio in alcohol withdrawal seizure patients

Group I—uncomplicated alcohol withdrawal seizures, Group II—seizures and delirium tremens, Group III—seizures and prolonged hallucinatory state

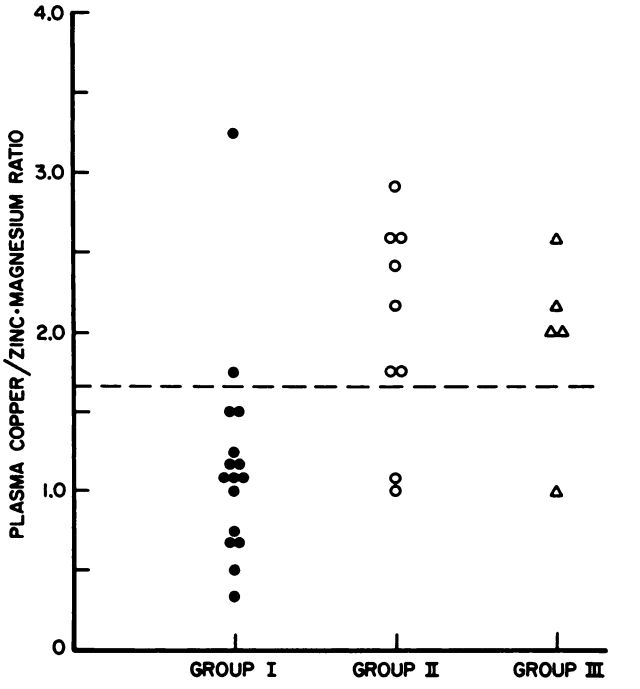

Fig. 2. Plasma Cu/Zn·Mg ratio in alcohol withdrawal seizure patients

Group I—uncomplicated alcohol withdrawal seizures, Group II—seizures and delirium tremens, Group III—seizures and prolonged hallucinatory state

plasma samples were collected before the onset of frank delirium tremens.

The patients who only had seizures are probably a heterogeneous group that includes some patients who have purely alcohol withdrawal seizures and others with underlying seizure disorders exacerbated by alcohol withdrawal, or failure to take anticonvulsant medications while alcohol intoxicated, or both. However, they serve as a suitable control for the other two groups which developed hallucinosis and delirium tremens.

The patients with hallucinosis comprise an interesting subgroup. Auditory and visual hallucinations and paranoia were prominent and there were occasional periods of confusion. This hallucinatory state prevailed for periods ranging from several days to longer than a week and was followed by uneventful recovery. Mild signs of withdrawal such as tremulousness and irritability were not uncommon in the hallucinosis group. However, violent agitation and severe signs of autonomic overflow such as hyperthermia, diaphoresis, and tachycardia were seen only in the patients in fully developed delirium tremens.

At the time of seizures and in the immediate postictal period all of these patients appear clinically similar, and most other clinical laboratory determinations have not been found to correlate consistently with the occurrence of neurologic signs of alcohol withdrawal (*2*). We therefore suggest that in this specific type of clinical setting the determination of the plasma Cu/Zn ratio or the Cu/Zn·Mg ratio, or both, early in the course of alcohol withdrawal could be of some value in indicating which patients have the most substantial underlying disease and metabolic imbalance, and so may be at increased risk for developing delirium tremens or prolonged hallucinosis.

It is not clear which pathophysiologic factors are most significant in our cases. In a large series of alcoholics, it is not unexpected to find some with abnormal plasma copper and zinc concentrations owing to cirrhosis. However, the reason for the significantly different values in the delirium tremens and hallucinosis groups is uncertain. Although it may reflect more severe exposure to alcohol and malnutrition with subsequent cirrhosis, results of liver-function tests were abnormal in only one of 16 cases in Group I and three of 14 in Groups II and III.

In a separate study the mean zinc concentration in cerebrospinal fluid was found to be significantly ($P < 0.001$) lower in 12 alcohol-withdrawal seizure patients, 47 ± 5 μg/liter, than in 69 other patients with various neurological diseases, 79 ± 7 μg/liter (R. A. Troiano and J. D. Bogden, unpublished data). The patient group studied, as well as the methods of cerebrospinal fluid analysis, have been described in detail elsewhere (*3*). Thus, the decreased plasma zinc in patients with alcohol withdrawal seizures is accompanied by decreased cerebrospinal fluid zinc.

Depressed plasma zinc and elevated copper and Cu/Zn ratios are not uncommon. This pattern of changes has been reported in alcoholic cirrhosis (*6*), in several other disorders (*3, 5, 8, 9, 11–15*), and in nonspecific catabolic and inflammatory states (*4*). The changes in concentrations in serum occur specifically during the active stages of the diseases (*4*). The factors affecting metal metabolism in these various conditions are complex; changes may be due to altered absorption and excretion, alterations in the distribution among body tissues, modified carrier protein concentrations, or a combination of these factors. It has recently been shown (*16*) that in inflammatory states, leukocytes release a substance, leukocytic endogenous mediator (LEM), which is associated with a net flux of amino acids into the liver with synthesis of acute-phase reactants such as fibrinogen and ceruloplasmin, an α_2-globulin that carries 95% of the copper in plasma. During this phase, hyperzincuria and low serum zinc as well as high serum copper

concentrations are seen (*16*). It has also been shown that intravenous infusion of corticotropin will cause depression of the serum zinc concentration, even in adrenalectomized patients (*4*).

Balance studies of zinc metabolism with ^{65}Zn in rats made cirrhotic with CCl_4 and in humans with alcoholic cirrhosis suggest a diminution in zinc pool size compatible with the concept of a true conditioned zinc deficiency (*17*). Tissue zinc concentrations have also been reported to be low in human cirrhosis and in rats made alcoholic (*18*). A clinical syndrome of acute zinc deficiency has recently been defined (*19*). The signs and symptoms include anorexia, dysfunction of taste and smell, acute brain syndrome, psychosis, tremor, ataxia, and dysarthria. Some of these signs are similar to those seen with the neurologic complications of alcoholism.

There is another possible role of zinc deficiency in the complications of alcoholism. Alcohol dehydrogenase (EC 1.1.1.1), a zinc metalloenzyme, is responsible for the hepatic metabolism of at least 80% of administered ethanol (*20*). A zinc deficiency could alter the metabolism and detoxification of alcohol especially if a large ethanol burden requires the induction of alcohol dehydrogenase synthesis. It has been shown that it is difficult to demonstrate impairment of some tissue zinc metalloenzymes, even in severe zinc deficiency in the pig (*21*). However, in the same study hepatic aminopeptidase (cytosol) (EC 3.4.11.1), ornithine carbamoyltransferase (EC 2.1.3.3), and liver and heart alcohol dehydrogenase were significantly decreased (*21*).

These data cannot necessarily be interpreted to mean that zinc or magnesium deficiency in alcohol withdrawal seizure cases promotes the development of delirium tremens or prolonged hallucinosis, although this is possible. The data suggest that increased copper/zinc or copper/zinc·magnesium ratios are to be expected in those alcohol withdrawal seizure patients with the most severe underlying diseases and metabolic or nutritional imbalance.

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