Influence of Microelement Concentration on the Intensity of Alcohol Withdrawal Syndrome

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Abstract — Aims: To establish a nutritional and constitutional profile concerning the micronutrient plasma concentration of patients who suffer from AWS. Method: Observational case control study to determine whether patients who exhibited symptoms of AWS (N = 60) had micronutrient plasmatic concentration deficiencies when compared with healthy controls (N = 34). Results: There were statistically significant differences between the concentrations of nutrients that are correlated with glutamate hyperactivity (zinc, magnesium and folate/vitamin B12/homocysteine). Conclusion: Evidence from literature and our experiment suggests that brain activity, especially the glutamatergic system, might be directly involved in micronutrient concentrations. Therefore, their supplementation to the AWS patient might improve symptom evolution.

INTRODUCTION

Alcohol withdrawal syndrome (AWS) is a complex psychiatric entity defined by the sudden stop in alcohol intake by a vulnerable patient who has already developed alcohol dependence (Mitchell and Herlong, 1986; Lieber, 2003; Moreno Otero and Cortés, 2008). It is composed of several physical manifestations (nausea, vomiting, heavy sweating hypertension) and psychiatric symptoms (hallucinations, psychomotor agitation and other possible psychotic-like behaviour) (Douaihy et al., 2013). Current treatments seek to control symptoms by using substances that mimic ethanol behaviour in GABAergic receptor systems, which reduces immediate symptoms but does not address the full aetiology of AWS (Noori et al., 2012).

It is established that alcohol-dependent patients tend to several nutritional deficiency syndromes, such as Wernicke–Korsakoff syndrome (thiamine deficiency), pellagra (B3 deficiency), protein caloric deficiency and syndromes due to malabsorption in the upper and lower intestines (Lieber, 2003; Delgado-Sanchez et al., 2008; Moreno Otero and Cortés, 2008). This tendency is related to the combination of the damaging effect of ethanol on mucous membranes in the digestive tract, which leads to chronic bleeding, inflammation, and eventual loss of functions in the stomach and upper and lower intestines (Lieber, 2003; Moreno Otero and Cortés, 2008), and malnourishment of the alcohol-dependent patient who may, for a number of reasons, have a poor diet. These reasons may include: (a) economic entanglement with alcohol dependence, in which domestic budget is used to acquire and consume alcohol instead of essential items; (b) the anorectic effect of alcohol in hunger and satiety centres of the hypothalamus; and (c) the loss of social and work activity roles due to dependence, causing loss of acquisitive power, which limits diet variety (Mitchell and Herlong, 1986; Lieber, 2003; Moreno Otero and Cortés, 2008; Noori et al., 2012).

Certain nutrients have been shown to affect the central nervous system pathways. These nutrients are ingested and needed in smaller amounts than protein or carbohydrates. Some nutrients, such as magnesium and zinc (Li-Smerin et al., 2001; Evans et al., 2007; Milton et al., 2008; Nechifor, 2008; Witkiewitz 2008; Prior and Galduróz, 2011), affect the glutamate pathway by controlling neuron excitotoxicity and death. Other nutrients function as components of the neuronal membrane (vitamin D), enabling full transport function, release of toxins to the extracellular environment; controlling second messenger concentration; and preventing apoptosis, malfunction of electrical and chemical transmission of signals in neuron pathways and the expression of receptors in the membrane (Ueland and Refsum, 1989; Lim and Heo, 2002; Guo et al., 2006; Harms et al., 2011; Sutachan et al., 2012). Many studies have demonstrated that element deficiency (such as folate, vitamin A and vitamin D, deficiencies) may be important in drug dependence, and may have an effect in destabilizing glutamatergic, serotoninergic and dopaminergic pathways, which contribute to the degenerating mental state these patients experience (Sullivan et al., 1989; Allen 2008; Cylikw et al., 2010; Sutachan et al., 2012). Other nutrients though important to normal brain function, have not been correlated with acute neuron malfunction in illnesses such as AWS.

Few studies have tried to establish a nutritional profile of alcohol-dependent patients, even those who are admitted in support services. Quantifying their proteic and lipid losses, as well as their micronutrient concentration, compared with their previous states, may be crucial for understanding the physical and metabolic causes and effects in AWS, and for establishing a possible treatment for their symptoms and conditions. Therefore, the objective of this study was to establish a nutritional and constitutional profile concerning the micronutrient plasma concentration of patients who suffer from AWS.

METHODS

This study was an observational, case control study involving sixty patients enrolled in the Centro de Referência de Tratamento de Álcool, Tabaco e outras Drogas (CRATOD), a multiprofessional institution dedicated to the treatment of drug-dependent patients with a focus on alcohol dependence. Inclusion criteria were male gender, age between 20 and 60 years, and no other psychiatric comorbidity diagnoses other than alcohol dependence. Exclusion criteria were any psychiatric comorbidity diagnoses other than AWS; use of any psychoactive drugs other than symptomatic benzodiaze-pines for withdrawal symptoms; diagnosis of hepatic cirrhosis or of any metabolic diseases. Tobacco users were not excluded.
The severity of withdrawal symptoms was quantified using the Clinical Institute Withdrawal Assessment for Alcohol (CIWAA), which comprises 10 questions concerning the occurrence of common AWS symptoms and measures their intensity, ranging from 1 (weak) to 7 (very severe). The maximum score is 67, and any score >10 indicates that pharmacological treatment of symptoms is appropriate (Sullivan et al., 1989). The scale was applied at the moment of enrolment and 2 weeks after enrolment.

The following micronutrients were selected for laboratory testing: magnesium, zinc, folate, cyanocobalamine (vitamin B12), retinoic acid (vitamin A), 1,25-Di-hydroxy vitamin D3, homocysteine and serum iron. Two blood samples were collected from each patient, at the moment of enrolment, when the patients exhibited several physical and mental manifestations of AWS, and 2 weeks after enrolment, when many patients exhibited clinical improvement. Laboratory data from patients were compared with data from healthy control individuals (N = 34) who were members of the Department of Psychobiology of Universidade Federal de São Paulo (UNIFESP) and had no history of mental disorder, substance abuse, physical comorbidities or withdrawal symptoms at the time of the single blood sample collection.

The project was approved by the Committee of Ethics in Research of the Universidade Federal de São Paulo (# 1451/11). Each participant provided informed consent and was assured the right to quit the study at any time, as well as confidentiality of identity.

### Statistical analysis

The comparison of the case group at enrolment (t = 0) and after 2 weeks of enrolment (t = 2 w) in their CIWAA scores and micronutrient serum concentration was assessed using paired Student’s t-test. The unpaired Student test was used to detect changes in micronutrient serum concentration between the case and control groups. Pearson’s r correlation test was performed between CIWAA (t0, t2w) and micronutrient concentrations, and an increase in magnesium, vitamin B12 and zinc (P < 0.001). The changes coincided with improvement in AWS symptoms in the case group (Table 2).

### RESULTS

The mean ± standard deviation for the alcohol-dependent group was 39.7 ± 4.54 years, all males, with a mean education level of 8.2 ± 1.2 years. The control group had a mean age of 31.0 ± 2.1 years, with a mean education level of 16 ± 0.6 years. This shows a statistically significant difference between groups (P < 0.001 for both age and educational level), which may indicate a greater predisposition to alcohol dependence amongst the less educated.

The mean Clinical Institute Withdrawal Assessment for Alcohol (CIWAA) scores at t = 0 was 25.5 ± 10.8, which reduced to 12.7 ± 2.1 in 2 weeks (P < 0.0001 (paired Student’s t-test)).

Table 1 compares the groups on micronutrient concentration at t = 0 and t = 2w. Only transferrin and vitamin A did not differ between control group and case group at t = 0. Between t = 0 and t = 2w, there was a significant decrease in transferrin and homocysteine concentrations, and an increase in magnesium, vitamin B12 and zinc (P < 0.001). The changes coincided with improvement in AWS symptoms in the case group (Table 2).

As shown in Table 1, there was a significant negative correlation between CIWAA and Mg at baseline (BCa 95% CI = −0.19, −0.55; P < 0.01). CIWAA at t = 2 also correlated negatively with baseline Mg (BCa 95% CI = −0.07, −0.56; P < 0.01) and positively with baseline Vitamin D (BCa 95% CI = 0.07, 0.60; P < 0.01). The following were obtained from the relevant Pearson’s correlations—CIWAA at t = 0 paired with magnesium concentrations (R² = 0.16), CIWAA at t = 2w paired with magnesium concentrations (R² = 0.12), CIWAA at t = 2w paired with vitamin D3 concentrations (R² = 0.16) (Figs 1 and 2).

Amongst the control group, the medium concentration of vitamin D3 was 16.9 ± 6.1, which is low compared to the standard medium of 30 in the general population. No such deficiency was documented in the case group at either timepoint. This result is most likely due to differences in sun exposure due to personal and occupational activities. It is notable that the control group members were workers and students from the Department of Psychobiology, with work shifts of mostly indoor activity ranging from 8 to 12 h in daytime. The case group was composed of street and construction workers, and venders, with much more exposure to sunlight.

### DISCUSSION

Our study demonstrated a possible connection between micronutrient deficiency and severity of AWS. Although we could not categorically state whether a single nutrient or any combinations of nutrients are singlehandedly correlated with symptoms, this study offers a treatment hypothesis for AWS. Two nutrients studied here may be highlighted as having a more direct role in the establishment of AWS: magnesium and vitamin D.

<table>
<thead>
<tr>
<th>Micronutrients</th>
<th>Control</th>
<th>Alcohol Dependents</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time zero (pre-treatment)</td>
<td>Time 2 weeks (post-treatment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin</td>
<td>62.4 ± 40.9</td>
<td>18.6 ± 4.6*</td>
<td>20.0 ± 9.4*</td>
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<tr>
<td>Folate</td>
<td>14.9 ± 4.7</td>
<td>2.4 ± 0.2*</td>
<td>2.4 ± 0.2*</td>
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</tr>
<tr>
<td>Homocysteine</td>
<td>9.1 ± 2.2</td>
<td>21.3 ± 4.6*</td>
<td>9.8 ± 1.8*</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>2.29 ± 0.1</td>
<td>0.7 ± 0.1*</td>
<td>1.3 ± 0.4*</td>
<td></td>
</tr>
<tr>
<td>Transferrin</td>
<td>290.7 ± 38.4</td>
<td>284.4 ± 90.5</td>
<td>240.7 ± 35.7*</td>
<td></td>
</tr>
<tr>
<td>Zina</td>
<td>24.2 ± 1.0</td>
<td>24.3 ± 5.6</td>
<td>25.7 ± 5.9</td>
<td></td>
</tr>
<tr>
<td>B12</td>
<td>272.96 ± 107.8</td>
<td>93.9 ± 8.6*</td>
<td>128.3 ± 15.2*</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>16.9 ± 6.1</td>
<td>33.7 ± 3.2*</td>
<td>34.1 ± 3.5*</td>
<td></td>
</tr>
<tr>
<td>Zinc</td>
<td>94.9 ± 19.6</td>
<td>38.1 ± 5.2*</td>
<td>75.8 ± 13.0*</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.01 (paired ‘t’ Student test)—Comparison between control group and alcohol-dependent group at Time zero.

†P < 0.01 (paired ‘t’ Student test)—Comparison between control group and alcohol-dependent group at Time 2 weeks.

†P < 0.01 (paired ‘r’ Student test)—Comparison between alcohol-dependent group at times zero and 2 weeks.
These nutrients participate in the $N$-methyl-$\alpha$-aspartate receptor (NMDA)-mediated excitotoxicity observed in many psychiatric conditions, including, but not limited to, AWS (Sullivan et al., 1989; Halliwell, 1992; Robinson and Berridge, 1993; Littleton, 1998; Bisaga et al., 2000; Sobolevsky and Yelshansky, 2000). The glutamatergic excitatory pathways are hyperactive in withdrawal patients, producing greater calcium influx through NMDA channels; an increase in nitric oxide synthetase activity and concentration; an increase in reactive oxygen species, and greater neuron membrane damage, loss of function and death (Halliwell, 1992; Robinson and Berridge, 1993; Littleton, 1998; Bisaga et al., 2000; Schneider et al., 2000; Sobolevsky and Yelshansky, 2000; Li-Smerin et al., 2001; Evans et al., 2007).

Magnesium is a natural NMDA receptor antagonist (Li-Smerin et al., 2001), reducing neuron excitotoxicity induced by glutamate hyperactivity. It has been hypothesized that the decrease in concentrations in magnesium, zinc and their coenzymes (mainly thiamine) is associated with sudden lack of ethanol intake, responsible for the severity of AWS symptoms. The increase in plasma concentrations of these micronutrients, after the period of 2 weeks, might be associated with mitigating symptoms, mainly due to decreased NMDA receptor activity (Robinson and Berridge, 1993; Frederickson et al., 2000; Cohen-Kfir et al., 2005).

Other nutrients, such as vitamin D, seem to indirectly interfere with neuron membrane integrity and function, and their shortage may contribute to neuron malfunction and death in
the same way glutamate hyperactivity does (Schneider et al., 2000; Kim et al., 2009; González-Reimers et al., 2011; Neupane et al., 2013).

Nutrient supplementation during AWS, according to our hypothesis, would most likely mitigate glutamatergic activation, preserving neuron integrity. New and broader studies are needed to establish whether the supplementation of selected nutrients via oral or parenteral methods reduces AWS symptoms and the physical and mental stress in these patients, thus corroborating the nutritional hypothesis of AWS.

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**REFERENCES**


