

Frequency of delirium and associated factors in patients from a neurological emergency department

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Abstract

Background: Delirium is an important cause of morbidity and mortality in the general hospitalized population. Few information exists on risk factors in patients with neurological disease. **Objective:** This study was to analyze risk factors for delirium in patients presenting to a neurological emergency department. **Methods:** This study was observational prospective cohort study. We included all patients with neurological disease, admitted to the emergency department with a stay of more than 8 h, in the period from January to April 2022. The confusion assessment method-intensive care unit delirium detection instrument and DSM-5 criteria were applied to all patients. We obtained information on epidemiological, clinical, and paraclinical variables at the time of admission. Through a univariate and multivariate logistic regression model, we analyzed risk factors for delirium. **Results:** Of 3661 patients treated in the emergency department, 189 patients were included, 60.8% male gender, age 48 ± 19 years; 44 (23.2%) met criteria for delirium, 81% were diagnosed on admission; delirium scale score/index 12 (interquartile range [IQR] 10-12), and duration of delirium 5 (IQR 2-11) days. Clinical history for risk of delirium: previous delirium (odds ratio [OR] 3.9, 95% CI 2.4-6.1, $p = 0.003$), stroke (OR 2.2, 95% CI 1.4-3.9, $p = 0.009$), neurosurgery (OR 2.1, 95% CI 1.2-3.8, $p = 0.024$), and use of psychoactive drugs (OR 2.5, 95% CI 1.3-4.6, $p = 0.021$). The following variables were independent risk factors for delirium through the multivariate logistic regression model: uncontrolled crisis [OR 5.4 (95% CI 1.2-22.9), $p = 0.023$], supratentorial structural brain lesion [OR 6.1 (95% CI 1.7-21.2), $p = 0.004$], and neuroinfection OR 9.6 (95% CI 2.9-31.4), $p \leq 0.001$. **Conclusions:** The frequency of delirium is 23.2% in patients presenting to the neurological emergency department; uncontrolled epilepsy, neuroinfection, and supratentorial brain lesions are independent risk factors for delirium.

Keywords: Delirium. Neurological disease. Clinical risk factors. Risk image factors. Frequency. Neurological emergencies.

Frecuencia de delirium y factores asociados en pacientes de un departamento de urgencias neurológicas

Resumen

Antecedentes: El delirium es una causa importante de morbi-mortalidad en la población general hospitalizada. Poca información existe sobre factores de riesgo en población con enfermedad neurológica. **Objetivo:** Analizar factores de riesgo para delirium en pacientes que acuden a un servicio de urgencias neurológicas. **Métodos:** Estudio observacional de cohorte prospectivo. Incluimos

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a todos los pacientes con enfermedad neurológica, ingresados al servicio de urgencias con estancia mayor a 8 horas, en el periodo de tiempo enero a abril de 2022. A todos los pacientes se les aplicó el instrumento para detección de delirium CAM-ICU y/o criterios DSM-5. Obtuvimos información de variables epidemiológicas, clínicas y paraclínicas al momento del ingreso. A través de un modelo de regresión logística univariable y multivariable analizamos factores de riesgo para delirium. **Resultados:** De 3661 pacientes atendidos en el periodo de tiempo señalado, 189 pacientes fueron incluidos, 60.8% género masculino, edad 48 ± 19 años; 44 (23.2%) cumplieron criterios para delirium, 81% fue diagnosticado al ingreso; puntuación en escala delirium/Inch 12 (RIQ 10-12), duración de delirium 5 (RIQ2-11) días. Antecedentes clínicos para riesgo de delirium: delirium previo (OR 3.9, IC 95% 2.4-6.1, $p = 0.003$), EVC (OR 2.2, IC 95% 1.4-3.9, $p = 0.009$), neurocirugía (OR 2.1, IC 95% 1.2-3.8, $p = 0.024$) y uso de drogas psicoactivas (OR 2.5, IC 95% 1.3-4.6, $p = 0.021$). A través del modelo de regresión logística multivariable, los siguientes factores de riesgo son independientes para delirium: epilepsia descontrolada OR 5.4 (IC 95% 1.2-22.9), $p = 0.023$; lesión cerebral estructural supratentorial OR 6.1 (IC 95% 1.7-21.2), $p = 0.004$; neuroinfección OR 9.6 (IC 95% 2.9-31.4), $p \leq 0.001$. **Conclusiones:** La frecuencia de delirium es de 23.2% en pacientes en el servicio de urgencias neurológicas; epilepsia descontrolada, neuroinfección y lesiones cerebrales supratentoriales son factores de riesgo independientes para delirium.

Palabras clave: Delirium. Enfermedades neurológicas. Factores clínicos de riesgo. Factores de imagen de riesgo. Frecuencia. Urgencias neurológicas.

Introduction

Delirium is a transient cause of mental dysfunction characterized by fluctuation in attention and alertness. It usually develops over a short period of time (hours to days) and may present with other cognitive symptoms such as memory, language, and visuospatial deficits, as well as disorientation or perceptual alterations¹. Delirium diagnosis is clinical and the most common diagnostic assessment instruments include DSM-5 and confusion assessment method-intensive care unit (CAM-ICU)².

There are several studies on delirium and its impact on prognosis in several diseases. Delirium occurs in up to 30% of patients in general wards, increases mortality risk in 60% of cases, and length of hospital stays^{3,4}. It is currently considered one of the main public health problems, not only in elderly patients, but in intensive care units, terminal patients, and out-of-hospital settings, since it is one of the pathologies that are related with greatest intrahospital costs^{5,6}.

Clinically, delirium is classified based on the pattern of behavior or psychomotor activity, subdividing into hypoactive, hyperactive, or mixed. The relevance of this classification lies in the prognosis, with the mortality rate being 33%, 34%, and 15%, respectively^{7,8}. Delirium appears to be the consequence of the interaction between an underlying predisposing factor and an acute stressor. Proposed mechanisms for delirium pathogenesis include neurotransmitters dysfunction, inflammatory, and neurodegenerative mechanisms, as well as endothelial and direct neuronal injury³.

Little information exists on the frequency and associated factors of delirium in patients in neurological emergency departments; therefore, this study aims to

determine the frequency and main risk factors associated with delirium in this group of patients.

Materials and methods

Study design and population

An observational prospective cohort study was conducted in a neurological emergency department of a single tertiary health-care center. We included patients from January to April 2022 who met the following inclusion criteria: (1) any gender, (2) neurological disease diagnosis, (3) inpatient for at least 8 h, (4) met diagnostic criteria for Delirium (according to the CAM-ICU and/or DSM-5), and (5) score of the RASS scale from -3 to +4 at the time of application of the CAM-ICU instrument. All patients with (1) RASS score of -4 and -5 at the time of application of the CAM-ICU instrument or (2) lactation or pregnancy were excluded from the study.

Follow-up evaluation

Data collection included age, gender, vital signs on admission, comorbidities, and history of neurological disease, diagnosis of neurological disease on admission, infection outside the CNS, number, and type of drugs on admission or during hospital stay. Results of paraclinical studies (complete blood count, blood chemistry, serum electrolytes, liver function tests, lumbar puncture cytochemical results), axial tomography, and/or magnetic resonance imaging were collected.

The CAM-ICU and DSM-5 diagnostic instruments were applied to all patients at the time of admission and during

Table 1. Predisposing risk factors in patients with neurological pathology with delirium and without delirium

Variables	Patients (n = 189)	No delirium (n = 145, 76.7%)	Delirium (n = 44, 23.3%)	OR (95% CI)	p-value
Demographic characteristics					
Male, n (%)	115 (60.8)	89 (61.3)	26 (59.1)		0.860
Age (years) - mean	48 ± 19	47 ± 18	53 ± 21		0.083
Age > 65 years, n (%)	39 (20.6)	26 (15.8)	13 (29.5)		0.135
Comorbidities (Charlson index)					
Index – median (IQR)	2 (0-3)	2 (0-3)	2 (0-4)		0.141
Low (0), n (%)	65 (34.3)	52 (35.8)	13 (29.5)		0.474
Medium (1-2), n (%)	60 (31.7)	49 (33.7)	11 (24.9)		0.356
High (3-4), n (%)	40 (21.1)	29 (19.9)	11 (24.9)		0.528
Very High (> 5), n (%)	23 (21.1)	14 (9.6)	9 (20.4)		0.67
Previous history					
Psychoactive drugs, n (%)	11 (5.8)	5 (3.4)	6 (13.6)	2.55 (1.39-4.69)	0.021
Visual deficit, n (%)	64 (33.8)	54 (37.2)	10 (22.7)		0.101
Audition deficit, n (%)	8 (4.2)	7 (4.8)	1 (2.2)		0.684
Neurological history					
Delirium, n (%)	6 (3.1)	1 (0.6)	5 (11.3)	3.91 (2.48-6.15)	0.003
Stroke, n (%)	24 (12.6)	13 (8.9)	11 (24.9)	2.29 (1.34-3.98)	0.009
Neurosurgical procedure, n (%)	20 (10.5)	11 (7.5)	9 (20.4)	2.17 (1.23-3.83)	0.024

their hospital stay by neurologists and/or psychiatrists who work within the institution in the Neurological Emergency Department or as medical interconsultants, to identify the patients who met criteria for delirium. Those who met 3 or more CAM-ICU criteria and/or DSM-5 criteria were considered as having delirium. The delirium subtype was classified based on the predominant pattern of psychomotor activity. Delirium severity at the time of diagnosis was calculated using the delirium index instrument.

In the follow-up, we consider resolution of delirium when the patients clinically stopped fulfilling diagnostic criteria of delirium by DSM-5 criteria (alteration of alertness, inattention, alteration of other cognitive function, and fluctuation of symptoms) and/or when they stopped fulfilling item 1 and 2 of the CAM-ICU scale, on any day of evolution at the decision of the treating physician.

Statistical analysis

For the distribution of continuous variables, we used the Kolmogorov–Smirnov test, and the variables were described in means (SD) or medians (interquartile range [IQR]) according to their distribution. Categorical variables were described in frequencies and percentages. To search for differences between groups, the χ^2 or Fisher's exact test was used for categorical variables; Student's t-test to compare means, and Mann–Whitney U-test to compare medians. $p < 0.05$ was considered statistically significant.

To analyze risk factors for delirium, we used a univariable and multivariable logistic regression model. In the multivariable analysis, we introduce the following variables: uncontrolled epilepsy, supratentorial structural brain lesion, right hemispheric structural brain lesion, neuroinfection (bacterial and viral), hydroelectrolyte imbalance, sepsis/septic shock (urinary and pneumonia), and polypharmacy. We assessed the goodness of fit by the Hosmer–Lemeshow test and the model performance by the area under the curve analysis. Statistical significance was evaluated at the 0.05 level. Results are reported as odds ratio (OR) with 95% confidence intervals (95% CI).

All statistical analyses were performed using the IBM SPSS Statistics version 26 statistical package system.

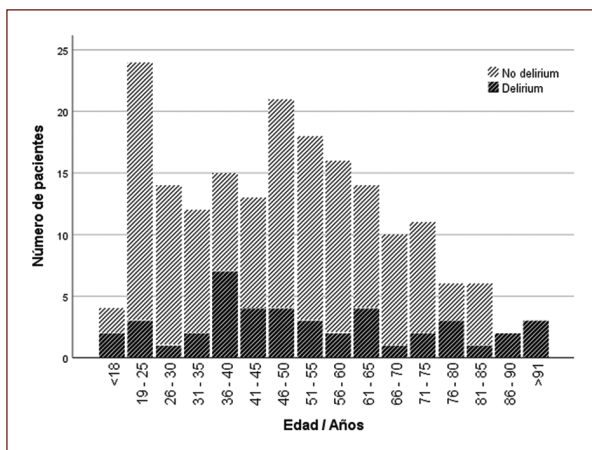
Results

Of 3661 patients treated, only 189 patients fulfilled inclusion criteria. The mean age of our population was 48 ± 19 years (Fig. 1), with male predominance (60.8%). Baseline clinical characteristics of our population are described in tables 1 and 2 which describe the main neurological diagnoses of admission.

Delirium occurred in 44 (23.2%) patients, with 36 (81%) diagnosed at admission, and 8 (18.1%) were during their hospital stay. The median severity of delirium (delirium index) at the time of diagnosis was 12 (IQR 10-16) points and the median duration was 5 (IQR 2-11) days (Fig. 2). The most prevalent subtype was

Table 2. Risk factors at hospital admission in patients with neurological pathology with delirium and without delirium

Variables	Patients (n = 189)	No delirium (n = 145)	Delirium (n = 44)	OR (95% CI)	p-value
Neurological diseases at admission					
Uncontrolled epilepsy, n (%)	14 (7.4)	5 (3.4)	9 (20.4)	3.21 (1.96-5.24)	0.001
Status epilepticus, n (%)	10 (5.2)	6 (4.1)	4 (9.1)		0.246
Stroke, n (%)	46 (24.3)	33 (22.7)	13 (29.5)		0.423
Brain hemorrhage, n (%)	35 (18.5)	24 (16.5)	11 (24.9)		0.267
CNS infection, n (%)	32 (16.9)	13 (8.9)	19 (43.1)		< 0.001
Bacterial, n (%)	11 (5.8)	5 (3.4)	6 (13.6)	3.72 (2.35-5.90)	0.021
Viral, n (%)	20 (10.5)	7 (4.8)	13 (29.5)	2.55 (1.39-4.69)	< 0.001
Autoimmune encephalitis, n (%)	14 (7.4)	9 (6.2)	5 (11.3)	3.54 (2.25-5.57)	0.321
Infection at admission					
Urinary tract infection, n (%)	11 (5.8)	4 (2.7)	7 (15.9)	3.06 (1.80-5.20)	0.004
Respiratory infection, n (%)	22 (11.6)	11 (7.5)	11 (24.9)	2.53 (1.50-4.24)	0.005
Sepsis/septic shock, n (%)	13 (6.8)	4 (2.7)	9 (20.4)	3.48 (2.18-5.56)	< 0.001
Admission drugs					
Multiple drugs, n (%)	100 (52.9)	61 (42.1)	39 (88.6)	6.94 (2.86-16.83)	< 0.001
Steroid use, n (%)	47 (24.8)	25 (17.2)	22 (49.9)	3.02 (1.85-4.93)	< 0.001
Vasoactive drugs, n (%)	9 (4.7)	2 (1.3)	7 (15.9)	3.78 (2.40-5.94)	0.001
Sedatives, n (%)	64 (33.8)	37 (25.5)	27 (61.3)	3.10 (1.83-5.25)	< 0.001
Hydroelectrolytic imbalance, n (%)	128 (67.7)	89 (61.3)	39 (88.6)	3.71 (1.82-13.19)	< 0.001
Structural lesions in brain imaging at admission					
Left hemisphere, n (%)	52 (27.5)	35 (24.1)	17 (38.6)		0.082
Right hemisphere, n (%)	52 (27.5)	32 (22.1)	20 (45.4)	2.19 (1.33-3.62)	0.004
Supratentorial, n (%)	86 (45.5)	57 (39.3)	29 (65.9)	2.31 (1.33-4.02)	0.003
Infratentorial, n (%)	16 (8.4)	13 (8.9)	3 (6.8)		0.767
Hospital stay					
Days of ER stay-median (IQR)	2 (1-2)	2 (2-3)	4 (2-5)		< 0.001
Total days of length stay-median (IQR)	2 (2-4)	2 (2-3)	7.5 (4-12)		< 0.001

**Figure 1.** Age ranges in patients with neurological pathology with and without delirium.

hypoactive (72.8%), followed by hyperactive (18.1%) and mixed (9.1%). The median total hospital stay for patients with delirium was 7.5 (IQR 4-13) days. Delirium resolved

in the emergency department in 29.5% of patients, persisted on discharge from the emergency department in 31 patients, of which 23 patients were admitted to hospitalization or ICU and were followed up during their stay. Fifty percentages of our patients were discharged without delirium. Clinical differences between patients with versus without delirium are described in [table 2](#).

Regarding identification of preexisting factors for delirium, the following was statistically significant: Previous delirium OR 3.91 (95% CI 2.48-6.15, $p = 0.003$), stroke OR 2.29 (95% CI 1.34-3.98, $p = 0.009$), neurosurgery OR 2.17 (95% CI 1.23-3.83, $p = 0.024$), and a history of psychoactive drug use OR 2.55 (95% CI 1.39-4.69, $p = 0.021$).

Precipitating factors for delirium at admission or during hospital stay include polypharmacy OR 6.94 (95% CI 2.86-16.83, $p \leq 0.001$), sepsis/septic shock OR 3.48 (95% CI 2.18-5.56, $p \leq 0.001$), hydroelectrolytic imbalance OR 3.71 (95% CI 1.82-13.19, $p \leq 0.001$), central nervous system infection OR 3.72 (95% CI 2.35-5.90, $p \leq 0.001$), and uncontrolled epilepsy OR 3.21 (95% CI 1.96-5.24, $p = 0.001$).

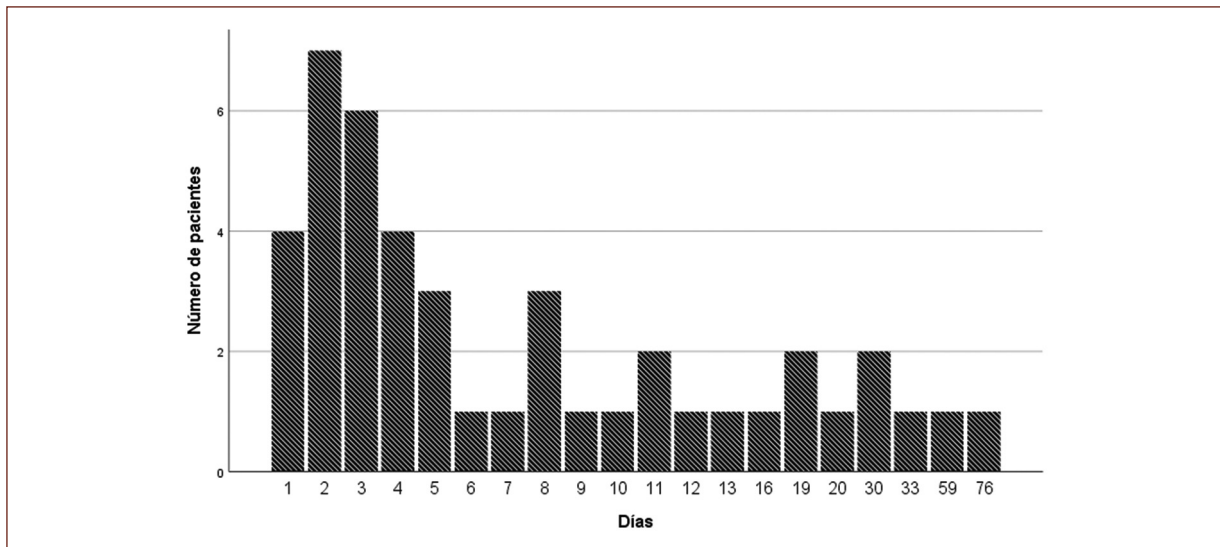


Figure 2. Duration of delirium in patients with neurological pathology.

Table 3. Risk factors associated with delirium

Variables	Univariate analysis				Multivariate analysis	
	No-Delirium (n = 145)	Delirium (n = 44)	OR (CI 95%)	p-value	OR (CI 95%)	p-value
Uncontrolled epilepsy, n (%)	5 (3.4)	9 (20.4)	3.21 (1.96-5.24)	0.001	5.4 (1.2-22.9)	0.023
Structural brain lesions (supratentorial), n (%)	57 (39.3)	29 (65.9)	2.31 (1.33-4.02)	0.003	6.1 (1.7-21.2)	0.004
Structural brain lesions (Right hemisphere), n (%)	32 (22.1)	20 (45.4)	2.19 (1.33-3.62)	0.004	0.9 (0.2-2.9)	0.90
Hydroelectrolytic imbalance, n (%)	89 (61.3)	39 (88.6)	3.71 (1.82-13.19)	< 0.001	2.0 (0.6-6.7)	0.26
Neuroinfection, n (%)	13 (8.9)	19 (43.1)	8.4 (3.6-19.5)	< 0.001	9.6 (2.9-31.4)	< 0.001
Multiple drugs, n (%)	61 (42.1)	39 (88.6)	6.94 (2.86-16.83)	< 0.001	4.7 (1.4-15.2)	0.009
Sepsis/septic shock, n (%)	19 (13)	27 (61.3)	5.0 (2.2-11.2)	< 0.001	3.4 (1.2-9.9)	0.02

Model: Chi-squared 74.443, GL 7, $p \leq 0.001$; Hosmer-Lemeshow: Chi-squared 8.225, GL 7, $p = 0.31$; Model performance: AUC = 0.874 (CI 0.82-0.92), $p \leq 0.001$

Among the findings in imaging studies, intraparenchymal left hemisphere OR 2.19 (95% CI 1.33-3.62, $p = 0.004$) and supratentorial lesions OR 2.31 (95% CI 1.33-4.02, $p = 0.003$) are risk factors for delirium (Tables 1 and 2).

The following variables were independent risk factors for delirium through the multivariate logistic regression model: uncontrolled crisis [OR 5.4 (95% CI 1.2-22.9), $p = 0.023$], supratentorial structural brain lesion [OR 6.1 (95% CI 1.7-21.2), $p = 0.004$], neuroinfection [OR 9.6 (95% CI 2.9-31.4), $p \leq 0.001$], multiple drugs [OR 4.7 (95% CI 1.4-15.2), $p = 0.009$], and sepsis/septic shock [OR 3.4 (95% CI 1.2-9.9), $p = 0.02$] (Table 3).

Discussion

Delirium occurs in 30% of hospitalized patients, increases up to 56% in patients older than 65 years, and is related with greater mortality risk, up to 60%^{3,4}. Neurological conditions such as stroke and prior cognitive impairment are risk factors for delirium in the general population⁴. In neurological hospitalization services, the population may differ from the general population as certain neurological or neurosurgical conditions are more frequent in young adult patients (for example: demyelinating diseases and primary tumors of the Central Nervous System). There is few information on the

frequency of delirium in neurological hospitalization areas. A study from a hospital in Spain reported a delirium frequency of 16.5% in a neurological service⁴. A previous report performed in the neurological emergency department of our center in 2006 reported that 14.9% of the patients admitted to the emergency department presented delirium⁹. However, the demand for specialized medical care in neurological, neurosurgical, and neuropsychiatric conditions has increased in recent decades in our hospital, increasing to 23.3%.

The time in which the delirium is established from hospital admission is a prognostic factor. The earlier delirium diagnosis is established in the emergency area directly impacts the length of hospital stay up to 10-23 days if it is detected within the first 24 h¹⁰. Other authors state that delirium diagnosed in the emergency department is not transitory; in fact, it persists in up to 77%¹¹. In our population, found similar data as 70.4% of our population presented transient delirium lasting between 1 and 10 days, while in the remaining 29.54%, delirium persisted for more than 10 days (Fig. 2). Delirium may persist after hospital discharge, as partial remission and non-recovery have been reported in up to 20.2% and 31.7%, respectively, even to 4 months after hospital discharge¹². In elderly patients, persistence of delirium has been reported in up to 25.6% and 21% at 3 and 6 months after hospital discharge¹³.

Delirium is very common in intensive care hospitalization with incidence in intensive care, ranges from 45% to 56%, increasing to 93% in terminally ill patients^{14,15}. In patients undergoing major surgery, delirium has been reported in 17-61%¹⁶. In our population, history of any neurosurgical procedure or stroke is risk factors for delirium. Other medical conditions that have been reported as risk factors for delirium, both in the general population and in the population with neurological disease, is history of previous delirium and cerebrovascular disease, which was observed in our study.

With the advent of new diseases such as COVID-19, which has been linked to long stays in the intensive care unit, delirium has occurred in 65-79%¹⁷; contrasting with outpatients with COVID-19 who arrive at the emergency department in whom delirium has presented as the main admission symptom in up to 28% of cases¹⁸. No patients with COVID-19 were included in our study since our center during the pandemic (2020 and 2021) was not a center for care of patients with suspected SARS-CoV-2 virus infection. Cerebrovascular disease is one of the most frequent diagnoses in the neurological population presenting with delirium.

Post-stroke delirium is a common complication in the acute phase, with incidences ranging from 11.8% to 66%.

Qu J et al. reported a prevalence of 14.6% in patients with ischemic stroke, most diagnosed between the 1st and 3rd day of hospitalization (13.4%), and only in a small part (1.1%) delirium was established after 5-7 days of hospitalization¹⁹. Fleischmann et al. demonstrated that, in most cases, delirium was established immediately after the acute cerebral infarction (within the first 72 h)²⁰, like that reported in cases associated with acute systemic diseases²¹. Our study reported a prevalence of post-stroke delirium of 29.5%. In patients with cerebrovascular disease, the most relevant risk factor for the development of delirium is the presence of a left cortical infarction, followed by a history of previous infarction and infections¹⁹, which is consistent with our findings. In our multivariate model, we analyzed that supratentorial brain lesions are an independent risk factor for delirium (Table 3). Although some other studies oppose this argument and show that post-infarction delirium is more closely related to right lobe cerebral infarcts^{22,23}. Delirium is a complication of cerebrovascular disease that must be addressed as soon as possible since these patients have a worse prognosis at 3 and 6 months compared to those who do not present it, and these patients also have a higher risk of developing delirium²⁴.

Other diagnoses of the neurological population that presents delirium are CNS infections and the lack of control of epileptic seizures. In our multivariate model, we demonstrate that both neuroinfections and uncontrolled epilepsy are independent risk factors for delirium in neurological patients, supporting previous reports⁹. Moreover, in our study, we reported that steroid treatment is a risk factor for delirium, which are used in support of the treatment of neuroinfection by *Streptococcus pneumoniae* or *Mycobacterium tuberculosis*, and in autoimmune diseases of the central nervous system. With respect to uncontrolled epilepsy as a risk for delirium in our population, we think that it is due to our population of patients with epilepsy, as most of them suffer from drug resistant epilepsy.

In the general population, infections such as electrolyte disturbances have been widely described as risk factors for delirium. In our study, which included only patients with neurological or neurosurgical conditions, only infections son independent risk factors for delirium³.

Limitations and strengths

The main limitations of the study: (1) the present study was only performed in a single center and (2) the time of the study for the recruitment of patients was very short. However, this study has several strengths: (1) in our country, it is the first study that is performed

with this type of population and (2) it is a prospective study.

Conclusion

The frequency of delirium in the population treated in a neurological emergency department is 23.3%. Stroke and delirium history, as well as neurosurgical procedures are risk factors for delirium in the neurological population. CNS infections and uncontrolled epilepsy, as well as presenting structural changes in the imaging study in supratentorial areas, are independent risk factors for delirium.

We agree that the present study provides important information on this issue in the population of our country; however, we consider that subsequent studies must be done, involving more centers and for a longer duration of patient recruitment.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of people and animals. The authors state that no experiments have been conducted on humans or animals for this research.

Confidentiality of data. The authors state that they have followed their workplace's protocols on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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