Drug and Alcohol Dependence 230 (2022) 109186

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Alcoholic Liver Disease Among Patients with Wernicke Encephalopathy: A Multicenter Observational Study

Ignacio Novo-Veleiro [a,1], Javier Herrera-Flores [b,1], Beatriz Rosón-Hernández [c], José-A. Medina-García [d], Roberto Muga [e], Joaquín Fernández-Solá [f], M.-Candelaria Martín-González [g], Elena Seco-Hernández [h], Carlos Suárez-Cuervo [i], Ana-M. Mateos-Díaz [j], Rafael Monte-Secades [k], Begoña Machado-Prieto [l], Rubén Puerta-Louro [m], Cristina Prada-González [n], Álvaro Fernández-Rial [o], Patricia Sabio-Repiso [p], Rocío Vázquez-Vigo [q], Ana-C. Antolí-Royo [r], Aina Gomila-Grange [c], Nieves-C. Felipe-Pérez [d], Arantza Sanvisens-Bergé [e], Emilia Antúnez-Jorge [f], Camino-M. Fernández-Rodríguez [g], Lucía Alvela-Suárez [s], Alba Fidalgo-Navarro [i], Joaquín Castro [t], María-A. Polvorosa-Gómez [u], Mario Del Valle-Sánchez [v], José López-Castro [w], Antonio-J. Chamorro [b,2], Miguel Marcos [b,*,2], on behalf of the Wernicke-SEMI Group, Alcohol and Alcoholism Group, Spanish Society of Internal Medicine (SEMI)

[a] *Department of Internal Medicine, Complexo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain*
[b] *Department of Internal Medicine, Hospital Universitario de Salamanca-IBSAL, University of Salamanca, Salamanca, Spain*
[c] *Department of Internal Medicine, Hospital Universitari de Bellvitge, Barcelona, Spain*
[d] *Department of Internal Medicine, Hospital Quirónsalud, Tenerife, Spain*
[e] *Department of Internal Medicine, Hospital Universitari Germans Trias i Pujol, Badalona. Universitat Autònoma de Barcelona, Barcelona, Spain*
[f] *Department of Internal Medicine, Hospital Clínic, Barcelona, Spain*
[g] *Department of Internal Medicine, Hospital Universitario de Canarias, Tenerife, Spain*
[h] *Department of Internal Medicine, Complexo Hospitalario Universitario de Ourense, Ourense, Spain*
[i] *Department of Internal Medicine, Hospital Central de Asturias, Oviedo, Spain*
[j] *Department of Internal Medicine, Hospital Virgen del Puerto, Plasencia, Cáceres, Spain*
[k] *Department of Internal Medicine, Hospital Universitario Lucus Augusti, Lugo, Spain*
[l] *Department of Internal Medicine, Complexo Hospitalario Universitario de Vigo, Vigo, Spain*
[m] *Department of Internal Medicine, Hospital de Povisa, Vigo, Spain*
[n] *Department of Internal Medicine, Hospital de León, León, Spain*
[o] *Department of Internal Medicine, Complexo Hospitalario Universitario de Ferrol, A Coruña, Spain*
[p] *Department of Internal Medicine, Hospital Clínico San Carlos, Madrid, Spain*
[q] *Department of Internal Medicine, Complexo Hospitalario Universitario de A Coruña, A Coruña, Spain*
[r] *Department of Internal Medicine, Complejo Asistencial de Ávila, Ávila, Spain*
[s] *Department of Internal Medicine, HM Rosaleda Hospital, Santiago de Compostela, A Coruña, Spain*
[t] *Hospital Santa Bárbara, Puerto Llano, Ciudad-Real, Spain*
[u] *Hospital Comarcal de Menorca, Mahón, Spain*
[v] *Hospital General de Soria, Soria, Spain*
[w] *Hospital Público de Monforte, Lugo, Spain*

ARTICLE INFO

Keywords:
Wernicke encephalopathy
Alcoholic liver disease
Alcohol use disorders

ABSTRACT

Background: data regarding the association between Wernicke encephalopathy (WE) and alcoholic liver disease (ALD) are scarce in spite of alcohol consumption being the main risk factor for WE.

* Correspondence to: Servicio de Medicina Interna. Hospital Universitario de Salamanca, Pº San Vicente, 58–156, Salamanca 37007, Spain.
E-mail address: mmarcos@usal.es (M. Marcos).
[1] Both authors are first authors of this manuscript
[2] Both authors are senior authors of this manuscript

https://doi.org/10.1016/j.drugalcdep.2021.109186
Received 7 September 2021; Received in revised form 5 November 2021; Accepted 5 November 2021
Available online 27 November 2021

Aims: to describe the frequency of ALD in a cohort of patients diagnosed with WE and alcohol use disorders (AUDs) and to compare the characteristics of WE patients with and without ALD.
Methods: we conducted an observational study in 21 centers through a nationwide registry of the Spanish Society of Internal Medicine. WE Caine criteria were applied and demographic, clinical, and outcome variables were analyzed.
Results: 434 patients were included in the study, of which 372 were men (85.7%), and the mean age was 55 ± 11.8 years. ALD was present in 162 (37.3%) patients and we found a higher percentage of cases with tremor, flapping and hallucinations in the ALD group. A total of 22 patients (5.0%) died during admission (7.4% with ALD vs 3.7% without ALD; $P = 0.087$). Among the ALD patients, a relationship between mortality and the presence of anemia (Odds ratio [OR]=4.6 Confidence interval [CI]95% 1.1–18.8; $P = 0.034$), low level of consciousness (OR=4.9 CI95% 1.1–21.2; $P = 0.031$) and previous diagnosis of cancer (OR=10.3 CI95% 1.8–59.5; $P = 0.009$) was detected. Complete recovery was achieved by 27 patients with ALD (17.8%) and 71 (27.8%) without ALD ($P = 0.030$).
Conclusion: the association of WE and ALD in patients with AUDs is frequent and potentially linked to differences in clinical presentation and to poorer prognosis, as compared to alcoholic patients with WE without ALD.

1. Introduction

Wernicke encephalopathy (WE) is a neurologic disorder caused by thiamine deficiency which typically presents three main signs: ocular abnormalities (nystagmus and/or ophthalmoplegia), mental status changes, and gait disturbances (Galvin et al., 2010; Thomson et al., 2008). Although WE can also appear in non-alcoholic patients, alcohol consumption is the main risk factor for its development (Chamorro et al., 2017). Since up to 90% of patients with alcohol use disorders (AUDs) can develop alcoholic liver disease (ALD) to some degree (Edmondson et al., 1967) and typical brain lesions of WE can be observed in the autopsies (12.5%) of patients with AUDs (Torvik et al., 1982), the presence of ALD is a common comorbidity in these patients. ALD may also increase the risk of WE development since liver storage of thiamine is compromised in patients with liver disease (Butterworth, 2009). Moreover, chronic liver disease, mainly ALD, could play a central role in the onset of brain damage and neuro-inflammation through different mechanisms, regardless of the appearance of WE (Alfonso-Loeches et al., 2012; Novo-Veleiro et al., 2014).

Despite this association, the prevalence and characteristics of the relationship between ALD and WE remain unclear due to the lack of available data (Chamorro Fernández et al., 2011). This coexistence is also relevant from a clinical point of view particularly regarding diagnosis. To establish a clinical diagnosis of WE, the presence of two Caine criteria (dietary deficiencies, oculomotor abnormalities, cerebellar dysfunction and altered mental state and mild memory impairment) are usually required (Caine et al., 1997). However, since many patients with AUDs may also develop hepatic encephalopathy (HE) due to ALD, the differential diagnosis between WE and HE may be difficult and could lead to a delay in the diagnosis and treatment of both pathologies (Day and del Campo, 2014; Planas-Ballvé et al., 2017). Apart from clinical criteria, magnetic resonance imaging (MRI) can be useful to support the diagnosis of WE, with a sensitivity and specificity of 53% and 93% respectively (Antunez et al., 1998). In this sense, some MRI findings have been described to be specific to alcohol-related WE (Zuccoli et al., 2009), but MRI findings in patients with AUDs could be related to a wide range of other possibilities, even to HE (Rovira et al., 2008; Sureka et al., 2015).

Taking these facts into account, the aim of the present study was to describe the frequency of ALD in a cohort of patients diagnosed with WE and AUDs and to analyze the main characteristics of patients with ALD and WE, compared to those who did not develop liver disease.

2. Patients and methods

2.1. Patient selection and data collection

We conducted a multi-center study through the Wernicke Spanish Society of Internal Medicine (SEMI) group and with the participation of 21 centers from all over Spain. The study was performed in accordance with the ethical standards of the Helsinki Declaration, and the ethics committees of all participating hospitals had approved the study protocol.

As previously described (Chamorro et al., 2017), the identification of patients was made possible by searching all hospital discharge diagnoses, in each participating center, recorded from January 1, 2000 to December 31, 2012 using codes from the International Classification of Diseases, Ninth Revision (291.1, 294.0, 265.1) and Tenth Revision (E51.2, F04). We recorded epidemiological, clinical, laboratory, and radiologic data (including age, sex, comorbidities, risk factors for WE, signs and symptoms of WE, imaging and laboratory findings, alcohol consumption, diagnosis of liver disease, treatment, duration of hospital stay, and hospital outcome) using a specific protocol.

2.2. Diagnosis criteria and definition of variables

WE diagnosis criteria were recorded according to Caine criteria (Caine et al., 1997): oculomotor abnormalities (ophthalmoplegia, nystagmus, or gaze palsy), cerebellar signs (ataxia, gait disturbances, or other signs of cerebellar dysfunction), dietary deficiencies (body mass index <18.5 kg/m2, clinical data like hypoalbuminemia and/or a record of clearly impaired dietary intake) and altered mental state (confusion, stupor, or disorientation) or mild memory impairment. The presence of other symptoms (fever, seizures, dyskinesia, or tremor) was also recorded. To avoid the inclusion of patients with an unlikely diagnosis of WE, only patients with a clinical diagnosis of WE and at least 2 Caine criteria were included in our study. In order to analyze only patients with WE and ALD, the patients who did not have alcoholism as a risk factor were excluded. Thus, only patients with high-risk alcohol consumption (>28 SDU [standard drink unit]/week for men and >17 SDU/week for women) or with active alcohol consumption and an established previous diagnosis of AUD were included. One SDU in Spain is equivalent to 10 g of absolute alcohol. Smoking or use of other drugs of abuse (cocaine, heroin, or cannabis) was also recorded.

Regarding ALD, patients were considered to have liver cirrhosis if they had a histological diagnosis or unequivocal clinical, endoscopic and/or ultrasonographic findings. Liver steatosis was diagnosed by histological or ultrasonographic findings. Alcoholic steatohepatitis was diagnosed by clinical, analytical and/or histological data. The remainder of patients with clinical or analytical signs of liver disease were classified as having indeterminate chronic liver disease.

The first post admission results of the biochemical, hematologic and coagulation tests were documented when available. In this sense, we considered as hyponatremia serum sodium values under 135 mmol/L, hypocalcemia when levels of calcium were below 4.5 mg/dL and hypomagnesemia with serum magnesium levels under 1.5 mg/dL. Regarding blood count, thrombopenia was coded when platelet count was below 150,000/μL and leukopenia when leukocyte count was below

4500/μL. We also recorded the date of in-hospital death, cause of death, timing of WE diagnosis, duration of hospitalization, and recovery status at the time of hospital discharge. The diagnosis within the first 24 h after admission was considered as early diagnosis and a length of stay in hospital over 10 days was coded as prolonged hospital stay. The clinical suspicion of HE was recorded as well as the final diagnosis according to each patient's medical record. The absence of signs or symptoms of WE at discharge was considered as complete recovery; partial recovery was defined as the presence of signs or symptoms at discharge with improvement during hospitalization; and no recovery was defined as the lack of improvement or worsening of signs or symptoms during hospitalization.

MRI findings were classified according to lesion location (mammillary bodies, thalamus, hypothalamic nuclei, periaqueductal-periventricular region, midbrain, fornix, cerebellum, or cerebral cortex) and symmetry. According to previous reports (Galvin et al., 2010; Sechi and Serra, 2007; Zuccoli et al., 2009), symmetric signal intensity alterations in the mammillary bodies, thalamus, midbrain, and periaqueductal-periventricular area were considered to be typical.

2.3. Statistical analysis

Categorical variables are presented as absolute and relative frequencies. Continuous variables are presented as mean (SD) or medians and interquartile ranges (IQRs) in cases of markedly abnormal distribution. Categorical variables were compared using the $\chi 2$ test or Fisher exact test when appropriate, and continuous variables were compared through the Student *t*-test or the Mann-Whitney *U* test. Two-tailed $P < 0.05$ was considered as significant. The Spearman rank correlation (r) test was used to analyze correlations between ordinal variables and Cox regression analysis were used to analyze the relationship of baseline characteristics with mortality and incomplete recovery. Statistical analyses were performed using SPSS software, version 20.0 (IBM Corp).

3. Results

3.1. General data

The whole study included a total of 569 patients diagnosed with WE. We excluded 33 patients due to the lack of a clinical diagnosis of WE (because of a prior diagnosis of WE or inconsistent or missing data) (Chamorro et al., 2017) and another 68 patients that did not have at least 2 of the Caine criteria. Thirty-four patients for which the main cause of WE was not alcohol consumption were also excluded. Thus, a total of 434 patients were included in this study. As previously described, the mean age of the patients was 55 ± 11.8 years and 372 of the patients (85.7%) were men. Average alcohol consumption was 99.8 ± 63 SDU/week (102 ± 62 in men and 88 ± 69 in women), 64.5% of patients were also smokers and 4% consumed other drugs. The presence of dietary deficiencies was established in 230 (53%) patients (Chamorro et al., 2017).

3.2. Clinical features

ALD was present in 162 (37.3%) patients: 63 (14.5%) had liver steatosis; 32 (7.4%) had confirmed liver cirrhosis; 10 (2.3%) presented alcoholic steatohepatitis; and the other 57 (13.1%) patients were classified has having indeterminate ALD. Among the patients with ALD, 9 patients (5.6%) had chronic hepatitis C virus (HCV) infection and 3 (1.9%) had chronic hepatitis B virus (HBV) infection as other causes of liver disease in addition to alcohol consumption. The differences in baseline characteristics between patients with and without ALD are shown in Table 1. There was a remarkable higher percentage of patients with dietary deficiencies in the ALD group, with a similar distribution of other epidemiological variables in both groups.

At admission, 432 (99.5%) patients presented at least one sign of the triad of classical symptoms, and alcohol withdrawal syndrome was present in 95 (22%) patients. Clinical presentation with all three signs of the classical triad appeared in 171 (39.4%) patients, 208 patients had 2 signs, 53 patients had 1 sign and 2 patients had no classical signs. The presence of the classical triad was similar when comparing patients with and without ALD (Table 1), aside from a higher frequency of mental status disturbances in patients with ALD. Regarding Caine criteria, 149 (34.3%) patients had 2 points, 186 (42.9%) had 3 points and 99 (22.8%) patients had 4 points, without differences between ALD and non-ALD groups. However, there were some significant differences between both groups when analyzing other signs and symptoms at diagnosis, with a much higher percentage of cases with tremor, flapping and hallucinations in patients with ALD (Table 1). The proportion of patients which developed alcohol withdrawal syndrome at the time of WE diagnosis was also higher in the ALD group (26.5% vs 19.1%), although this difference did not achieve statistical significance (Table 1). In 19 (4.4%) cases (12 with ALD and 7 without ALD), HE was also recorded as a clinical diagnosis at admission. There was a significant correlation between the number of Caine criteria and the number of classical triad signs in the whole cohort ($\rho = 0.705$; $P < 0.001$) and also in patients with ALD ($\rho = 0.693$; $P < 0.001$) and without ALD ($\rho = 0.717$; $P < 0.001$).

Table 1
Differences in baseline characteristics and form of presentation at diagnosis between patients with and without alcoholic liver disease.

Variable	ALD (n = 162)	No ALD (n = 272)	*P*
Male	135 (83.3)	237 (87.1)	0.274
Age (years)	54.7 (11)	55.4 (12)	0.549
Number of SDU per week	101.7 (53)	98.5 (69)	0.720
Diabetes mellitus	10 (6.2)	26 (9.6)	0.216
Smoking	104 (64.2)	176 (64.7)	0.915
Other drugs	11 (6.8)	7 (2.6)	0.033
Cancer	9 (5.6)	11 (4)	0.468
GI surgical intervention	16 (9.9)	13 (4.8)	0.040
Dietary deficiencies	97 (60)	133 (49)	0.027
Classic triad	62 (38.3)	109 (40.1)	0.710
Ataxia	138 (85.2)	230 (84.6)	0.860
Ocular alterations	99 (61.1)	186 (68.4)	0.123
Mental status alterations	146 (90.1)	223 (82)	0.022
Seizures	9 (5.6)	24 (8.8)	0.214
Low level of consciousness	19 (11.7)	18 (6.6)	0.065
Tremors	43 (26.5)	38 (14)	0.001
Flapping	17 (10.5)	9 (3.3)	0.002
Hallucinations	57 (35.2)	58 (21.3)	0.002
Tachycardia	39 (24.1)	52 (19.1)	0.220
Clinical diagnosis of HE	12 (7.4)	7 (2.6)	0.017
Concomitant AWS	43 (26.5)	52 (19.1)	0.070

ALD: Alcoholic Liver Disease; SDU: Standard Drink Units; GI: Gastro-Intestinal; HE: Hepatic Encephalopathy; AWS: Alcohol Withdrawal Syndrome. Variables are presented as mean (standard deviation) or absolute (relative) frequencies. Relative frequencies are calculated by excluding any missing data for each variable.

3.3. Laboratory data

Hyponatremia was detected in 105 (24.2%) patients, hypocalcemia in 75 (17.3%) and hypomagnesemia in 21 (4.8%). There was a significant difference ($P = 0.002$) in the case of hypocalcemia when comparing ALD and non-ALD patients (Table 2). The presence of thrombopenia and leukopenia was much frequent in patients with ALD and the levels of albumin were lower in this group. Patients with ALD had significantly increased levels of aspartate transferase (AST), alanine transferase (ALT) and gamma-glutamyl transpeptidase (GGT) ($P < 0.05$ for all comparisons).

3.4. Radiological findings

Overall, 309 (71.2%) patients underwent cerebral computerized tomography (TC) and 229 (52.8%) underwent an MRI, with the results

Table 2
Differences in biochemical parameters and radiological findings between patients with and without alcoholic liver disease.

Variable	ALD (n = 162)	No ALD (n = 272)	*P*
Hyponatremia	38 (23.8)	67 (25.3)	0.723
Hypomagnesemia	9 (18.8)	12 (16.7)	0.769
Hypocalcemia	41 (31.3)	34 (16.7)	0.002
AST (IU/L)	73 (81)	58 (60)	0.037
ALT (IU/L)	52 (45)	43 (41)	0.048
GGT (IU/L)	287 (414)	187 (300)	0.007
Albumin (g/dL)	3.2 (0.6)	3.3 (0.5)	0.049
Anemia	69 (43.1)	112 (41.3)	0.715
Thrombopenia	55 (34.6)	51 (19)	< 0.001
Leukopenia	24 (15)	14 (5.2)	< 0.001
Total cholesterol (mg/dL)	166 (52)	163 (45)	0.539
MCV (fL)	100 (9)	99 (8)	0.166
Alterations in imaging tests	121 (82.3)	181 (80.8)	0.715
Typical WE MRI findings	34 (38.2)	44 (31.4)	0.292
Cortico-subcortical atrophy	117 (72.2)	163 (59.9)	0.010
Mamillary bodies damage	10 (6.2)	16 (5.9)	0.902
Thalamus damage	11 (6.8)	19 (7)	0.938
Mesencephalic damage	4 (2.5)	9 (3.3)	0.620
Leukoaraiosis	36 (22.2)	38 (14)	0.027
Cerebellar vermis damage	16 (9.9)	32 (11.8)	0.544

ALD: Liver Disease; WE: Wernicke Encephalopathy; MRI: Magnetic Resonance Imaging; AST: Aspartate Transferase; IU: international units; ALT: Alanine Transferase; GGT: Gamma-Glutamyl Transpeptidase; MCV: Mean Corpuscular Volume. Variables are presented as mean (standard deviation) or absolute (relative) frequencies. Relative frequencies are calculated by excluding any missing data for each variable.

showing similar percentages for patients with and without ALD. The presence of cerebral alteration in the imaging examination was found in 121 (82.3%) patients with ALD and in 181 (80.8%) without ALD; the main difference being that between ALD and non-ALD patients there was a higher prevalence of cortico-subcortical atrophy and leukoaraiosis in patients with ALD (72.2% and 22.2% vs 59.9% and 14% respectively). Also, the number of WE-related and WE-typical lesions detected was similar in patients with and without ALD. The complete comparison of the results from the image testing is shown in Table 2. We found no correlation between the number of affected sites and the number of Caine criteria or classic triad signs in any group.

3.5. Evolution during hospital stay

WE diagnosis was made after a median of 1 (Interquartile range [IQR] = 2) day, and in 293 (67.5%) patients the diagnosis was established within the first 24 h, with non-significant differences between ALD (62.3%) and non-ALD patients (70.6%) ($P = 0.076$). The average time to diagnosis was 1 day in both groups (IQR = 3 in ALD group and IQR = 2 in non-ALD group) and the average length of stay in hospital was 15.5 (IQR = 20) days for ALD patients and 13 (IQR = 17) days for non-ALD patient, with 110 patients (68%) requiring 10 or more days of hospital stay in the first group and 180 patients (66%) in the latter. There were no significant differences when comparing both groups regarding time to diagnosis and length of stay in hospital. However, patients with certain signs had a delayed diagnosis compared with patients without these manifestations, such as those patients with tremor [n = 77; mean of 4.4 (SD = 7.9) days vs. 2.7 (SD = 5.3) days, $P = 0.019$].

Most of the patients included in this study (96.8%) received thiamine treatment and no adverse events were reported. A total of 22 patients (5.0%) died during admission, with a trend towards a higher mortality rate when comparing ALD vs. non-ALD patients (7.4% vs 3.7%, $P = 0.087$). Among the ALD patients, we found a significant and independent relationship between mortality and the presence of anemia (Hazard ratio [HR]=3.8 Confidence interval [CI] 95% 1.01 – 14.6; $P = 0.048$), low level of consciousness at diagnosis (HR=4.3 CI 95% 1.3 – 14.6; $P = 0.021$), and previous diagnosis of cancer (HR=5.2 CI 95% 1.4 – 19.9; $P = 0.017$). A total of 98 patients (22.5%) showed a complete recovery at discharge, of which 27 patients (17.8%) achieved a complete recovery in the ALD group and 71 (27.8%) in the non-ALD group (P = 0.030). In this sense, we found that significant and independent factors associated with incomplete recovery among non-ALD patients were mental status alterations (HR=3.1 CI 95% 1.4 – 6.9; $P = 0.007$), cortico-subcortical atrophy (HR=3.3 CI 95% 1.7 – 6.4; $P = 0.001$), and thrombocytopenia (HR=3.5 CI 95% 1.1 – 11.1; $P = 0.032$). Among ALD patients, variables associated with incomplete recovery were cortico-subcortical atrophy (HR=4.5 CI 95% 1.6 – 12.7; $P = 0.005$) and the presence of delirium at diagnosis (OR=6.1 CI 95% 1.3 – 28.1; $P = 0.022$).

4. Discussion

Our results show that ALD is frequent in patients with WE (approximately one third of patients in our series), and that patients with WE and ALD present specific clinical, analytical and radiological characteristics compared with those without ALD. Although limited by sample size, the presence of ALD may be potentially linked to higher mortality, delayed diagnosis (particularly if some symptoms are present) and worse clinical recovery. This information could be useful to establish a correct prognosis and identify high-risk patients for subsequent proper management.

Regarding the prevalence of ALD among WE patients, very few data are available with regard to this relationship; in fact, previous studies involving large series do not even refer to the presence or absence of ALD (Harper et al., 1986; Victor et al., 1971). Although the potential relationship between both diseases is clear, not only regarding alcohol consumption but also due to the central role the liver plays in thiamine storage (Bémeur and Butterworth, 2014), only a few cases of liver disease, arising from any cause, among patients with WE have been specifically reported (Onishi et al., 2005; Soulaidopoulos et al., 2015; Zhang et al., 2010; Zhao et al., 2016), and the largest series reported only nine cases diagnosed through autopsy (Kril and Butterworth, 1997). Thus, to our knowledge, this is the largest series reporting the relationship between WE and ALD. Our main finding is that the coexistence of liver disease among WE patients is common, in spite of the limitation that some patients with mild liver disease (e.g., liver steatosis) may have been misclassified as not having ALD. Indeed, the percentage found in our series (37.5%) is similar to that found in series of patients with alcohol withdrawal syndrome or general patients with AUDs (Jarque-López et al., 2001). From a clinical point of view, our data clearly indicates that liver disease should be systematically screened for in patients with WE.

Our study has also identified some differences between WE patients with and without ALD. Although the age and the sex of the patients are similar between these two groups, and consistent with those described in other series (Kril and Butterworth, 1997; Victor et al., 1971), the presence of dietary deficiencies was significantly more frequent in those with ALD, which may reflect that malnutrition is more common in patients with advanced liver disease. No differences were found in the presence of typical signs or the number of Caine criteria between both groups. However, the number of patients who presented alteration of mental status, tremors, flapping and hallucinations, in addition to having ALD, was higher. This fact may either reflect that WE presents a different clinical profile in patients with ALD or coexistence with HE or alcohol withdrawal syndrome. Indeed, a high number of patients developed alcohol withdrawal syndrome in the ALD group, although the difference was not significant with non-ALD patients. Neuroinflammatory pathways may be modified in patients with ALD compared with those patients with excessive alcohol consumption but without liver disease; but further supporting evidence is still required (Alfonso-Loeches et al., 2012; Wang et al., 2010). And also, although clinical diagnosis of WE was not clearly delayed in patients with WE and ALD in our series, clinicians should pay close attention to any potential confounding effect of the presence of ALD on the diagnosis of WE (Galvin et al., 2010) and discard WE if neurological symptoms are

present.

Regarding laboratory findings, most of the differences in our study between ALD and non-ALD patients correspond to the expected laboratory alterations which reflect chronic liver damage and portal hypertension such as transaminase elevation or thrombopenia (Seitz et al., 2018). In the case of hypocalcemia, it has been previously described in patients with ALD in the context of vitamin D deficiency, other nutritional deficits (Bjørneboe et al., 1988; González-Reimers et al., 2015) and acute alcohol intoxication (Fernández López et al., 2012). Although hypocalcemia, arising from any cause, is linked to some neurological diseases (Mannstadt et al., 2017), a potential role in WE development has, to date, not been described.

We found no significant differences between ALD and non-ALD patients regarding radiological findings specific to WE, but more signs of brain damage (e. g., cortico-subcortical atrophy) were found in the first group. Since all patients with AUDs can develop brain atrophy (García-Valdecasas-Campelo et al., 2007), and no differences in alcohol intake between groups were found, this difference could reflect the potential role of ALD in neuroinflammation or the fact that patients with ALD may be also more sensitive to brain damage. Specific studies are still need to clarify this potential relationship (Wang et al., 2010).

Another relevant point is the non-significantly higher mortality and poorer outcome found when comparing patients with and without ALD. Our overall mortality rate was much lower than that reported in the classic series from Victor et al. (1971), which limits the interpretation of our data. However, the presence of advanced liver disease is a well-known risk factor for mortality among patients with other conditions(Kang et al., 2011) and, although current guidelines of WE and ALD do not reflect the relevance of this association (Galvin et al., 2010; Singal et al., 2018), our findings suggest that the existence of ALD should alert physicians to the higher risk of mortality and poorer prognosis when diagnosing WE.

The main limitations of our study are caused by its retrospective design, justified by the low prevalence of WE, and the absence of standard diagnosis criteria, which is a common problem in this field of research. The analysis of variables related with mortality or recovery is also limited by the lack of follow-up after discharge in the overall dataset, although long-term survival has been previously reported from some centers (Sanvisens et al., 2017). Despite this, we believe that the present study represents the largest series describing the association of ALD and WE, including patients from many centers, and could provide useful information for making decisions in relation to these types of patients.

We can conclude that the association of WE and ALD in patients with AUDs is frequent and potentially linked to differences in clinical presentation and to poorer prognosis as compared to alcoholic patients with WE without ALD. Physicians should consider the presence of ALD in patients with WE and, at the same time, the presence of neurological symptoms, albeit atypical, as patients with ALD should prompt the suspicion of WE, leading to early detection and the appropriate treatment.

Role of Funding Source

This work was partially funded by the SEMI-Spanish Society of Internal Medicine (Working Group on Alcohol and Alcoholism) and by grants from the Ministry of Economy and Competitiveness, the Carlos III Health Institute (Networks for Cooperative Research in Health-RETICS, RD16/0017/0023, RD16/0017/0003, and RD RD16/0017/0018) and the European Fund for Regional Development.

Contributors

All authors have reviewed and approved the final version of this manuscript. The specific contributions of each author are detailed in the "Contributors" section.

Conflict of Interest Disclosures

No conflict declared.

CRediT authorship contribution statement

Antonio-J. Chamorro: Funding acquisition. **Miguel Marcos:** Funding acquisition Antonio-J. Chamorro and Miguel Marcos designed the study and analyzed data. Ignacio Novo-Veleiro and Javier Herrera-Flores analyzed data and drafted the first version of the manuscript. All authors collected data, revised the manuscript and approved the final version.

Acknowledgments

Amaia Iñurrieta Romero, MD[p], Arturo González-Quintela PhD[a] and F-Javier Laso PhD[b] for their contributions to this work.[a]Department of Internal Medicine, Complexo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain.[b]Department of Internal Medicine, Hospital Universitario de Salamanca-IBSAL, University of Salamanca, Salamanca, Spain[p]Department of Internal Medicine, Hospital Clínico San Carlos, Madrid, Spain.

References

Alfonso-Loeches, S., Pascual, M., Gómez-Pinedo, U., Pascual-Lucas, M., Renau-Piqueras, J., Guerri, C., 2012. Toll-like receptor 4 participates in the myelin disruptions associated with chronic alcohol abuse. Glia 60, 948–964. https://doi.org/10.1002/glia.22327.

Antunez, E., Estruch, R., Cardenal, C., Nicolas, J.M., Fernandez-Sola, J., Urbano-Marquez, A., 1998. Usefulness of CT and MR imaging in the diagnosis of acute Wernicke's encephalopathy. AJR Am. J. Roentgenol. 171, 1131–1137. https://doi.org/10.2214/ajr.171.4.9763009.

Bémeur, C., Butterworth, R.F., 2014. Nutrition in the management of cirrhosis and its neurological complications. J. Clin. Exp. Hepatol. 4, 141–150. https://doi.org/10.1016/j.jceh.2013.05.008.

Bjørneboe, G.E., Bjørneboe, A., Johnsen, J., Skylv, N., Oftebro, H., Gautvik, K.M., Høiseth, A., Mørland, J., Drevon, C.A., 1988. Calcium status and calcium-regulating hormones in alcoholics. Alcohol. Clin. Exp. Res. 12, 229–232. https://doi.org/10.1111/j.1530-0277.1988.tb00185.x.

Butterworth, R.F., 2009. Thiamine deficiency-related brain dysfunction in chronic liver failure. Metab. Brain Dis. 24, 189–196. https://doi.org/10.1007/s11011-008-9129-y.

Caine, D., Halliday, G.M., Kril, J.J., Harper, C.G., 1997. Operational criteria for the classification of chronic alcoholics: identification of Wernicke's encephalopathy. J. Neurol. Neurosurg. Psychiatry 62, 51–60. https://doi.org/10.1136/jnnp.62.1.51.

Chamorro, A.J., Rosón-Hernández, B., Medina-García, J.-A., Muga-Bustamante, R., Fernández-Solá, J., Martín-González, M.-C., Seco-Hernández, E., Novo-Veleiro, I., Suárez-Cuervo, C., Mateos-Díaz, A.M., Monte-Secades, R., Machado-Prieto, B., Puerta-Louro, R., Prada-González, C., Fernández-Rial, Á., Sabio-Repiso, P., Vázquez-Vigo, R., Antolí-Royo, A.-C., Gomila-Grange, A., Felipe-Pérez, N.-C., Sanvisens-Bergé, A., Antúnez-Jorge, E., Fernández-Rodríguez, C.-M., Alvela-Suárez, L., Fidalgo-Navarro, A., Marcos, M., Wernicke-SEMI Group, Alcohol and Alcoholism Group, Spanish Society of Internal Medicine (SEMI), 2017. Differences between alcoholic and nonalcoholic patients with wernicke encephalopathy: a multicenter observational study. Mayo Clin. Proc. 92, 899–907. https://doi.org/10.1016/j.mayocp.2017.02.019.

Chamorro Fernández, A.J., Marcos Martín, M., Laso Guzmán, F.J., 2011. Wernicke encephalopathy in alcoholic patients. Rev. Clin. Esp. 211, 458–463. https://doi.org/10.1016/j.rce.2011.04.001.

Day, G.S., del Campo, C.M., 2014. Wernicke encephalopathy: a medical emergency. CMAJ Can. Med. Assoc. J. J. Assoc. Med. Can. 186, E295 https://doi.org/10.1503/cmaj.130091.

Edmondson, H.A., Peters, R.L., Frankel, H.H., Borowsky, S., 1967. The early stage of liver injury in the alcoholic. Medicine 46, 119–129. https://doi.org/10.1097/00005792-196703000-00006.

Fernández López, M.T., García Bargo, M.D., Rivero Luis, M.T., Álvarez Vázquez, P., Saenz Fernández, C.A., Mato Mato, J.A., 2012. Alcoholic ketoacidosis and reversible neurological complications due to hypophosphataemia. Nutr. Hosp. 27, 936–939. https://doi.org/10.3305/nh.2012.27.3.5692.

Galvin, R., Bråthen, G., Ivashynka, A., Hillbom, M., Tanasescu, R., Leone, M.A., EFNS, 2010. EFNS guidelines for diagnosis, therapy and prevention of Wernicke encephalopathy. Eur. J. Neurol. 17, 1408–1418. https://doi.org/10.1111/j.1468-1331.2010.03153.x.

García-Valdecasas-Campelo, E., González-Reimers, E., Santolaria-Fernández, F., De La Vega-Prieto, M.J., Milena-Abril, A., Sánchez-Pérez, M.J., Martínez-Riera, A., Rodríguez-Rodríguez, E., 2007. Brain atrophy in alcoholics: relationship with

alcohol intake; liver disease; nutritional status, and inflammation. Alcohol. Alcohol. Oxf. Oxfs. 42, 533–538. https://doi.org/10.1093/alcalc/agm065.
González-Reimers, E., Quintero-Platt, G., Rodríguez-Rodríguez, E., Martínez-Riera, A., Alvisa-Negrín, J., Santolaria-Fernández, F., 2015. Bone changes in alcoholic liver disease. World J. Hepatol. 7, 1258–1264. https://doi.org/10.4254/wjh.v7.i9.1258.
Harper, C.G., Giles, M., Finlay-Jones, R., 1986. Clinical signs in the Wernicke-Korsakoff complex: a retrospective analysis of 131 cases diagnosed at necropsy. J. Neurol. Neurosurg. Psychiatry 49, 341–345. https://doi.org/10.1136/jnnp.49.4.341.
Jarque-López, A., González-Reimers, E., Rodríguez-Moreno, F., Santolaria-Fernández, F., López-Lirola, A., Ros-Vilamajo, R., Espinosa-Villarreal, J.G., Martínez-Riera, A., 2001. Prevalence and mortality of heavy drinkers in a general medical hospital unit. Alcohol. Alcohol. Oxf. Oxfs. 36, 335–338. https://doi.org/10.1093/alcalc/36.4.335.
Kang, C.-I., Song, J.-H., Chung, D.R., Peck, K.R., Yeom, J.-S., Ki, H.K., Son, J.S., Lee, J.S., Kim, Y.-S., Jung, S.-I., Kim, S.-W., Chang, H.-H., Ryu, S.Y., Kwon, K.T., Lee, H., Jung, D.S., Moon, C., Heo, S.T., Kim, E.S., Rhee, J.-Y., Korean Network for Study on Infectious Diseases, 2011. Liver cirrhosis as a risk factor for mortality in a national cohort of patients with bacteremia. J. Infect. 63, 336–343. https://doi.org/10.1016/j.jinf.2011.07.012.
Kril, J.J., Butterworth, R.F., 1997. Diencephalic and cerebellar pathology in alcoholic and nonalcoholic patients with end-stage liver disease. Hepatology 26, 837–841. https://doi.org/10.1002/hep.510260405.
Mannstadt, M., Bilezikian, J.P., Thakker, R.V., Hannan, F.M., Clarke, B.L., Rejnmark, L., Mitchell, D.M., Vokes, T.J., Winer, K.K., Shoback, D.M., 2017. Hypoparathyroidism. Nat. Rev. Dis. Prim. 3, 17055. https://doi.org/10.1038/nrdp.2017.55.
Novo-Veleiro, I., González-Sarmiento, R., Cieza-Borrella, C., Pastor, I., Laso, F.-J., Marcos, M., 2014. A genetic variant in the microRNA-146a gene is associated with susceptibility to alcohol use disorders. Eur. Psychiatry J. Assoc. Eur. Psychiatr. 29, 288–292. https://doi.org/10.1016/j.eurpsy.2014.02.002.
Onishi, H., Sugimasa, Y., Kawanishi, C., Onose, M., 2005. Wernicke encephalopathy presented in the form of postoperative delirium in a patient with hepatocellular carcinoma and liver cirrhosis: a case report and review of the literature. Palliat. Support. Care 3, 337–340. https://doi.org/10.1017/s1478951505050510.
Planas-Ballvé, A., Grau-López, L., Morillas, R.M., Planas, R., 2017. Neurological manifestations of excessive alcohol consumption. Gastroenterol. Hepatol. 40, 709–717. https://doi.org/10.1016/j.gastrohep.2017.05.011.
Rovira, A., Alonso, J., Córdoba, J., 2008. MR imaging findings in hepatic encephalopathy. AJNR Am. J. Neuroradiol. 29, 1612–1621. https://doi.org/10.3174/ajnr.A1139.
Sanvisens, A., Zuluaga, P., Fuster, D., Rivas, I., Tor, J., Marcos, M., Chamorro, A.J., Muga, R., 2017. Long-term mortality of patients with an alcohol-related wernicke-korsakoff syndrome. Alcohol. Alcohol. 52 (4), 466–471. https://doi.org/10.1093/alcalc/agx013.
Sechi, G., Serra, A., 2007. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. Lancet Neurol. 6, 442–455. https://doi.org/10.1016/S1474-4422(07)70104-7.
Seitz, H.K., Bataller, R., Cortez-Pinto, H., Gao, B., Gual, A., Lackner, C., Mathurin, P., Mueller, S., Szabo, G., Tsukamoto, H., 2018. Alcoholic liver disease. Nat. Rev. Dis. Prim. 4, 16. https://doi.org/10.1038/s41572-018-0014-7.
Singal, A.K., Bataller, R., Ahn, J., Kamath, P.S., Shah, V.H., 2018. ACG clinical guideline: alcoholic liver disease. Am. J. Gastroenterol. 113, 175–194. https://doi.org/10.1038/ajg.2017.469.
Soulaidopoulos, S., Ioannidou, M., Chalevas, P., Cholongitas, E., 2015. Wernicke encephalopathy: a complication of acute liver failure. Nutr. Clin. Pract. . Publ. Am. Soc. Parenter. Enter. Nutr. 30, 847–848. https://doi.org/10.1177/0884533615602001.
Sureka, B., Bansal, K., Patidar, Y., Rajesh, S., Mukund, A., Arora, A., 2015. Neurologic manifestations of chronic liver disease and liver cirrhosis. Curr. Probl. Diagn. Radiol. 44, 449–461. https://doi.org/10.1067/j.cpradiol.2015.03.004.
Thomson, A.D., Cook, C.C.H., Guerrini, I., Sheedy, D., Harper, C., Marshall, E.J., 2008. Wernicke's encephalopathy revisited. Translation of the case history section of the original manuscript by Carl Wernicke "Lehrbuch der Gehirnkrankheiten fur Aerzte and Studirende" (1881) with a commentary. Alcohol. Alcohol. Oxf. Oxfs. 43, 174–179. https://doi.org/10.1093/alcalc/agm144.
Torvik, A., Lindboe, C.F., Rogde, S., 1982. Brain lesions in alcoholics. A neuropathological study with clinical correlations. J. Neurol. Sci. 56, 233–248. https://doi.org/10.1016/0022-510x(82)90145-9.
Victor, M., Adams, R.D., Collins, G.H., 1971. The Wernicke-Korsakoff syndrome. A clinical and pathological study of 245 patients, 82 with post-mortem examinations. Contemp. Neurol. Ser. 7, 1–206.
Wang, H.J., Zakhari, S., Jung, M.K., 2010. Alcohol, inflammation, and gut-liver-brain interactions in tissue damage and disease development. World J. Gastroenterol. WJG 16, 1304–1313. https://doi.org/10.3748/wjg.v16.i11.1304.
Zhang, X., Lu, Y., Huang, W., 2010. Wernicke encephalopathy following splenectomy in a patient with liver cirrhosis: a case report and review of the literature. J. Zhejiang Univ. Sci. B 11, 433–436. https://doi.org/10.1631/jzus.B1000016.
Zhao, P., Zhao, Y., Wei, Z., Chen, J., Yan, L., 2016. Wernicke encephalopathy in a patient with liver failure: clinical case report. Medicine) 95, e3651. https://doi.org/10.1097/MD.0000000000003651.
Zuccoli, G., Santa Cruz, D., Bertolini, M., Rovira, A., Gallucci, M., Carollo, C., Pipitone, N., 2009. MR imaging findings in 56 patients with Wernicke encephalopathy: nonalcoholics may differ from alcoholics. AJNR Am. J. Neuroradiol. 30, 171–176. https://doi.org/10.3174/ajnr.A1280.