Epidemiological profile of epileptic seizures related to alcohol withdrawal syndrome

Perfil epidemiológico das crises epilépticas relacionadas à síndrome de abstinência alcoólica

Perfil epidemiológico de las crisis epilépticas relacionadas con el síndrome de abstinencia alcohólica

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Resumo

Introdução. A síndrome de abstinência alcoólica (SAA) pode ocorrer em aproximadamente metade dos pacientes com transtornos relacionados ao uso do álcool que reduzem abruptamente ou cessam o consumo dessa substância, sendo a crise epiléptica uma das possíveis manifestações. Objetivo. Avaliar dados epidemiológicos, características clínicas, duração da internação e recorrência de atendimento médico de emergência entre pacientes com crises epilépticas relacionadas a SAA. Método. Trata-se de um estudo observacional retrospectivo, com coleta de dados de prontuário de pacientes tratados com crises epilépticas relacionadas a SAA em um hospital público de Minas Gerais durante o período de um ano. Estatística inferencial de associação entre variáveis nominais foram avaliadas por tabulação cruzada com o teste qui-quadrado. Resultados. 45 pacientes foram incluídos no estudo. A faixa etária mais prevalente foi de 35 a 45 anos (37,7%). Em 46,6%, foi descrito um diagnóstico prévio de epilepsia. Houve associação entre o diagnóstico prévio de epilepsia e a presença de crises epilépticas (p<0,001). O tipo de crise era tônico-clônico generalizada em 92% dos casos. 78% tiveram crises num período de até 48 horas após o último consumo de bebida alcoólica. A taxa de recorrência no departamento de emergência durante o ano foi de 31%. Conclusão. As crises epilépticas relacionadas a SAA afetam predominantemente homens jovens e estão associadas a alta taxa de recorrência de atendimento hospitalar de urgência e emergência, sendo um problema de saúde pública complexo. Esses dados apontam para a necessidade de fortalecer estratégias para prevenção primária. Unitermos. Abstinência Alcoólica; Crises epilépticas; Epidemiologia

Abstract

Introduction. Alcohol withdrawal syndrome (AWS) can occur in about half of patients with alcohol use disorder who abruptly reduce or cease consumption of this substance. Epileptic seizures are one of the possible manifestations. **Objective.** Evaluate epidemiological data,

clinical characteristics, length of hospital stay and recurrence of emergency medical care between patients with alcohol withdrawal-related epileptic seizures. **Method.** This is a retrospective observational study, with data collection from medical records of patients treated for epileptic seizures caused by AWS in a public hospital in Minas Gerais within a year. Inferential statistical association between nominal variables was assessed by cross-tabulation with the chi-square test. **Results.** 45 patients were included in the study. The most prevalent age group was 35 to 45 years (37.7%). In 46.6%, it was described a previous diagnosis of epilepsy. There was an association between the previous diagnosis of epilepsy and the presence of epileptic seizures (p<0.001). The type of seizure was generalized tonic-clonic since the onset in 92% of cases. 78% had seizures up to 48 hours after the last alcohol consumption. The rate of recurrence at the emergency department during the year was 31%. **Conclusion.** AWS-related epileptic seizures predominantly affect young men and are associated with a high recurrence rate of need of emergency hospital care, being a complex public health problem. These data point to the need to strengthen strategies for primary prevention.

Keywords. Alcohol Withdrawal; Seizures; Epidemiology

Resumen

Introducción. El síndrome de abstinencia alcohólica (SAA) puede presentarse en aproximadamente la mitad de los pacientes con transtorno por consumo de alcohol que reducen o suspenden bruscamente el consumo de esta substancia, siendo las crisis epilépticas una de las posibles manifestaciones. Objetivo. Evaluar los datos epidemiológicos, las características clínicas, la duración de la estancia hospitalaria y la recurrencia de la atención médica de emergencia entre los pacientes con crisis epilépticas relacionadas con el SAA. Método. Se trata de un estudio observacional retrospectivo, con recolección de datos de prontuarios de pacientes tratados con crisis epilépticas asociadas con el SAA en un hospital público de Minas Gerais durante un período de un año. Las estadísticas inferenciales de asociación entre variables nominales se evaluaron mediante tabulación cruzada con la prueba del chi-cuadrado. Resultados. 45 pacientes fueron incluidos en el estudio. El grupo de edad más prevalente fue el de 35 a 45 años (37,7%). En el 46,6% se describió un diagnóstico previo de epilepsia. Hubo asociación entre el diagnóstico previo de epilepsia y la presencia de crisis epilépticas (p<0,001). El tipo de crisis fue tónico-clónico generalizado en el 92% de los casos. El 78% presentó convulsiones en un período de hasta 48 horas después del último consumo de bebida alcohólica. La tasa de recurrencia del servicio de urgencias durante el año fue del 31%. Conclusión. Las crisis epilépticas, relacionadas con el SAA afectan predominantemente a hombres jóvenes y se asocian con una alta tasa de recurrencia de la atención hospitalaria de urgencia y emergencia, siendo un problema complejo de salud pública. Estos datos apuntan a la necesidad de fortalecer las estrategias de prevención primaria.

Palabras clave. Abstinencia alcohólica; ataques de epilepcia; Epidemiología

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INTRODUCTION

Alcohol addiction is a worldwide public health problem. It is estimated that 3.8% of deaths worldwide and about 4.6% of potential years of life lost are attributable to alcohol¹.

An epidemiological study carried out in Brazil, in the state of São Paulo, showed a population prevalence of alcohol dependence or abuse of 10.4% in men and 2.6% in women. In this study, 1,646 adults were interviewed using a questionnaire that evaluates alcohol dependence or abuse². In all regions of the world, men consume more alcohol than women, although the exact proportion varies, with women consuming a higher proportion in high-income countries than in low-income countries¹.

An acute symptomatic seizure is defined as a clinical seizure that occurs at the time of a systemic insult or in close temporal association with a documented brain insult, including alcohol intoxication and withdrawal³. Alcohol is one of the factors causing acute symptomatic seizures in people without epilepsy, and usually occurs after prolonged consumption or in high doses³. In patients diagnosed with epilepsy, even small doses can lead to seizures⁴. Alcohol intoxication can lead to falls and head trauma, which can result in post-traumatic injuries and cause structural epilepsy. Other causes of symptomatic seizures also occur more frequently in alcohol-dependent patients than in the general population, such as traumatic brain injury (TBI) and stroke⁵.

The alcohol withdrawal syndrome can occur in about half of the patients with chronic alcohol use disorder, who substantially reduce the consumption of this substance or who abruptly stop drinking⁶. Some of the symptoms are

tremors, muscle stiffness, *delirium tremens* and epileptic seizures⁷.

Seizures due to alcohol withdrawal usually occur between 6 and 48 hours after the last drink⁸. Due to clinical repercussions, patients with epileptic seizures caused by withdrawal, in general, are classified as severe cases⁹. In the United States, it is estimated that 2 million people each year require treatment for alcohol withdrawal seizures. It is estimated that between 2 and 7% of patients who use alcohol excessively and are admitted to general medical care will develop severe abstinence¹⁰.

Although acute symptomatic seizures due to AWS are an apparently common in Brazilian usually overcrowded emergency room services, this recurrent health problem has been poorly addressed.

This study aimed to describe the sociodemographic and clinical profile of patients attended for seizures due to AWS, characterize the recurrence rate of hospital admission and explore the relationships between AWS, previous diagnosis of epilepsy, anticonvulsants use, TBI and chronic cerebral structural alterations on computed tomography (CT). This real-world evidence can contribute to the recognition of critical points in patient care and produce useful information for the development of public care policies for patients with AWS.

METHOD Sample

This is a descriptive, observational, transversal, retrospective and quantitative study. Data collection was obtained from medical records end the Consent Form was obtained from all patients.

The study included patients older than 18 years, who had one or more epileptic seizures on the day of admission or in the last 3 days prior to admission, with trustworthy reports of being a chronic alcoholic and who had drunk alcohol on the day of the first seizure or even in the last 7 days before that event. The report of chronic alcoholism, described in these terms or in similar terms in the medical record, such as a long-term drinker and long-term alcohol user, was accepted as an inclusion criterion, even if the years of alcohol use or the amount of daily or weekly drink intake were not quantified.

For this statement to be considered, it should have been provided by the patient himself or by a patient's companion and not just indirectly inferred by the professionals. Patients were included regardless of whether or not they had a previous diagnosis of epilepsy.

The study excluded those who presented at least one of the criteria detailed in Table 1.

The research was approved by the Fundação Hospitalar do Estado de Minas Gerais Ethics Committee (approval number 34197620.4.0000.5119).

Table 1. Exclusion criteria for the study.

At least one of the following criteria from A to H:
A) Use of illicit drugs in the last 48 hours
B) Traumatic brain injury with acute tomographic alteration
C) Acute ischemic or hemorrhagic stroke
D) Hypoglycemia (<60mg/dl)
E) Systemic infections
F) Central nervous system infections
G) Electrolyte imbalances (Na, Mg, Ca, P)
H) Patient evasion from ED

Na=sodium; Mg=magnesium; Ca=calcium; P=phosphorus; ED=emergency department.

Procedure

An Excel spreadsheet was made available to researchers, containing the number of the medical records of all medical care performed in the Hospital Regional de Barbacena (Minas Gerais, Brazil) emergency room during 2019, together with the International Classification of Diseases - tenth edition (ICD-10) registered for each of these visits, noting that each record contained only one ICD registered.

All medical records containing the following ICD-10 were selected: G40.0 - idiopathic epilepsy and epileptic syndromes with seizures of focal onset; G40.9 - Epilepsy, unspecified; F10.3 - Mental and behavioral disorders due to the use of alcohol - withdrawal (state); F10.2 - Mental and behavioral disorders due to alcohol use - dependence syndrome; F100 - Mental and behavioral disorders due to alcohol use - acute intoxication; R56 - Convulsions, not

elsewhere classified; R56.8- Other and unspecified convulsions.

The researchers accessed all these medical records with the ICDs described above through the Integrated Hospital Management System (IHMS) for patients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria for AWS.

Some medical records were duplicated, which corresponded to the same patient who returned to the evaluation for care throughout the year, for the same reason (seizures related to alcohol withdrawal syndrome). These cases were evaluated and counted in the items "recurrence of care" and "number of recurrences", if they again met the inclusion criteria and did not have any exclusion criteria.

Statistical analysis

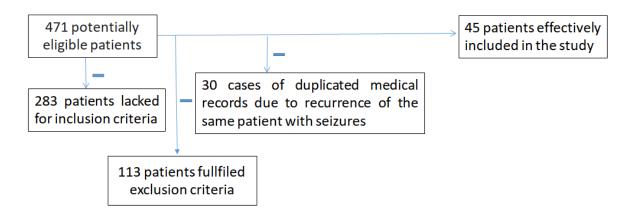
The results were tabulated in Office Excel spreadsheets for Windows 10 and presented in numerical values, graphics, and percentages. The software used for the statistical analysis was JASP version 0.13.1 (University of Amsterdam).

Descriptive statistics were performed using absolute and relative frequencies. The value of statistical significance (p) was set at 5% (p< 0.05), with a 95% confidence interval. Cross-tabulation tests were used to assess statistical association between two variables, using Chi-Square test.

RESULTS

471 records were selected. Of these, 283 did not contain all the inclusion criteria and, therefore, were excluded. Of the remaining 188, 113 had at least one exclusion criteria. From the 75 eligible medical records, 30 were recurrence of care for patients already selected. Thus, a total of 45 different patients were selected for the research, as can be seen in Figure 1 flowchart.

Figure 1. Diagram of patient selection.



The selection process involved three stages: fulfillment of all inclusion criteria, absence of any exclusion criteria and elimination of duplication. 45 patients were enrolled for the research.

Regarding the exclusion criteria, Table 2 shows the number of medical records excluded for specific causes.

Table 2. Absolute number of medical records excluded by specific causes.

Specific Cause	Frequency
Illicit drugs use	36
Electrolyte disorders or hypoglycemia	37
Traumatic brain injury with abnormal head CT scan	18
Acute ischemic stroke	0
Patient evasion from ED	3
Infections	13
More than one cause	3
Total	113

CT = computed tomography; ED = emergency department.

Sociodemographic characteristics

The patients were distributed by age range groups. Most patients had between 35 and 45 years (37.7%), followed by 45 to 55 years (31.1%) and 55 years or more (22.2%). Only one patient was aged between 18 and 25 years old (2.2%) and only three between 25 and 35 years old (6.6%). 13% of the patients were female and 87% male. There was a difference between the patients' sex (p<0.01).

Previous medical history

34 patients (75.5%) had previously had an epileptic seizure, 10 (22.2%) had never had an epileptic seizure before, and one medical record (2.2%) did not contain this information. Of the 34 who had previously had seizures, 11 (32.3%) described epileptic seizures caused by alcohol. Regarding the previous use of anti-epileptic drugs (AEDs), it was found that 21 patients (46.6%) used this type of medication, but in 20 of them (95.2%) it was described in

the medical records that they used the medication incorrectly.

21 patients (46.7%) had already the diagnosis of epilepsy. 17 patients (37.8%) had no previous diagnosis of epilepsy and in seven records (15.5%) this data was not included. There was an association between previous diagnosis of epilepsy and the presence of epileptic seizures (p<0.001).

Semiology of epileptic seizures and CT scan

35 patients (77.8%) had a single seizure related to alcohol withdrawal syndrome lasting less than five minutes and 10 patients (22.2%) had recurrent seizures, but only two of these fullfiled *status epilepticus* definition (Table 3).

Table 3. Recurrence of seizures profile.

More than one epileptic seizure	Frequency (percentage)
No status epilepticus	8 (17.8)
Status epilepticus*	2 (4.4)
Total	10 (22.2)

^{*} Status epilepticus is defined as prolonged seizures (five minutes or more) or recurrent clinical or electroencephalographic seizures without recovery of consciousness between them.

Of the 27 patients in which the type of seizure was described, 92% were generalized tonic-clonic at onset and 8% had focal onset, with or without secondary generalization.

Head trauma was present in eight patients with seizure related to alcohol withdrawal syndrome (18%). Skull

computed tomography (CT) was performed in 10 patients (22.2%) and in the remaining 35 (77.7%) the exam was not performed during the period the patient remained in the hospital.

Of the 10 patients who underwent cranial tomography, eight had no previous abnormalities on the exam and two had only diffuse cortical atrophy. The presence of acute abnormalities on tomography, such as hematomas and hemorrhages, was part of the exclusion criteria of the study and, therefore, none of the patients in the study had these findings. There was no association between epileptic seizures and the presence of traumatic brain injury (p=0.15), nor between epileptic seizures and the presence of an old alteration in the cranial CT scan (p=0.62).

Pattern of alcohol consumption

Regarding what type of drink the patient used to consume most of the time in the last few months, four (8.8%) consumed distilled drinks, two (4.4%) fermented drinks and for 39 patients this data was missing on medical records. Table 4 shows the daily or weekly frequency of alcohol consumption by patients.

The data found in relation to the last day on which the patient consumed alcoholic beverages before the epileptic seizure were as follows: only one (2.2%) had consumed alcohol less than six hours before the seizure, two (4.4%) had consumed between six and 24 hours before the seizure, 29 (64.4%) reported having used it before 24 hours of the

seizure (but the interval was not specified), three (6.6%) drank alcohol between 24 and 48 hours before and 10 (22%) drank more than 48 hours before the seizure that lead the patient to the emergency room.

Table 4: Daily or weekly frequency of alcohol consumption by patients.

Frequency of alcohol consumption	Frequency (percentage)
Everyday or at least six times a week	8 (17.8)
Between three and five times a week	0 (0)
Less than three times a week	1 (2.2)
Missing data	36 (80)
Total	45 (100)

Hospital care

The place where the patient received the first care at the hospital was divided into a critical care room (20% of the patients) and a non-critical room (80% of the patients). Patients admitted in the critical care room had more prolonged hospital stay (p=0.01). Table 5 shows the length of stay in the hospital where the patient was admitted.

Table 5. Time spent on hospital care.

Length of hospital stay (days)	Frequency (percentage)
One	22 (48.8)
Two or three	18 (40)
Four to seven	4 (8.8)
Eight to 14	0 (0)
At least 15	1 (2.2)
Total	45 (100)

Of the 45 patients, only 17 (38%) were evaluated by a psychiatrist or a neurologist during the hospital stay. There was no statistically association between having received referral to a mental health service after hospital discharge and absence of recurrence of care at the hospital (p=0.16).

From the 45 patients, 14 (31%) went back again to the emergency room for the treatment of new seizures related to alcohol withdrawal syndrome. From these, seven (50%) went once more, three (21.4%) went twice more and 4 (28.6%) went three times or more for the same reason. There was no significant difference between the presence of old abnormalities in skull CT and the recurrence of seizures (p=0.57) in the patients with alcohol withdrawal syndrome.

DISCUSSION

This study aimed to make an epidemiological assessment of clinical and sociodemographic variables related to acute symptomatic seizures related to AWS in an emergency room.

Epileptic seizures related to AWS was predominant in those over 35 years of age. This data is worrisome, since it affects an economically active population and problematic alcohol use is an important cause of absenteeism at work. A recent study conducted in Uganda, sub-saharan Africa, showed that the probability of drinking increased significantly with age (35 years of age or more)¹¹.

A study carried out in the state of São Paulo, Brazil, found a different prevalence of alcohol abuse, with a higher

percentage in the 20-29 age group (33.8%)² which may point to regional differences in Brazil. As for sex, the prevalence was higher in men (87%) and significant. This data is compatible with several other studies in the literature, which show a higher incidence of epileptic seizures due to alcohol withdrawal syndrome in men and also a higher consumption of alcohol in male individuals^{1,2,11,12}.

The patients from this research using prophylactic antiepileptic drugs accounted for almost a half of them (46.6%). Patients with seizures caused by alcohol withdrawal syndrome generally do not benefit from prophylaxis with anti-epileptic drugs such as carbamazepine, valproic acid and others, because they are not effective for such seizures. In addition, medication adherence by alcoholic patients is low, which was also verified in the sample of our study¹³.

The previous diagnosis of epilepsy, reported by patients or family members, was described in 46.6% of these patients, although it was not specified, in any medical record, which were the criteria used for this diagnosis. It is known that the current diagnostic criteria for epilepsy defined by International League Against Epilepsy (ILAE) do not include epileptic seizures caused by an acute insult, such as alcohol withdrawal syndrome^{3,8,14}.

Therefore, it is not known whether this percentage corresponds to patients with primary epilepsy or if, in fact, it represents a group of individuals who had recurrent seizures caused by alcohol withdrawal syndrome and, thereby, where misdiagnosed as having idiopathic epilepsy. This information

may be difficult to achieve in an emergency room, but can be obtained by contacting the attending physician or in a family medicine primary care set.

A study evaluated the type of epileptic seizure caused by alcohol withdrawal and found that 95% of the 241 patients evaluated had generalized tonic-clonic seizures and only 5% had focal seizures⁸. Another study, carried out in south India showed that 88% had generalized tonic-clonic seizures and none had status epilepticus¹⁵. Our study found a very similar data regarding the type of seizure: 92% of the patients had generalized tonic-clonic seizures.

The presence of congenital or acquired intracranial structural abnormalities are risk factors for epilepsy¹⁶. It is known that people who abuse alcohol are more at risk of having structural brain abnormalities that can contribute to these epileptic seizures, such as injuries caused by head trauma^{17,18}. In our study, 18% of patients had mild traumatic brain injury (TBI) due to fall during the seizure, without acute skull CT abnormalities. There were no statistically significant association between TBI and the presence of epileptic seizures, which may suggest that in patients without acute brain injuries, an isolated TBI without radiologic alterations may not have been the causal factor.

22% of all patients with alcohol withdrawal syndrome underwent skull CT. Of this sample, 70% did not have any chronic abnormalities in the exam. However, it should be noted that this prevalence may be underestimated, because patients with acute intracranial injuries (and so those with

concomitant chronic alterations) were excluded from our research, precisely because this is a bias factor in determining the cause of the seizure. Interestingly, our study points out that the presence of old brain structural lesions may be a finding that is overestimated as causal factor for seizures, since there was no significant association between these two outcomes in our sample (p=0.62) of patients with alcohol withdrawal syndrome.

Epileptic seizures caused by alcohol withdrawal syndrome generally occur between six and 48 hours after alcohol consumption⁸. A study that evaluated 186 patients with seizures caused by alcohol and found that 92.3% had their first seizure within 48 hours after drinking alcohol¹⁹. In general terms, our research found a predominance of seizures occurring within 48 hours of drinking (78%).

Most patients were discharged from the emergency department shortly after resolution of the seizure and initial clinical stabilization. Patients admitted in the critical care room had longest hospital stay (p=0.01). This association was already expected since admission to the critical care room reflects the presence of greater severity.

Patients with alcohol use disorder need a multidisciplinary approach with pharmacological and non-pharmacological interventions for treatment, in addition to a singular therapeutic project that takes into account the family and community support²⁰. The data from this research did not find a significant association between having been referred to a mental health service and absence of

recurrence of need for health care at emergency room within a year (p=0.16). However, this should be interpreted with caution, since maybe patient and family have not sought the service. In addition, even those who sought the service, they may not have adhered to long-term follow-up or to the treatment. These questions are beyond the scope of this study and, furthermore, reveal a knowledge gap that may direct future research.

The recurrence of attendance of the same patient at the emergency service within one year was of 31%. This data is important to warn about the need to invest in primary and secondary prevention measures for these patients with alcohol use issues.

The findings of this study reinforce the need to treat problematic alcohol use prophylactically in Psychosocial Care Centers, especially for vulnerable young men, before these patients develop AWS and seizures. Perhaps a more structured connection between patient's family and social assistance service at the time of hospital discharge could help to change the outcome of seizure recurrence by promoting adherence to continued outpatient treatment.

Furthermore, differentiate patients who have acute symptomatic seizures unrelated to idiopathic epilepsy from those with epilepsy superimposed with AWS may be of benefit, since the treatment strategies are different^{13,16}.

The lack of correlation between seizures and TBI without CT scan acute alterations and even with chronic alterations may point to the absence of need to routinely

indicate CT scan for all patients with seizures related to AWS, but only in selected cases: first alcohol-related seizure; focal seizure; TBI with transient loss of consciousness; focal neurological deficit on neurological exam or other characteristics that may point to seizure due to a secondary origin¹³.

Some limitations of this study were the modest sample size and the observational and retrospective design, making it difficult to assess whether or not the associations made have a causal relationship with each other. Some demographic data, for example the previous medical history and pattern of alcohol consumption may also be affected by information bias, since were provided by medical record.

CONCLUSION

In this study, we evaluated 45 patients with epileptic seizures related to AWS in a hospitalar emergency room within a year. In general terms, the clinical and epidemiological characteristics are consistent with those found in literature. The study revealed that seizures are more prevalent in men, with a poorly documented history of epilepsy, a high rate of recurrence and non-adherence to treatment, even when an outpatient care project is indicated at discharge.

Our data reinforces those epileptic seizures related to AWS is a complex and recurrent public health problem, and points to the need to strengthen strategies for primary and secondary prevention of AWS as a way to promote health. This may include a more structured connection between patient's family and social assistance service at the time of hospital discharge.

Furthermore, patients with epileptic seizures may benefit of a more systematically diagnostic approach including a differentiation between acute symptomatic seizure related to AWS and alcohol-related seizures in a previous epileptic patient, which may impact in the rational indication of skull CT scan and anticonvulsants.

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