

Profile of Patients Presenting with Acute Seizures: Is Alcohol-Related Seizures a Big Problem in Lithuania?

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Abstract

Purpose: The goal of the study is to determine the proportion of alcohol-related seizures (ARS) among acute onset seizure patients, and to assess the results within the context of previous studies. The secondary goal of the study is to compare the characteristics and lab test results between ARS and non-ARS subgroup.

Method: We retrospectively evaluated demographical, laboratory and clinical data of 550 patients who have suffered an acute onset seizure and were admitted to the emergency department of Republican Vilnius University Hospital (RVUH) in Lithuania between February 2019 and October 2019.

Results: A total of 273 (49,6%) cases of seizures were determined to be alcohol-related, 201 (73,6%) of which had an ICD-10-AM codes F10 or T51.0 attributed to them. Medical records of 72 (26,4%) patients were significant for history of alcohol abuse. The majority (84,2% vs 57,2%, $p = 0,001$) of the ARS patients were male, they have suffered more frequently from new-onset seizures (31,5% vs. 21,3%, $p = 0,007$) and more commonly presented with tongue biting (20,9% vs. 7,9%, $p < 0,001$) compared to non-ARS patients. Patients in ARS subgroup had a less pronounced neurological disease profile (brain tumours 0,4% vs 8,3; stroke 1,1% vs 14,38%; $p = 0,001$), but more often suffered from alcohol-related liver disease (ARLD), compared to non-ARS patients (11,4% vs. 1,4%; $P < 0,001$).

Conclusion: ARS is a big problem in Lithuania, while approximately half of the patients had seizures related with alcohol abuse.

Keywords: Alcohol-Related Seizure; Epilepsy; Chronic Alcohol Abuse

Introduction

It is well established that excessive alcohol consumption (or rather the withdrawal) may trigger seizures in an otherwise healthy person. The association between seizures and alcohol has not been fully delineated, but the incidence of epilepsy among alcohol-dependent patients is 3 times higher than in the general population [1]. Alcohol-related seizures are also the third leading cause for an admittance to the emergency department [2]. According to literature, as many as 41 - 49% of patients with acute seizure-related conditions (status epilepticus, first-onset seizures, or recurrent epileptic seizures) have abused alcohol [3,4]. Available evidence also shows that patients with alcohol-induced seizures face up to four times greater risk for mortality than the general population [5-7].

According to the latest data, Lithuania remains one of the top three EU countries with alcohol intake at around 15 liters per person per year (compared with the EU average of 9,8 liters per person) [8], yet the prevalence of alcohol-induced seizures has not yet been fully investigated. We hypothesize that the occurrence of ARS cases in our hospital (a large, tertiary care center) possibly exceeds that of the European countries and set ourselves the goal to determine the proportion of ARS in seizing patients, and to assess the results within the context of previous studies. The secondary goal of the study is to compare the characteristics and lab test result values between ARS and non-ARS subgroup.

Patients and Methods

Data collection

We retrospectively evaluated demographical, laboratory and clinical data of 550 consecutive patients who have suffered an acute onset seizure (either epileptic or of other origin) and were admitted to the emergency department of Republican Vilnius University Hospital (RVUH) in Lithuania between February 2019 and October 2019.

All the patients (age ≥ 18 years) presenting with an acute seizure, labeled as ICD-10-AM codes G40 (all forms of epilepsy), G41 (status epilepticus) or R56.8 (other and unspecified convulsions) to the ED were included in the study. The patients were divided into two major subgroups based on the origin of seizures - patients who experienced ARS and those whose seizures were of other origin. ARS in this study were defined as a seizure that occurred within temporal relation to alcohol use (< 72 h). We documented whether the patient has ever experienced seizures in the past to identify patients with new-onset seizures.

Data were retrieved from medical record files and included baseline demographic characteristics (age, sex) and comorbidities present on admission such as history of pre-existing epilepsy, head trauma, stroke, brain tumor, myocardial infarction (MI), hypertension, congestive heart failure (CHF), dysrhythmias and other chronic underlying diseases, such as various cancers, diabetes mellitus (DM), liver cirrhosis, mental and behavioral disorders. We also collected data regarding chronic alcohol abuse from past social and family history and ICD-10-AM codes related to alcohol abuse, such as F10 (mental and behavioral disorders due to alcohol use) and T51.0 (toxic effect of ethyl alcohol). We documented information about the administered treatment (the use and dose of diazepam, antiepileptic drugs) and whether the tongue biting occurred during present seizure.

Laboratory findings such as complete blood count, hemoglobin concentration (Hb), liver panel (total bilirubin concentration, Aspartate transaminase (AST), Alanine transaminase (ALT), Gamma-glutamyl transferase (GGT) activity), blood electrolyte panel (sodium, potassium, chloride ion concentrations) and blood ethanol and creatinine concentration were collected.

Ethical approval for the study was obtained from hospital bioethical committee.

Statistical analysis

Data were analyzed using IBM SPSS 23. Categorical and nominal variables were analyzed using Chi square test with a confidence interval of 95% and are presented as frequencies with percentages. Continuous data were presented in the form of either mean \pm standard deviation and median (interquartile range, IQR). The Kolmogorov-Smirnov test was conducted to determine the distribution of the data. The assumption for string variable equality were tested with parametric (independent samples t-test) and non-parametric (Mann-Whitney-U) tests where appropriate. Statistical significance level (p) was set below 0.05.

Results

550 patients presented to the ED with seizures. There was a total of 273 (49,6%) patients with ARS, 201 (73,6%) of which had ICD-10-AM F10 or T51.0 codes attributed to them. Medical records of 72 (26,4%) patients with ARS were significant for alcohol abuse (Figure 1).

Baseline demographic and descriptive characteristics are summarized in table 1. 402 (73,1%) of the patients were male. The median age was 49,6 (37-61) years. The most common primary diagnosis at admission was epilepsy (243 cases, or 44,2%) and seizures (239 cases, or 43,5%). The patients presenting with seizures most commonly suffered from pre-existing epilepsy (45,8%), head trauma (20,2%), stroke (8%), and brain tumors (4,4%).

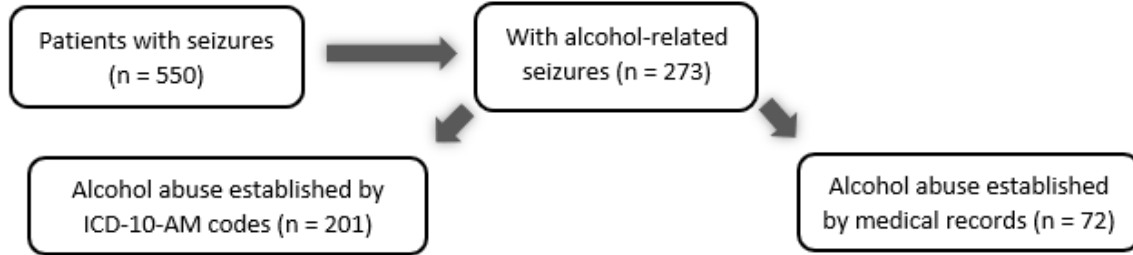


Figure 1: Participants in the study sample.

Characteristic	Value
Male	402 (73,1%)
Female	148 (26,9%)
Age, median (IQR)	49,6 (37-61)
Primary diagnosis at admission, No. of patients	
Epilepsy	243 (44,2%)
Seizures	239 (43,5%)
Toxic effect of ethyl alcohol	21 (3,8%)
Head/ facial injuries	24 (4,4%)
Other injuries (trunk, extremities)	5 (0,9%)
Status epilepticus	3 (0,5%)
Syncope and collapse	3 (0,5%)
Other	12 (2,2%)
Seizures, No. of patients	
First ever seizure	145 (26,4%)
History of seizures	351 (63,8%)
Unknown	54 (9,8%)
Type of seizures in the past (N = 351), No. of patients	
ARS	127 (31,8%)
Non-ARS	160 (40,1%)
Unknown	112 (28,1%)

Table 1: Baseline characteristics and descriptive statistics.

As depicted by table 2, 69,1% of patients presenting to the emergency department received treatment. Most commonly administered drug was Diazepam, received by 62,6% with median dose of 10 mg. Other most frequently given medications were Carbamazepine (10%), Haloperidol (6,2%), Valproic acid (5,1%), Levetiracetam (2,7%) and Quetiapine (2,2%).

Characteristic	Value (n =)
Received medical treatment	380 (69,1%)
Medication administered	
Diazepam dose, median (IQR), mg	344 (62,6%) 10 (10-20)
Carbamazepine	55 (10%)
Valproic acid	28 (5,1%)
Levetiracetam	15 (2,7%)
Lamotrigine	9 (1,7%)
Quetiapine	12 (2,2%)
Haloperidol	34 (6,2%)
Topiramate	2 (0,4%)
Propofol	8 (1,5%)
Other	8 (1,5%)

Table 2: Treatment approach.

Baseline demographics of ARS and non-ARS patients are summarized in table 3. Among the 550 patients, ARS accounted for 49.6% (273 patients). There was a statistically significant difference in distribution of gender, with 84,2% of ARS patients being male, compared to 57,2% of non-ARS patients (p = 0,001). ARS patients were also significantly younger, with median age of 44 years (vs. 55 years for non-ARS, p = 0,001) and more commonly presented with tongue biting during the seizure (20,9% vs. 7,9%, p < 0,001). ARS patients more frequently suffered from new-onset seizures (31,5% vs. 21,3%, p = 0,007) and have received medical treatment at the ED (78,8% vs. 59,6%, p < 0,001).

Characteristic	ARS (n = 273)	Non-ARS (n = 277)	P value
Sex (male), n (%)	230 (84,2%)	172 (57,2%)	0,001*
Hospitalisation, n (%)	15 (5,5%)	62 (22,4%)	0,001*
New-onset seizures, n (%)	86 (31,5%)	59 (21,3%)	0,007*
History of seizures, n (%)	157 (57,5%)	194 (70,0%)	0,002*
Age, y, median, (IQR)	44 (37,5-53)	55 (37-69)	0,001*
Pre-existing epilepsy, n (%)	116 (42,5%)	139 (49,1%)	0,120
AH, n (%)	27 (9,9%)	62 (22,4%)	0,001*
DM, n (%)	3 (1,1%)	12 (4,3%)	0,02*
Dysrhythmias, n (%)	5 (1,8%)	22 (7,9%)	0,01*
Stroke, n (%)	3 (1,1%)	41 (14,8%)	0,001*
History of head trauma, n (%)	53 (19,4%)	58 (20,9%)	0,656
Mental and behavioural disorders, n (%)	14 (5,1%)	24 (8,7%)	0,102
History of brain tumours, n (%)	1 (0,4%)	23 (8,3%)	0,001*
ARLD, n (%)	31 (11,4%)	4 (1,4%)	< 0,001*
Received medical treatment, n (%)	215 (78,8%)	165 (59,6%)	< 0,001*
Tongue biting, n (%)	57 (20,9%)	22 (7,9%)	< 0,001*

Table 3: Comparison of baseline characteristics and descriptive statistics between subgroups.

Key: AH: Arterial Hypertension; DM: Diabetes Mellitus; ARLD: Alcohol-Related Liver Disease; *: Values indicate statistical significance.

Non-ARS patients more often had a history significant for brain tumours (8,3% vs. 0,4%; $p = 0,001$) and stroke (14,38% vs. 1,1%; $p = 0,001$) and displayed a significantly higher prevalence of arterial hypertension (22,4% vs. 9,9%; $P = 0,001$), diabetes mellitus (4,3% vs. 1,1%; $p = 0,02$) and dysrhythmias (7,8% vs. 1,8%; $P < 0,01$). However, the ARS patients significantly more often suffered from ARLD, compared to non-ARS patients (11,4% vs. 1,4%; $P < 0,001$).

There was no significant difference in distribution of history of pre-existing epilepsy, head trauma and mental and behavioural disorders.

Characteristic	ARS	Cases, No.	Non-ARS	Cases, No.	P value
Diazepam dose, median (IQR), mg	10 (10-20)	n = 172	10 (10-20)	n = 172	0,079
Hgb, g/l, mean \pm SD (N = 363)	141,4 \pm 17,4	n = 163	137,8 \pm 17,9	n = 200	0,642
Hct, %, mean \pm SD	42,2 \pm 4,9	n = 163	41,0 \pm 5,0	n = 200	0,864
Plt, *10 ⁹ /L, mean \pm SD	176,1 \pm 84,4	n = 163	230,9 \pm 77,5	n = 200	0,084
MCV, fl,	98 (93-103)	n = 163	93 (89-97)	n = 200	0,001*
WBC, *10 ⁹ /L	8,4 (6,1-10,3)	n = 164	8,3 (6,1-10,8)	n = 200	0,579
AST, IU/L (N = 178)	80 (44-138)	n = 87	28 (22-40)	n = 91	< 0,001*
ALT, IU/L	53 (33-82)	n = 87	24 (16-36)	n = 91	< 0,001*
GGT, U/L (N = 73)	62 (30,5-241)	n = 41	27 (14,3-100,8)	n = 32	0,008*
TB, μ mol/l (N = 154)	20,0 (12,4-30,1)	n = 66	14,2 (8,5-21)	n = 88	0,001*
Creatinine, μ mol/L (N = 286)	70 (58,3-84)	n = 112	73 (63,5-84)	n = 177	0,196
Sodium (Na), mmol/L (N = 349)	138 (16-141)	n = 163	138 (16-141)	n = 186	0,978
Potassium (K), mmol/L (N-350)	4 (3,7-4,4)	n = 163	4,1 (3,7-4,5)	n = 187	0,493
Chloride (Cl), mmol/L (N = 310)	99 (95-102)	n = 151	102 (97-104)	n = 159	0,002*
Ethanol, g/L	0,0 (0-1,75)	n = 124	0,0 (0-0)	n = 18	< 0,001*

Table 4: Comparison of laboratory test values on admission between subgroups.

Key: Hgb: Hemoglobin; Hct: Hematocrit; PLT: Platelets; MCV: Mean Cell Volume; WBC: White Blood Cells; RBC: Red Blood Cells; AST: Aspartate Transaminase; ALT: Alanine Transaminase; GGT: Gamma-Glutamyl Transferase; TB: Total Bilirubin; *: Values indicate statistical significance.

As presented in table 4, complete blood count values were comparable between the subgroups, except for a significantly higher MCV values in the ARS patients (98 vs. 93 fl, $p = 0,001^*$). Total bilirubin (20 μ mol/l vs. 14,2 μ mol/l, $p < 0,001$) and liver enzyme levels were also more frequently elevated in ARS subgroup (AST 80 U/L vs. 28 U/L, $p < 0,001$, ALT 53 U/L vs. 24 U/L $p < 0,001$, GGT 62 U/L vs. 27 U/L $p = 0,008$). Electrolyte panel values did not differ significantly, except for a lower chloride concentration in ARS subgroup (99 mmol/l vs. 102 mmol/l, $p = 0,002$). Median ethanol concentration in both subgroups was 0,0 g/l, though the range of IQR was significantly higher in ARS subgroup ($p < 0,001$).

Discussion

According to our data, ARS patients significantly more frequently suffered from new-onset seizures (31,5% vs. 21,3%, $p = 0,007$), a rather expected finding considering alcoholism and alcohol consumption is a risk factor for both triggering epileptic seizures and developing the first episode of generalized seizures [9,10]. The latter is evidenced as well by the results of the study published by M Leone., *et al.* [11], though one must acknowledge that our numbers may be an underestimated due to patients' self-reporting error and retrospective study design. However, there was also no association between history of head trauma and ARS, a finding that is commonly reported in other studies, as alcohol intoxication is bidirectionally linked to and frequently co-occurs with traumatic brain injury [3,5,12,13].

In the present study an overwhelming majority (84,2%) of the ARS patients were male, and there was no significant difference of distribution of gender in the non-ARS subgroup. This finding is consistent with the results of previous studies and could generally be attributed to a higher prevalence of alcohol abuse among male population in Europe [14]. Furthermore, heavy drinking is prevalent in Lithuania and is over two-fold more common among men compared to women (70,8% vs 31,6%) [15].

Further statistical analysis revealed that contrary to the findings of the other studies [3,5], non-ARS patients significantly more often have suffered a stroke in the past (14,38% vs. 1,1%; $p = 0,001$), a finding that can be explained at least in part by a significantly older age (55y vs 44y, $p = 0,001$) and more prominent comorbidity profile predisposing stroke (significantly higher rates of arterial hypertension (22,4% vs. 9,9%; $P = 0,001$), diabetes mellitus (4,3% vs. 1,1%; $p = 0,02$) and dysrhythmias (7,8% vs. 1,8%; $P < 0,01$).

It is remarkable that tongue biting was observed in 20,9% of ARS patients, a significantly higher proportion compared to only 7,9% of non-ARS patients ($P < 0,001$). These results are to be expected as alcohol abuse and withdrawal seizures are associated with generalized tonic-clonic seizures [16] and tongue biting usually occurs in the clonic phase. Though tongue biting is not a sensitive indicator [17], it indirectly leads to an assumption that ARS patients more frequently suffered generalized seizures.

In our study ARS patients received treatment at the ED more frequently than those of non-ARS subgroup (78,8% vs 59,6%, $p < 0,001$). The most commonly administered drug was diazepam. This is in line with current guidelines, as benzodiazepines are a first-line treatment of choice for alcohol-withdrawal seizures [18] and are recommended to be administered timely to prevent recurrence of seizures within the same withdrawal episode [19].

One of the weaknesses of our study is the fact that we didn't further distinguish the exact seizure etiology within the ARS subgroup, as the seizures could both be caused by alcohol withdrawal or induced directly by ethanol as a neurotoxin, not to mention other possible alcohol-induced conditions (such as hypoglycemia, electrolyte imbalance etc.). In the ED seizures often present a diagnostic challenge as one must accurately identify the underlying cause to exclude life-threatening conditions and provide both timely and efficient treatment to the seizing patient [20]. Blood alcohol content can be valuable as it helps to identify direct toxic effect of ethanol [21]. In our study the median blood ethanol concentration was 0,0 in both subgroups (though the range was considerably wider in ARS subgroup), making the idea that ARS patients presenting to our center suffer mostly withdrawal seizures rather probable. As evidenced by the latter observation, blood ethanol concentration has little diagnostic value in differentiating ARS and non-ARS patients, therefore it is a challenge to identify patients with chronic alcohol abuse, considering self-reported social history is often unreliable.

In cases of inconclusive history of alcohol consumption there are several well-established biomarkers associated with long-term alcohol consumption (MCV, liver enzymes: AST/ALT ratio and GGT), most of them, however, lack in specificity or need further investigation to be applied in practice (homocysteine) [22]. In our study, the MCV values in the ARS subgroup exceeded the normal range: 98 fl vs. 93 fl. Hepatic enzyme (ALT, AST, and GGT) levels were also statistically significantly higher in the ARS subgroup. An increase in ALT and AST (the AST/ALT ratio of ≥ 2 more specifically), similar to GGT, indicates liver damage, in our study cohort likely caused by alcohol toxicity [23,24], as alcohol-related liver disease was almost 8-fold more common in the ARS subgroup (11,4% vs. 1,4%). However, numerous comorbidities, especially liver-related conditions such as cirrhosis, hepatic insufficiency and hepatitis may skew the results [20]. Also, the specificity and sensitivity of liver enzymes as indicators of alcohol use is affected by the amount of alcohol consumed, time since the last alcoholic drink, pattern of alcohol use etc [25,26].

One promising direct marker that helps to differentiate alcohol abuse from social drinking is Phosphatidylethanol (PEth), as it accumulates with chronic alcohol consumption and its blood levels correlate well with the amount of alcohol consumed [27]. It is a promising new indicator of alcohol abuse, although further research is needed as there are numerous undetermined factors influencing PEth metabolism [28].

Though our study did not reveal any significant difference in head injury rates between the subgroups, traumatic brain injuries such as brain contusion, subdural and subarachnoid hematomas are quite common among ARS patients [29], therefore it is highly recommended to perform a head computed tomography (CT) scan to patients presenting with a history of alcohol abuse and a new-onset seizure both to prevent further complications and to exclude pathological intracranial processes [30]. Alcohol abuse can not only trigger seizures but also worsen them by precipitating status epilepticus [31], which among other things (notably irreversible brain damage) causes an acute life-threatening complication of Rhabdomyolysis [32]. Therefore, well-timed and adequate treatment of ARS is essential to prevent major complications. Nevertheless, many ARS patients present to the ED post-ictus and the key mission shifts to preventing the recurrence of seizures.

Conclusion

The patients presenting with ARS were predominantly male, significantly younger, more likely to bite their tongue during seizures compared to non-ARS patients. In addition, ARS patients have suffered more frequently from new-onset seizures. Our study shows that alcohol abuse is a significant socioeconomic burden on healthcare system in Lithuania, while approximately half of the patients had seizures related with alcohol overuse and were treated at the ED and highlights the need for an intervention in health system to combat this problem.

Disclosure of Interest

No potential conflict of interest was reported by the authors.

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