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Folate deficiency in patients seeking treatment of alcohol use disorder

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ABSTRACT

Introduction: Nutritional deficiency is frequent in patients with an alcohol use disorder (AUD). We aimed to analyze serum and erythrocyte folate deficiency in a case series of patients that initiated treatment of AUD.
Patients and methods: A cross-sectional study in patients admitted for detoxification between 2007 and 2015 was performed. Sociodemographic characteristics, history of alcohol consumption, type of alcohol, and medical comorbidity were assessed at admission. Blood samples for biochemistry and hematological parameters were collected at admission. Logistic regression models were used to establish predictors of folate deficiency.
Results: 211 patients (79.1% men) were eligible; age at admission was 46 years [IQR:40-51], and the amount of alcohol consumption was of 160 g/day [IQR:120-200]. Thirty four percent of patients had macrocytosis (MCV > 100 fL), 12.8% had anemia, 23% of cases presented with serum folate deficiency and 7% presented with erythrocyte folate deficiency. Most (69%) of the patients with serum folate deficiency had normal erythrocyte folate levels. In univariate analysis, macrocytosis (OR = 3.4, 95%CI:1.7-6.6), alcohol-related liver disease (ARLD) (OR = 2.5, 95%CI:1.0-6.1) and drinking alcoholic beverages other than beer (OR = 3.3, 95%CI:1.5-7.3) were associated with folate deficiency. However, only macrocytosis was significantly associated with serum folate deficiency in multivariate analysis (OR = 3.1, 95%CI:1.1-8.9). Macrocytosis ($P < 0.001$), ARLD ($P = 0.01$) and the type of alcohol consumption ($P < 0.001$) were factors associated with erythrocyte folate deficiency in univariate analysis. In multivariate analysis only macrocytosis remained significantly associated to erythrocyte folate deficiency ($P = 0.037$).
Conclusion: Folate deficiency is a relatively frequent finding in contemporary, middle-aged patients with AUD, and macrocytosis is significantly associated with the deficiency.

1. Introduction

Folate is a key nutrient for health; its inadequate consumption is the principal cause of folate deficiency in the general population. Nutritional deficiencies are common in patients with alcohol use disorder (AUD) (Lieber, 1995). Folate deficiency in AUD is attributed to an inadequate diet, although diseases that increase folate requirements (i.e., malignancies, renal dialysis), malabsorptive conditions, impaired hepatic uptake with reduced storage of endogenous folates, increased renal excretion and some drugs (anticonvulsivants, metformin) have been associated with folate deficiency (Halsted et al., 2010; Hamid et al., 2007). Furthermore, recent studies have shown that folic acid has an important antioxidant effect increasing ROS (Reactive Oxygen Species) production in the kidney and in the liver (Hwang et al., 2011).

Regarding clinical consequences, folate deficiency can lead to serious complications such as megaloblastic anemia and cognitive impairment (Koike et al., 2012; Weir and Scott, 1999); furthermore, folate deficiency has been associated with an increased risk of malignancy, such as breast or colorectal cancer (Mason and Choi, 2005; Nazki et al., 2014). Folate deficiency can play an important role in the pathogenesis and progression of alcohol-related liver disease (ARLD) (Halsted and Medici, 2012; Medici et al., 2010).

Folic acid is absorbed in the small bowel after being hydrolyzed to monoglutamate from polyglutamate; once in plasma it couples with specific transporter proteins (Nazki et al., 2014). A balanced diet provides 200–500 μg/day of folic acid and the daily requirements of the vitamin are 20–100 μg/day; folate deposits (5–20 mg) are stored in the liver, erythroblasts and the central nervous system. This vitamin is key in processes such as cellular division and growth. Rapidly dividing cells such as erythrocytes, leukocytes or platelets can be affected by folate

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deficiency (Bailey et al., 2015). Furthermore, the role of folate in the human cells is key in maintaining fundamental metabolic processes such as nucleic acid synthesis and homocysteine methylation which can become relevant in the pathogenesis of cardiovascular disease, psychiatric disorders or cancer (Kim, 2003; Nazki et al., 2014).

Serum folate is considered a marker of recent ingestion of the vitamin and cannot be used to establish its chronic deficiency. In the absence of an adequate diet, the decrease of serum folate will be observed in a few weeks. Conversely, erythrocyte concentration reflects the state of body storage of the vitamin. The liver stores 50% of body folate deposits; additionally, conjunctive tissue, erythrocytes, the kidneys and the gastrointestinal tract also contain deposits (Shane, 2008).

The decrease of erythrocyte folate, or tissue deficiency of the vitamin, will occur weeks or months after insufficient ingestion. Factors such as age, gender, body mass index (BMI) or tobacco are associated with different folate concentrations (Bradbury et al., 2014).

Otherwise, macrocytosis is associated with folate deficiency in individuals with unhealthy alcohol use (Aslinia et al., 2006); however, the etiology of macrocytosis in patients with AUD can be multifactorial, including the toxicity of ethanol on hematopoetic precursors regardless of folate deficiency. Furthermore, other etiologies can occur in the differential diagnosis of macrocytosis, such as chronic liver disease, hypothyroidism, hemolysis, hemorrhage with reticulocytosis, bone marrow dysfunction or drugs (Kaferle and Strzoda, 2009; Lindenbaum and Roman, 1980).

Nutritional anemia in the hospitalized alcoholic patient was documented decades ago (Lindenbaum and Roman, 1980; Savage and Lindenbaum, 1986). In the context of patients with acute concurrent illness (i.e., infections, decompensated liver disease) the prevalence of folate deficiency was described as 50% (Savage and Lindenbaum, 1986). However, folate deficiency in large series of patients who primarily seek AUD treatment has been scarcely documented. Moreover, very few studies have centered on analyzing whether the type of alcohol influences folate deficiency (Cravo et al., 1996; Mennen et al., 2003).

The goal of this study is to characterize serum and erythrocyte folate deficiency in contemporary patients seeking treatment of AUD. In doing so we are updating the epidemiology and clinical outcomes of a relatively frequent nutritional deficiency in middle-aged adults with AUD.

2. Methods

Cross-sectional study in AUD patients admitted for detoxification between January 1, 2007 and March 31, 2015 in the Addiction Unit of the Hospital Universitari Germans Trias i Pujol, Badalona, Spain.

The patients were referred to the Addiction Unit from primary healthcare centers in the area and from an outpatient clinic dedicated to the treatment of substance use disorders in the city. All patients had received a diagnosis of alcohol abuse and/or dependence according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association, 2000).

The main criteria for patients being referred to inpatient detoxification were: having a medical comorbidity (i.e., diabetes), having failed ambulatory detoxification, demonstrating risk of developing severe alcohol withdrawal and/or lacking family support to undergo successful outpatient treatment.

At admission, a medical history and physical exam were performed. Information regarding alcohol and drug use was collected in the medical history, including age at first use, type of alcohol (beer, wine, liquor and distilled spirits), the daily amount of alcohol consumption, history of previous AUD treatment, tobacco smoking and current use of cocaine. The type of alcohol consumption was available from June 2008 onward.

Pharmacological treatment during admission included benzodiazepines and other medications depending on the apparition of symptoms and signs of withdrawal or comorbidity. On average, the length of stay was 6 days and upon discharge patients were referred to their original centers. On discharge, pharmacological treatment of AUD with acamprosate, naltrexone, or disulfiram was recommended in the majority of cases, as well as individual and group psychotherapy.

The blood analysis performed during the first 24-h included complete biochemistry parameters, liver function tests [aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamil transferase (GGT), alkaline phosphatase, and total bilirubin], serum folate, erythrocyte folate, vitamin B12, albumin and serologic markers for hepatitis C virus (HCV). Anthropometric data was obtained as well (height and weight).

The Reference Values (RVs) of parameters were established by the hospital laboratory. For folate levels, the Hematology lab modified their method of analysis and the RVs three times through the study period. Thus, the RVs that established serum and erythrocyte folate deficiency between January 2007 and April 2012 were those under 2.2 ng/mL and 150 ng/mL, respectively (Access® Folate, Beckman Coulter, Inc. France). Between May 2012 and March 2014, values under 3.3 ng/mL for serum folate and 220 ng/mL for erythrocyte folate (Cobas®, Roche Diagnostics, Germany). After March 2014, values under 3.5 ng/mL and 450 ng/mL established the deficit of serum and erythrocyte folate, respectively (Cobas®, Roche Diagnostics, Germany).

Anemia was defined by hemoglobin levels < 13 g/dL in men and < 12 g/dL in women. Macrocytosis was defined by mean corpuscular volume (MCV) > 100 fL. Cobalamin deficiency was set under 250 pg/mL between January 2007 and December 2010 and under 180 pg/mL after January 2011.

The laboratories of Hematology and Clinical Chemistry at Hospital Universitari Germans Trias i Pujol meet the standards of ISO 9001:2000 and are accredited as competent in their respective areas.

For the purpose of this study we defined ARLD if patients had two or more of the following criteria (Lucey et al., 2009; O'Shea et al., 2010):

1) AST elevation comprised between 74 U/L and 300 U/L
2) AST/ALT ≥ 2
3) Total bilirubin > 1.2 mg/dL

Types of alcohol were sorted into three categories (not mutually exclusive):

1) Beer (5–7%)
2) Wine (12–14%), and
3) Distilled spirits or liquor ($\geq 20\%$).

Patients taking folate antagonist medications and/or folate supplements at the time of admission were excluded.

All patients gave written informed consent, which was approved by the Ethics Committee of Hospital Universitari Germans Trias i Pujol; methods used for conducting this study complied with the ethical standards for medical research and the principles of good clinical practice in accordance with the World Medical Association's Declaration of Helsinki.

2.1. Statistical analysis

Bivariate analyses were performed to establish factors associated with folate deficiency. Chi-squared, Fisher's Exact test, Student's *T* test, and ANOVA were used to detect significant differences between serum and erythrocyte folate deficiency as appropriate.

The relation between serum and erythrocyte folate was established through Pearson's correlation coefficient (r).

Logistic regression models were used to establish predictors of serum folate deficiency; sociodemographic variables, those related to alcohol consumption, as well as the principal laboratory alterations were chosen. The covariates included in the multivariate analysis were those that were found to be statistically significant in the univariate