Editorial
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Ildefonso Rodríguez-Leiva

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We begin a new year, and as each cycle that begins, new purposes, ideas, goals, dreams, come to our mind, and the desire to make them come true seems firm, and we intend to fulfill them.

Our country, like the whole world, seems to be still looking for the best solutions in politics and the diversity of visions of the left, right, of communist, socialist, capitalist tendencies are among each other if dictatorship or democracy is the collective behavior that must be followed. The answer seems to continue to be sought by societies in different latitudes, and concordance is not yet established.

In health policies, the most effective, fair, and incorruptible model that serves the majority and that offers the best programs for prevention and treatment of the disease is also sought, through a system of education, vaccination, and proper ranking of health levels for each condition we face.

Medical science, however, is not democratic; it is not of economic convenience, although unfortunately, until now, it is more easily accessible to those who have more possibilities, at least in our homeland. Medical science seeks the truth, and for those who try to practice it, it is always challenging to find answers to the questions that appear daily in our professional practice.

In this issue, we try to answer questions in original investigations that give solutions, which, although they seem logical, provide us with certainty in the daily activities in neurology.

What are the differences in the risk factors, presentation, evolution, and outcome in the cancer patients concerning those who do not present stroke? In a study conducted at the National Cancer Institute of Mexico, these questions are answered.

In a second investigation, another fundamental question is answered. Is there a relationship between drug resistance in epilepsy and the presence of structural abnormalities seen in the magnetic resonance image? A study conducted at the Central Hospital of San Luis Potosí concludes on the need we have in Mexico to improve the infrastructure to perform early epilepsy surgery.

A third original work, carried out in the pediatric population and carried out at the Pediatric Hospital of Legaria in Mexico City, corroborates the desirability of managing with human immunoglobulin G since not having it increases the severity and complications at discharge four-fold.

The vascular neurology group of the University Hospital of Nuevo León, Mexico, presents a case of cardiogenic thromboembolism managed with apixaban, reviewing the literature of an infrequent problem (< 1%) but that we could face in our neurological practice and that could be applied to other situations of stroke.

Finally, a review paper is presented in this issue that all of us who are involved in neurosciences are passionate about; what is the variation of brain neurotransmitters in circadian rhythms? What are the external factors besides the light and dark that favor modification in

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neurotransmitters levels? As these variations modify not only our behavior but also our ability to respond to environmental aggressors and our systemic functionality. Although these contributions will surely have a modest impact on the health policies of our countries, the gift that each one of the authors shares with what they learn in their daily work will allow to make a difference, even if they seem to be only a drop of water that falls into the sea.

On behalf of all of those who work in this publication, I wish a new year full of strength, success, and happiness for each one of our readers. Moreover, we share the hope that everywhere in the world and in our country there exists the sincere wish of improving our education, our justice, and our health.

Finally, we would like to extend a special thank you to our reviewers and associate editors for their invaluable contribution to the journal.
Differences in stroke patterns and outcomes between cancer and non-cancer patients

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Abstract

Introduction: One in 10 patients with stroke concurrently has cancer; however, the impact of their combination on survival has not been well established; consequently, stroke and cancer are likely to have unrecognized associations. Objective: The objective of the study was to compare the stroke risk factors, presentations, and outcomes between stroke patients with and without cancer, to recognize this as an added hazard element that might impact mortality rates. Methods: Data were prospectively acquired at a cancer referral center from March 2011 to February 2018. Patients with histologically confirmed diagnosis of cancer, who were sent for neuro-oncology consultation and showed evidence by MRI of suffering a stroke during follow-up were compared with a previously reported cohort of patients with stroke and similar demographic characteristics (RENAMEVASC and PREMIER studies), employing Student’s t-test after determining the mean and standard deviation using Hazen’s equation. Results: A total of 270 patients with cancer-related stroke were compared to 2000 patients with non-cancer stroke. Stroke risk factors for the cohort of patients with cancer were dyslipidemia, alcohol abuse, and tobacco use, with a median follow-up after the stroke of 13.8 months. Mortality rates at 30 and 90-days were similar between both groups; however, at 6 and 12-months they were higher in patients with cancer-related stroke (6 months: 37% vs. 23%, RR 1.62, p < 0.0001; 12 months: 43% vs. 29%, RR 1.48, p = 0.00001). Conclusion: Mid-term and long-term survival rates were worse in cancer patients with stroke compared with those without cancer.

Key words: Cancer. Stroke. Survival. Mortality rates.

Diferencias y desenlaces acorde al patrón de presentación de eventos vasculares cerebrales (EVC) en pacientes con cáncer y sin cáncer

Resumen

Introducción: Uno de cada 10 pacientes que sufre un EVC tiene algún tipo de cáncer concomitante, sin embargo, el impacto de esta combinación no ha sido bien establecido. En consecuencia, es probable que el EVC y el cáncer presenten asociación...
cions no reconocidas. **Objetivo:** Comparar factores de riesgo, formas de presentación y desenlace en pacientes con cáncer y sin cáncer que sufrieron EVC, en función de reconocerlo como elemento adicional de riesgo que puede impactar sobre las tasas de mortalidad. **Métodos:** Se recopilaron datos prospectivamente en un centro de referencia oncológico desde marzo 2011 a febrero 2018. Pacientes con diagnóstico de cáncer confirmado por histopatología que fueron enviados a consulta de neuro-oncológia y evidenciaron por medio de IRM algún tipo de EVC durante el seguimiento, se compararon contra una cohorte previamente reportada de pacientes con EVC sin relación a cáncer y características demográficas similares (estudios RENAMEVASC y PREMIER), empleando t de Student después de determinar la media y la desviación estándar con la ecuación de Hozo. **Resultados:** Se comparó un total de 270 pacientes con EVC relacionado a cáncer contra 2,000 pacientes con EVC. Los factores de riesgo de EVC para la cohorte de pacientes con cáncer fueron dislipidemia, abuso de alcohol y uso de tabaco, con una mediana de seguimiento de 13.8 meses después del EVC. La tasa de mortalidad a 30 y 90 días fue similar en ambos grupos; sin embargo, a 6 y 12 meses fue mayor en el grupo de EVC relacionado a cáncer (6 meses: 37% vs. 23%, RR 1.62, p < 0.0001; 12 meses: 43% vs. 29%, RR 1.48, p = 0.00001). **Conclusión:** A mediano y largo plazo las tasas de supervivencia empeoraron en pacientes con EVC relacionado a cáncer. **Palabras clave:** Cáncer. Evento vascular cerebral. Supervivencia. Tasa de supervivencia.

**Introduction**

In recent years, deaths related to stroke, the third most common cause of mortality worldwide\(^1\), have increased by 26%, whereas the number of stroke survivors has increased by 84%; there are slightly more than 33 million people who are currently living after stroke\(^2\). Conversely, cancer is the second most common cause of death, which has shown an increasing trend between 2005 and 2015, with a 17% rise in the number of cancer-related deaths globally\(^3\).

One in 10 patients with stroke concurrently has cancer\(^3\), and the impact of their combination on survival has not been well established\(^4,5\). There are no studies specifically examining the common cardiovascular risk factors and comparing the mortality rates in patients with cancer and stroke. Stroke has been described as the first manifestation of cancer\(^6-8\), and it also has been associated with a worse prognosis\(^9\), consequently, stroke and cancer are likely to have unrecognized associations, for example, cryptogenic stroke is more frequent in cancer patients\(^10,11\). Due to the high prevalence of stroke in cancer patients and vice-versa, we aimed to analyze the stroke risk factors and outcomes in patients with cancer, which were compared with a socio-demographically similar population of stroke patients with no history of cancer, to recognize this as an added hazard element that might impact mortality rates and provide better care and prompt support.

**Material and methods**

This study included information from a computerized database, which was created in 2010 to collect data of patients with cancer at Instituto Nacional de Cancerología in Mexico City, a cancer referral center, who were followed up during the neuro-oncologic consultation between January 2011 and February 2018. Inclusion criteria considered patients of ≥18 years with histologically confirmed diagnosis of cancer at our institute who showed evidence by magnetic resonance image (MRI) of suffering a stroke during surveillance. Exclusion criteria apply for those with a diagnosis of stroke before cancer. The data included: demographic characteristics, cancer history, stroke characteristics, follow-up duration, and time to death. Stroke type and other characteristics were obtained directly from the registry database, corroborated by MRI, and validated by a board-certified neurologist. Data on age, sex, stroke risk factors (diabetes mellitus, hypertension, hypercholesterolemia, obesity, smoking, and alcohol abuse), and mortality in this cohort were compared to those of patients with no known cancer within a previously reported cohort of stroke patients from the national registry of cerebrovascular disease. The latter cohort was reported in the RENAMEVASC study (2000 stroke patients: 1134 ischemic, 806 hemorrhagic, and 60 cerebral venous thrombosis\(^12\) and PREMIER study (2702 ischemic stroke patients\(^13\) The institutional ethics and investigation committee approved data acquisition (INCAN/CI/837/17) waiving the need for written consent given the characteristics of the study.

**Statistical analysis**

Comparisons between groups were performed to obtain risk ratios with 95% confidence intervals (CIs). \(p < 0.001\) was used to define statistical significance. To compare ages, Student’s t-test was used after determining...
the mean and standard deviation using Hazen’s equation\textsuperscript{14}, where \( p \) value is the area of the \( t \) distribution with \( n_1 + n_2 - 2 \) degrees of freedom, which falls outside ± \( t \).

All statistical analyses were performed with IBM SPSS Statistics for Windows, version 25 (IBM Corp. Armonk, N.Y., USA).

**Results**

A total of 270 patients with cancer and stroke were compared to a previously assembled cohort of 2000 patients with stroke and no history of cancer. The median follow-up of the cancer patients after the stroke was 13.8 months (interquartile range [IQR] of 1.3–52.4 months); after 12 months of surveillance, 11 patients were lost to follow-up. General characteristics of both cohorts are presented in table 1, with type of cancer and age subgroups details in Supplementary tables 1 and 2 (available online). Briefly, for oncology patients, gynecologic cancer was more frequently observed in ischemic stroke, while hemorrhagic and cerebral venous thrombosis were more frequent in patients with hematologic cancer; subgroup of age <45 years presented higher frequency (50.8%) for hemorrhagic stroke; nonetheless, ischemic stroke leads all ages ≥45 years.

Stroke risk factors that were more common in the cohort of patients without cancer were hypertension (\( p < 0.0001 \)) and obesity (\( p = 0.0006 \)), whereas dyslipidemia (\( p = 0.027 \)), alcohol abuse (\( p = 0.0008 \)), and tobacco use (\( p = 0.0028 \)) were more frequent in the cohort of patients with cancer. Analysis of the cohorts based on the stroke type revealed that the rate of hemorrhagic stroke was higher in the cohort of patients without cancer (\( p = 0.0002 \)) and that the rate of ischemic strokes was higher in the cancer cohort (\( p < 0.0001 \)); however, no difference was observed in the rate of cerebral venous thrombosis between the two groups. The analysis of the 30-day mortality rates due to ischemic stroke, according to the TOAST (Trial of Org 10172 in acute stroke treatment)\textsuperscript{15} criteria in both cohorts, presented in table 2, revealed that there was no significant difference between the two cohorts. Table 3 presents 30-day, 90-day, 6-month, and 12-month mortality rates for ischemic stroke in both cohorts. Briefly, the mortality rates at 30 and 90 days were similar between the two cohorts; however, the 6-month and 12-month mortality rates were higher in the cohort of stroke patients with cancer than in the cohort of stroke patients without cancer (\( p < 0.001 \)).

**Discussion**

The comparison between 270 cancer patients who had a stroke and a cohort of 2000 stroke patients with no history of cancer from the same general population revealed that the frequency of ischemic stroke, along with the mid-term and long-term mortality rates were higher in the stroke patients with cancer. In addition, several variables associated with stroke, including alcoholism, tobacco use, and dyslipidemia were more common in the cohort of cancer patients with stroke compared to stroke patients.

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**Table 1. General characteristics of patients with cancer compared to a cohort of same populations without cancer\textsuperscript{14}**

<table>
<thead>
<tr>
<th></th>
<th>Cancer patients n = 270 (%)</th>
<th>Non-cancer patients n = 2,000 (%)</th>
<th>RR (95%CI)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (IQR), years</strong></td>
<td>58 (46-68)</td>
<td>64 (49-75)</td>
<td>-</td>
<td>( p &lt; 0.0001 )</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>178 (65.9)</td>
<td>1,103 (55.1)</td>
<td>1.2 (1.08-1.31)</td>
<td>( p = 0.0002 )</td>
</tr>
<tr>
<td>Male</td>
<td>92 (34.1)</td>
<td>897 (44.9)</td>
<td>0.76 (0.64-0.9)</td>
<td>( p = 0.0018 )</td>
</tr>
<tr>
<td><strong>Stroke type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>191 (70.7)</td>
<td>1,134 (56.7)</td>
<td>1.25 (1.14-1.36)</td>
<td>( p &lt; 0.0001 )</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>74 (27.4)</td>
<td>806 (40.3)</td>
<td>0.68 (0.56-0.83)</td>
<td>( p = 0.0002 )</td>
</tr>
<tr>
<td>Cerebral venous thrombosis</td>
<td>5 (1.9)</td>
<td>60 (3)</td>
<td>0.62 (0.25-1.5)</td>
<td>( p = 0.29 )</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>105 (38.9)</td>
<td>1,180 (59)</td>
<td>0.66 (0.56-0.77)</td>
<td>( p &lt; 0.0001 )</td>
</tr>
<tr>
<td>Diabetes</td>
<td>68 (25.2)</td>
<td>515 (25.8)</td>
<td>0.98 (0.78-1.21)</td>
<td>( p = 0.84 )</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>57 (21.1)</td>
<td>318 (15.9)</td>
<td>1.32 (1.03-1.7)</td>
<td>( p = 0.027 )</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>65 (24.1)</td>
<td>323 (16.2)</td>
<td>1.49 (1.18-1.88)</td>
<td>( p = 0.0008 )</td>
</tr>
<tr>
<td>Smoking</td>
<td>86 (31.9)</td>
<td>476 (23.8)</td>
<td>1.34 (1.1-1.6)</td>
<td>( p = 0.0028 )</td>
</tr>
<tr>
<td>Obesity</td>
<td>45 (16.7)</td>
<td>540 (27)</td>
<td>0.62 (0.47-0.81)</td>
<td>( p = 0.0006 )</td>
</tr>
<tr>
<td>Cardiac ischemic disease</td>
<td>19 (7)</td>
<td>180 (9)</td>
<td>0.78 (0.49-1.23)</td>
<td>( p = 0.28 )</td>
</tr>
</tbody>
</table>
One study reported that the typical risk factors for stroke were less common in cancer patients, whereas others described that hypertension and dyslipidemia were the risk factors for stroke in this patient population. In the current study, we found that dyslipidemia, smoking, and alcoholism were the risk factors for stroke that was more frequent in cancer patients with stroke than in stroke patients, which agrees with other studies. Cryptogenic stroke, observed more commonly in patients with occult cancer, with some studies reporting a frequency of 51%, was previously found to be associated with a poor prognosis. In our analyses, the etiology of the stroke could not be determined despite comprehensive evaluation in almost 30% of the cancer patients with stroke.

In the general population, the mortality rates after an ischemic stroke were reported to be approximately 15%, 25%, and 50% at 1 month, 1 year, and 5 years, respectively. The REVAMEVASC cohort presented lower mortality rates at 6-month and 12-month follow-up, suggesting worse mid-term and long-term prognoses for stroke patients with cancer and indicating the severe impact of stroke on survival in individuals that already have a life-threatening condition. A previous report demonstrated that patients who had the only stroke and later in life developed cancer had a worse prognosis during their clinical course.

There are several limitations to the current study. First, a selection bias cannot be denied in this single-center study. To minimize information bias, the principal investigator (BCD) supervised all data. It must also be stated that this study did not use Chi-square or other comparative analyses since both database were independently acquired and were not paired for age, gender, or other condition. A future study would be ideal to compare these variables. Furthermore, Kaplan–Meier curves with log-rank to analyze survival are not reported, considering that access for information regarding survival or event-free survival in the REVAMEVASC database was not available. In spite of that, patients in both cohorts included in the current study share the same ethnic and demographic backgrounds, which is a strength of the study. Another major limitation was the lack of information regarding treatment and direct cause of death in many patients, which restrained our analysis.

**Conclusion**

Cancer and stroke are two common causes of mortality that often occur concomitantly. The frequency of ischemic stroke and the mid-term and long-term mortality rates were higher in stroke patients with cancer compared with a cohort of stroke patients with no history of cancer that shared the same sociodemographic characteristics, which should be confirmed with future, large-scale studies.

**Conflicts of interest**

All authors of the manuscript declare no conflicts of interest or relationship with the pharmaceutical industry.

### Table 2. 30-day mortality among patients with ischemic stroke with cancer (n = 191) or without cancer (n = 981) 

<table>
<thead>
<tr>
<th>TOAST</th>
<th>Cancer patients n (%)</th>
<th>Non-cancer patients n (%)</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large Artery Atherosclerosis</td>
<td>11/63 (17.5)</td>
<td>8/84 (9.5)</td>
<td>1.83 (0.78-4.3)</td>
<td>p = 0.16</td>
</tr>
<tr>
<td>Lacunar</td>
<td>2/24 (8.3)</td>
<td>5/213 (2.5)</td>
<td>3.55 (0.73-17.3)</td>
<td>p = 0.11</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>10/42 (23.8)</td>
<td>44/188 (23.4)</td>
<td>1.02 (0.56-1.85)</td>
<td>p = 0.96</td>
</tr>
<tr>
<td>Undetermined</td>
<td>8/27 (29.6)</td>
<td>86/442 (19.5)</td>
<td>1.52 (0.83-2.8)</td>
<td>p = 0.18</td>
</tr>
</tbody>
</table>

### Table 3. Mortality frequency of patients with ischemic stroke with or without cancer

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Cancer patients n (%)</th>
<th>Non-cancer patients n (%)</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 days</td>
<td>32/191 (16.8)</td>
<td>156/1040 (15)</td>
<td>1.11 (0.79-1.6)</td>
<td>p = 0.53</td>
</tr>
<tr>
<td>90 days</td>
<td>44/191 (23)</td>
<td>178/937 (19)</td>
<td>1.21 (0.91-1.6)</td>
<td>p = 0.19</td>
</tr>
<tr>
<td>6 months</td>
<td>71/191 (37.2)</td>
<td>196/854 (23)</td>
<td>1.62 (1.3-2.02)</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>12 months</td>
<td>82/191 (42.9)</td>
<td>238/821 (29)</td>
<td>1.48 (1.21-1.8)</td>
<td>p = 0.00001</td>
</tr>
</tbody>
</table>
Funding source
This manuscript has no external funding source.

Acknowledgments
None.

Ethical disclosures
Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References
### Supplementary Table 1

Type of stroke (ischemic \[n = 191\], hemorrhagic \[n = 74\], cerebral venous thrombosis \[n = 5\]) presented according to the primary type of cancer \(n = 270\)

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>(n) (%)</th>
<th>Ischemic (%)</th>
<th>Hemorrhagic (%)</th>
<th>Cerebral Venous Thrombosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gynecologic</td>
<td>104 (38.5)</td>
<td>83 (43.5)</td>
<td>20 (27)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>50 (18.5)</td>
<td>26 (13.6)</td>
<td>21 (28.4)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>28 (10.4)</td>
<td>21 (11)</td>
<td>7 (9.5)</td>
<td>0</td>
</tr>
<tr>
<td>Lung</td>
<td>21 (7.8)</td>
<td>18 (9.4)</td>
<td>3 (4.1)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>22 (8.1)</td>
<td>15 (7.9)</td>
<td>7 (9.5)</td>
<td>0</td>
</tr>
<tr>
<td>Urologic</td>
<td>30 (11.1)</td>
<td>16 (8.4)</td>
<td>13 (17.6)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Soft tissue and skin</td>
<td>14 (5.2)</td>
<td>11 (5.8)</td>
<td>3 (4.1)</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.4)</td>
<td>1 (0.5)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Supplementary Table 2

Type of stroke (ischemic \[n = 191\], hemorrhagic \[n = 74\], cerebral venous thrombosis \[n = 5\]) presented according to group age \(n = 270\)

<table>
<thead>
<tr>
<th>Group age</th>
<th>(n) (%)</th>
<th>Ischemic (%)</th>
<th>Hemorrhagic (%)</th>
<th>Cerebral venous thrombosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 45 years</td>
<td>59 (21.9)</td>
<td>25 (42.4)</td>
<td>30 (50.8)</td>
<td>4 (6.8)</td>
</tr>
<tr>
<td>45-49 years</td>
<td>90 (33.3)</td>
<td>69 (76.7)</td>
<td>20 (22.2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>60-74 years</td>
<td>93 (34.4)</td>
<td>73 (78.5)</td>
<td>20 (21.5)</td>
<td>0</td>
</tr>
<tr>
<td>≥ 75 years</td>
<td>28 (1.4)</td>
<td>24 (85.7)</td>
<td>4 (14.3)</td>
<td>0</td>
</tr>
</tbody>
</table>
A relationship between drug-resistant epilepsy and structural abnormalities in neuroimaging

Alejandro Flores-Sobrecueva¹, Santiago Paláu-Hernández¹,², Juan L. Cruz-Rosales¹,², Héctor G. Hernández-Rodríguez²,³, Jorge G. Reyes-Vaca²,⁴, Juan M. Shiguetomi-Medina²,⁵, and Ildefonso Rodriguez-Leyva¹,²*

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Abstract

Background and objectives: The purpose of the study was to seek a relationship between drug-resistant epilepsy and structural alterations in neuroimaging to strengthen the link between the clinical and surgical management. A second objective was to determine an association between drug-resistant epilepsy and subject gender, the age of first seizure, and the type of seizure. Materials and methods: Over 632 medical records were scrutinized in search of those satisfying the inclusion criteria to end up with a sample of 108 subjects. Neuroimaging specialists reviewed each of the magnetic resonance imaging (MRI) studies looking for abnormalities to make the structural diagnosis and define it. Results: Of the 108 patients included in the study, 51 patients (Group A) were refractory to medical treatment and 57 patients (Group B) showed an improvement with medical treatment. We quantified the frequency of structural lesions confirmed by neuroimaging in both groups. The results showed a statistically significant difference of 84.31% of patients in Group A with a confirmed structural lesion in an MRI study versus 52.63% of patients in Group B (p = 0.004 [odds ratio = 4.85, 95% confidence interval: 2.01-11.66]). Conclusion: Our results support the association between structural lesions diagnosed with MRI and drug-resistant epilepsy. Thus, this finding gives a chance of an opportune and precise approach for the surgical treatment of these patients.

Key words: Epilepsy. Drug-resistant epilepsy. Epilepsy surgery. Epilepsy neuroimaging.
de inclusión para terminar con una muestra de 108 sujetos. Los especialistas en neuroimagen revisaron cada estudio de resonancia magnética (IRM) para diagnosticar si había una lesión estructural presente y determinar cuál. **Resultados:** De los 108 pacientes incluidos en el estudio, 51 pacientes (grupo A) fueron refractarios al tratamiento médico y 57 pacientes (grupo B) mostraron una mejora con el tratamiento médico. Cuantificamos la frecuencia de lesiones estructurales confirmadas por neuroimagen en ambos grupos. Los resultados mostraron una diferencia estadísticamente significativa de 84.31% de pacientes en el grupo A con una lesión estructural confirmada en un estudio de IRM versus 52.63% de pacientes en el grupo B (p = 0.004 [OR = 4.85, CI 95%: 2.01-11.66]). **Conclusión:** Nuestros resultados respaldan la asociación entre las lesiones estructurales diagnosticadas con IRM y la epilepsia farmacorresistente. Por lo tanto, este hallazgo brinda la posibilidad de un enfoque oportuno y preciso para el tratamiento quirúrgico de estos pacientes.

**Palabras clave:** Epilepsia. Epilepsia farmacorresistente. Cirugía de epilepsia. Neuroimagen en epilepsia.

**Introduction**

Epilepsy is the neurological disorder with the highest prevalence in our service and a considerable percentage of our patients are resistant to drug treatment. There are plenty of original articles and reviews which state that these groups of individuals could obtain a benefit from surgical treatment. The neuroimaging studies have aided in localizing potentially resectable zones improving the surgical approach.

In 2008, the International League Against Epilepsy (ILAE) defined drug-resistant epilepsy as the epileptic condition with “a failure of adequate trials of two tolerated, appropriately chosen and used anticonvulsant drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.”

To fit inside this definition, four criteria should be considered: (1) the antiepileptic treatment should be selected depending on the type of seizure, (2) an adequate dose should be used for a significant period of time before discontinuing the drug trial, (3) the drugs should be well tolerated and free of adverse reactions, and (4) the lack of attachment to the treatment should not be the cause of drug failure.

In the United States, there are 750,000 patients with drug-resistant epilepsy. Only 7,500 surgical procedures per year are done for these patients resulting in a low number of patients treated with a potential ameliorative procedure.

The neuroimaging techniques can provide information about the structural abnormalities and, therefore, data about the probable etiology of the seizures which in return will suggest a potential focus. The advantages of these studies are the null invasivity, the possibility of patient selection for surgery, and the ability to predict a prognosis posterior to surgery.

Both in adults and children, the main etiologies of imaging provable epilepsy are hippocampal sclerosis, cortical development malformations, and brain tumors. In patients with drug-resistant focal epilepsy that is candidates to surgical treatment, there is an identifiable relevant abnormality in 85% of the cases on a magnetic resonance imaging (MRI). In the remaining percentage, there is a possibility that the underlying cause is a subtle cortical development malformation or gliosis. By spectroscopy, it is feasible to find a reduction in the NAA/(Cho + Cr) ratio, which is a feature reported for brain regions that shelter an epileptic focus.

The most successful drug combination for seizure management consists in drugs with different mechanisms of action. It must not be forgotten that the adverse effects can be a consequence of AED combination rather than the effects of an AED alone. Therefore, a personalized treatment plan must be formulated for each case and information for the patient and their family must be issued in any given possibility that seizure control state would not be easily achieved. Furthermore, patients with drug-resistant epilepsy must be informed of the risk of developing sudden death related to epilepsy and take appropriate cautions.

Kwan and Brodie reported in 2000 a study of 525 subjects on a period of 13 years where 27% of the cases were classified as idiopathic epilepsy (without a recognizable but possibly genetic etiology), 29% secondary to a structural lesion, and 45% as cryptogenic (with an undetermined but probably structural etiology). Seizure control was accomplished in 63% of the cases. About 43% with epilepsy secondary to a structural lesion persisted with seizures after drug treatment in comparison with 26% with idiopathic epilepsy.

It has been described that the prognosis and the success of the drug treatment depend on the cause of epileptic seizures. The patients without an identifiable structural lesion have a better prognosis to remain free of seizures (50%). Instead, the patients with cortical development malformation have a chance of 25% and with unilateral hippocampal sclerosis of 11%.

In 2005, Cochrane realized a meta-analysis, in which 177 studies (16,253 patients) were identified searching...
for the outcome of the candidates who underwent epilepsy surgery. The majority were retrospective studies and four were clinical trials. Of all the 16,253 candidates, 65% (10,518) had a satisfying outcome\textsuperscript{12}.

Two ECA studies reported by JAMA on 2015 with a total of 118 patients with temporal lobe epilepsy found a higher percentage of seizure free on patients who underwent an epilepsy surgery compared to those who underwent a continuous pharmacologic therapy (58% vs. 8% \([n = 80]\) and 73% vs. 0% \([n = 38]\), \(p \leq 0.001\)). The epilepsy surgery was less effective when the lesions were extratemporal when the etiology was not related to a structural abnormality or both. Hippocampal sclerosis and benign brain tumors were associated with better results compared to other pathologies\textsuperscript{13}.

As a result of the failure to control seizures in drug-resistant epilepsy, the risk of premature death increases, quality of life decreases, and it is highly likely that patients with this problem may have an identifiable lesion through an MRI study. Our objective is to determine a relationship between drug-resistant epilepsy and lesions discovery through neuroimaging with the purpose to consider a surgical approach and offer an improved treatment. To prove said relationship, we will analyze the brain MRI studies of a sample of patients with and without the diagnosis of drug-resistant epilepsy with the hope of obtaining and comparing the frequency, in which the structural lesions are present in both types of epilepsies.

### Materials and methods

Subject selection was carried out in the follow-up of patients of the Epilepsy Clinic of the Neurology Service at the Central Hospital “Dr. Ignacio Morones Prieto” by the review of the medical record of all patients with the diagnosis of epilepsy from January 2017 to September 2018 (632 patients). Afterward, we applied the inclusion and exclusion criteria to end up with our final sample \((n = 108)\) (Table 1). We defined and selected a group of drug-resistant epilepsy patients in accordance with the ILAE criteria (51 subjects). The control group was confirmed by patients with the diagnosis of non-resistant epilepsy (57 subjects) and depending on the age and sex similarities with the group being studied (i.e. the drug-resistant epilepsy group). The diagnosis was supported by a least one electroencephalographic study in all patients. Due to the age group, patients with infantile epileptic syndromes that are resistant to antiepileptic drug treatment were not taken into consideration for this study.

<table>
<thead>
<tr>
<th>Table 1. Inclusion and exclusion criteria for the study</th>
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<tr>
<td><strong>Inclusion criteria</strong></td>
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<tr>
<td>– Patients older than 15 years of age</td>
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<tr>
<td>– Having at least one brain MRI study</td>
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<tr>
<td>– Having at least one EEG confirming the epilepsy diagnosis (although the absence of abnormal EEG does not rule out epilepsy, this was an inclusion criterion).</td>
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<tr>
<td>– Meeting the ILAE criteria for drug-resistant epilepsy from Kwan et al., 2010\textsuperscript{14}.</td>
</tr>
<tr>
<td><strong>Exclusion criteria</strong></td>
</tr>
<tr>
<td>– Poor attachment to antiepileptic drug therapy</td>
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<tr>
<td>– Going through antiepileptic drug adjustment</td>
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<tr>
<td>– Not to having a wish to participate in the study</td>
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<tr>
<td>– Having undergone an epilepsy surgery</td>
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All patients were classified according to the either acquired or congenital presence or absence of abnormalities in brain imaging. At the same time, the lesions or malformations were classified in groups: hippocampal sclerosis, cortical development malformation, tumor, neurocysticercosis (NCC)/calcification, stroke, and other causes of minor prevalence.

We used an HD2 G5 1.5 T with an eight-channel neurovascular exploration coil MRI equipment. All available brain imaging studies were included whether they were conducted inside our institution or outside. Analysis of the imaging studies was done by a group of neurologists trained for neuroimaging interpretation and corroborated by a neuroradiologist of the Central Hospital to determine the presence or not of a structural abnormality. Successively, if a lesion was present to clarify which structural lesion was it about. For the diagnosis of hippocampal sclerosis, the increase in T2 signal with changes in fluid-attenuated inversion recovery, the N-acetyl aspartate/(choline + creatinine) index below 0.71, and hippocampal atrophy by comparison between hemispheres in T1 was considered\textsuperscript{15-18}. The most common cortical development malformation found was focal cortical dysplasia, which was diagnosed as cortical thickness changes, effacement of the gray matter-white matter union, and T1 cortical hyperintense signal regarding a normal cortex, while in T2 a radial white matter hyperintense signal beneath the area of the dysplasia\textsuperscript{19}. Stroke lesions were diagnosed with the usual parameters for a chronic ischemic lesion seen as a cavitated cystic encephalomalacia in the area of the old ischemia. As NCC is a prevalent infectious disease on our medium, we decided to include the brain MRI studies displaying the nodular calcified state seen as hypointensities in T1- and T2-weighted image\textsuperscript{20}. 

EEG: electroencephalogram.
**Statistical analysis**

To capture the data, we used a Microsoft Office Excel® (2010) spreadsheet. The variables under study (frequency of drug resistance and neuroimaging confirmed structural lesions) were written down as absolute and relative frequencies. The quantitative variables were kept as means and for determining their dispersion, the standard deviation, the minimum, and maximum were used.

The analysis and realization of graphics were carried out in MegaStat and Microsoft Office Excel®. This analysis was made in parallel with the program SPSS v.18.0. The comparison of categorical variables was made through crosstabs using the Chi-square test or the hypergeometric distribution as appropriate to determine variable independence considering $p < 0.05$ as statistically significant. Similarly, a multivariate analysis and logistic regression were done to establish the attributable risk.

**Protocol approval and ethical aspects**

The realization of this investigation was approved by the Investigation and Ethics Committee of the Central Hospital “Dr. Ignacio Morones Prieto” previous to the start of the medical record selection. All patients gave their consent for the usage, manipulation, and publication of their record data and brain MRI study.

**Results**

We examined 632 medical records with the diagnosis of epilepsy confirmed by electroencephalogram. Only 108 met the inclusion criteria. The main causes of exclusion were the lack of brain imaging, the poor attachment to drug therapy, or being through drug therapy adjustment. Of the 108 patients included in the study, 55 were female (50.92%) and 53 male (49.07%) with an age range from 16 to 72, a mean of 34 years, and a median 30 years.

All the selected candidates were classified in one of two groups. Group A of the drug-resistant epileptic was confirmed by 51 patients (47%) and Group B of the non-drug-resistant epileptic by 57 patients (53%) (Table 2). Four variables were contemplated (age, gender, age of first seizure onset, and type of seizure) for the secondary objective. Of those, only two showed a statistically significant difference between the control group and the drug-resistant group.

We calculated the frequency of structural lesions on neuroimaging depending on the presence or not of abnormalities on the brain. The results reported a statistically significant difference indicating that 84.31% of the patients of Group A showed a structural lesion on MRI compared with the control Group B, in which 52.63% presented a lesion, with $p = 0.004$ (odds ratio = 4.85, 95% confidence interval: 2.01-11.66). This association explains that for every drug-resistant epileptic patient with no evidence of structural lesion, there are almost five patients that do have a lesion (Table 3).

The lesions observed were classified in both groups making a comparative analysis of the frequencies of each group. We noticed that the risk of drug resistance was different between the types of lesion being hippocampal sclerosis the most frequently associated to drug resistance (78.57%) followed by the cortical development malformations (60%) (Table 4).

Taking the age of onset into consideration, the subjects who had their first epileptic seizure between the 1st year of age and 5 years had a resistance frequency of 62.5%; in an inverse manner, when the first seizure presented after the 18 years of age, the percentage of resistance decreases 20%. In the in-between group (6-18

<table>
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<th>Table 2. Patient demographics Percentage of the frequency of drug-resistant and non-resistant epilepsy with a given variable</th>
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<tr>
<td>Variable</td>
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<tr>
<td>-----------</td>
</tr>
<tr>
<td>Mean age</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Age of onset</td>
</tr>
<tr>
<td>&lt; 5</td>
</tr>
<tr>
<td>6 – 18</td>
</tr>
<tr>
<td>&gt; 18</td>
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<tr>
<td>Type of seizure</td>
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<tr>
<td>Focal onset</td>
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<tr>
<td>Generalized onset</td>
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<tr>
<th>Table 3. The frequency of structural lesions on each group</th>
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<tr>
<td>Group</td>
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<tr>
<td>-------</td>
</tr>
<tr>
<td>Group A</td>
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<tr>
<td>Group B</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>
The age of onset of epileptic seizures appears to be a risk factor for developing drug resistance. The results showed an association curve in which the lower the age of onset the higher the risk of developing drug resistance. This finding is similar to the one reported in a Chinese pediatric sample where it is described that the patients presenting the first seizure in their 1st year of age had a predisposition to develop drug resistance.22

Another fact that supports the final result is the difference found in the type of crisis, where the focal onset was present in 94% of the drug-resistant patients keeping an association with the higher percentage of structural lesions found in this patients compared with the non-drug-resistant ones (84% vs. 52%). This fact was described in a previous study realized in our country.23

There were not effectiveness differences within the variety of AED used as described by the comparisons made by Cochrane studies between the effectiveness of AED in monotherapy.24 Even when valproate-lamotrigine combination is considered in those patients with drug resistance, as this therapy has demonstrated to be superior to others in some studies,24 in our medium, the patients do not always count with the economic support to acquire this specific AED combination, and in the majority of occasions, the most affordable AED therapy is used.

Stroke is frequently identified as an acute cause of epileptic seizures in adults of < 65 years and 25% of the patients could have drug-resistant epilepsy.25 The results we found tell us that 50% of our patients presenting with post-stroke epilepsy had AED resistance. However, we recommend to not consider this percentage due to the few cases we revised (only 10 subjects) and further research is advised.

A study from India indicates that a low proportion of subjects exhibit drug-resistant epilepsy while having an underlying NCC lesion or a cause-effect relationship between an NCC calcification and hippocampal sclerosis.26 Another study from Brazil states that NCC alone (or isolated) only counts in a low percentage (15.6%) of the etiologies of drug-resistant epilepsy and that NCC calcification associated lesions account for a higher percentage of the causes (27%). This calcification appears to be deeply correlated with hippocampal sclerosis (p ≤ 0.001).27 All things considered, as our study included a low number of subjects with NCC (nine individuals) and cysticercosis incidence varies depending on the endemicity of each country, we advise not

<table>
<thead>
<tr>
<th>Type of lesion</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
<th>Drug resistance (%)</th>
</tr>
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<tbody>
<tr>
<td>0. Normal</td>
<td>8</td>
<td>27</td>
<td>35</td>
<td>22.86</td>
</tr>
<tr>
<td>1. Calcifications/NCC</td>
<td>5</td>
<td>4</td>
<td>9</td>
<td>55.56</td>
</tr>
<tr>
<td>2. Hippocampal sclerosis</td>
<td>22</td>
<td>6</td>
<td>28</td>
<td>78.57</td>
</tr>
<tr>
<td>3. Stroke</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>4. Tumor</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>5. Cortical developmental malformations</td>
<td>6</td>
<td>4</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>6. Others</td>
<td>5</td>
<td>9</td>
<td>14</td>
<td>35.71</td>
</tr>
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</table>

Discussion

The data found supported the relationship between structural lesions observed on an MRI study and drug-resistant epilepsy. However, this affirmation does not mean that any type of lesion could be a risk factor for the development of drug resistance. For this reason, the lesions were classified resulting in hippocampal sclerosis and cortical development malformation occupying the higher percentage of found lesions in the drug-resistant patients.

In particular, the hippocampal sclerosis is the most studied pathology in the epileptic patients and with an excellent success rate after a surgical procedure, having an absence of crisis to almost 70% of the cases and with a low frequency of neurological complications and mortality (< 1%).21

years of age), the number of resistant and non-resistant was equivalent (49% vs. 51%, respectively). Hence, there is statistical evidence of an association between the beginning of the seizures at a young age and the probability to develop drug-resistant epilepsy (p = 0.005).

If the seizure onset was focal, then the probability to present drug resistance was higher compared to the generalized onset. In the drug-resistant Group A, there was a high prevalence of focal onset seizures (94%) with only three patients displaying a generalized onset (6%), whereas in the control Group B, 21 patients (36.84%) had a generalized onset and 36 (63.15%) a focal onset (p = 0.0001).

The more used antiepileptic drugs by the patients were carbamazepine (51%), levetiracetam (45%), and valproate (37%). With a minor usage was Lamotrigine (22%) and topiramate (17%), whereas oxcarbazepine, primidone, lacosamide, and phenytoin were the less frequent (<10%). There was not a significant difference in the usage between A and B groups.
to take for granted our result on infectious etiologies of drug-resistant epilepsy.

In our study, there were included few patients with brain tumors due to not fulfilling the inclusion criteria and the management of the majority of them is in charge of the service of neurosurgery of this institution. For this reason, we could not obtain strong conclusions with respect to this population and recommend further research. Likewise, there were not included patients under the age of 16 that are treated by the service of neuropediatrics.

There is a relationship between the structural lesions seen in MRI study and the probability to develop drug-resistant epilepsy, and this is the reason that for every patient who does not have visible injuries, there are almost five patients who have it.

The risk of resistance is different within the distinct types of lesion, the variety of ages of seizure onset, and the type of onset of the seizure. Hippocampal sclerosis, the early onset of epilepsy and the focal onset seizures are more related to resistance.

Those results allow us to perform an MRI in this type of patient and analyze this study thoroughly and intensively, guided by clinical data in search of lesions, especially in those patients with drug-resistant focal epilepsy. We hope that this sort of study contributes to a patient that could potentially and finally benefit from this alternative therapeutic approach.

Conflicts of interest

None of the authors has any conflicts of interest to disclose.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

Clinical severity and associated complications in pediatric patients with Guillain-Barré syndrome

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Abstract

Background: Guillain-Barré syndrome (GBS) is an acute demyelinating polyradiculoneuropathy, of autoimmune origin, with heterogeneous clinical variants. It is the most frequent cause of flaccid paralysis in children. Incidence of 0.38-0.91 cases per 100,000, rare in children under 2 years. Objective: The objective of the study was to describe the clinical severity and complications in pediatric patients aged 1-18 years with GBS. Methods: A descriptive and retrospective analysis was carried out. We collected data from clinical files of patients of Legaria Pediatric Hospital with stellate ganglion block, period of 3 years (January 2015-December 2017). Results: Twenty-four patients, 18 men (75%) and 6 women (25%) were included in the study. The average age of 7.33 years (range: 1-16 years). School patients were the most affected (45.8%). Nearly 62.5% had previous respiratory infection. The most frequent clinical variant was acute inflammatory demyelinating (62.5%), axonal motor syndrome (29.2%), and Miller Fisher syndrome (8.3%). Nearly 16.7% presented dysautonomies requiring mechanical ventilation. Nearly 50% presented albuminocytological dissociation. The most frequent degree of clinical severity at admission was Grade IV on the Hughes scale (54.2%). The degree of clinical severity most frequent at discharge was Grade II on the Hughes scale (33.3%). Only 41.7% of patients received treatment with intravenous immunoglobulin (IVIG) at 1 g/kg/dia for 2 days. Conclusions: By means of contingency tables, the association between degree of severity at admission and discharge of GBS with respect to treatment with IVIG was determined. There is a 3.8 times greater risk of severity in patients without receiving the ideal treatment.

Key words: Guillain Barre. Pediatrics. Mechanic Ventilation.

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Severidad clínica y complicaciones asociadas en pacientes pediátricos con Síndrome de Guillain Barré

Resumen

Introducción: El Síndrome de Guillain Barré (SGB) es una poliradiculoneuropatía desmielinizante aguda, de origen autoinmune, con variantes clínicas heterogéneas. Es la causa más frecuente de parálisis flácida en niños. Incidencia de 0.38-0.91 casos por 100,000, rara en menores de 2 años. Objetivo: Describir la severidad clínica y complicaciones en pediátricos de 1-18 años con SGB. Métodos: Se realizó un análisis de tipo descriptivo y retrospectivo. Se recabaron datos de expedientes clínicos de pacientes del Hospital Pediátrico Legaria con SGB, en un período de 3 años (enero 2015 - diciembre 2017). Resultados: Se incluyeron 24 pacientes, 18 hombres (75%) y 6 mujeres (25%). La edad promedio fue de 7.33 años (rango: 1-16 años). Los pacientes escolares fueron los más afectados (45.8%). El 62.5% tuvo infección respiratoria previa. La variable clínica más frecuente fue la desmielinizante inflamatoria aguda (62.5%), el Síndrome Motor Axonal (29.2%) y Síndrome de Miller Fisher (8.3%). El 16.7% presentaron disautonomías requiriendo ventilación mecánica. El 50% presentó disociación aluminocitológica. El grado de severidad clínica más frecuente al ingreso fue el Grado IV en escala de Hughes (54.2%). El grado de severidad clínica más frecuente al egreso fue el Grado II en escala de Hughes (33.3%). Solo el 41.7% de pacientes recibió tratamiento con inmunoglobulina intravenosa (IgIV) a 1 gr/kg/día por 2 días. Conclusiones: Mediante tablas de contingencia se determinó la asociación entre grado de severidad al ingreso y egreso del SGB respecto al tratamiento con IgIV, existiendo 3.8 veces mayor riesgo de severidad en pacientes sin recibir el tratamiento ideal.


Introduction

Guillain-Barré syndrome (GBS) is an acute demyelinating polyradiculoneuropathy, of autoimmune origin, with heterogeneous clinical variants. In most cases, there is a pattern of infection before the clinical manifestations of GBS (acute paralysis, paresthesia, and numbness). Moreover, progressive weakness of lower extremities with subsequent inability to ambulate.

The first cases of GBS were described in 1857 by Landry, specifying that patients with GBS present ascending paralysis of motor predominance, respiratory failure, and death. These clinical characteristics were delimited in 1916 by Guillain et al., demonstrating the presence of motor deficit and areflexia, but with minimal or no sensory involvement. In addition, they established that albuminocytological dissociation is part of the comprehensive diagnosis of stellate ganglion block (SGB).

In 1990, after the review of the GSB diagnostic criteria, Asbury and Comblath, they proposed electrodiagnostic criteria, the main characteristic being the delay in the conduction velocity of two or more motor nerves.

GBS is the most frequent cause of flaccid paralysis in previously healthy children. Worldwide, the annual incidence is 0.6-2.4 cases per 100,000 inhabitants, in any age group, it affects both genders with an H/ratio.

For years worldwide, due to the introduction of vaccination schemes, there was a considerable decrease in the frequency of polio cases, with the eradication of this disease in some countries. In Mexico, the last reported case of poliomyelitis was October 18, 1990, in Jalisco. In April 1995, the wild poliovirus eradication certificate was granted in Mexico. Therefore, after the reduction of polio cases, GBS disease became the main cause of acute flaccid paralysis (AFP) worldwide at all ages.

During 1988 and 1996, in Mexico, within the framework of the global eradication of poliomyelitis and through the participation of the epidemiological surveillance system of the AFP, a study was conducted where 3730 cases of AFP were analyzed, specifying that 63% of the cases he had a final diagnosis of GBS, constituting since then the main cause of paralysis in patients under 15 years of age.

The epidemiology of GBS at the national level is unknown because there is little information available. Depending on the author consulted, the prevalence of GBS is diverse. In a study conducted at the National Institute of Pediatrics, during January 1988 and December 1996, GBS accounted for 77.9% of all acute flaccid paralyses analyzed by the epidemiology service. The risk of developing GBS during the course of any patient’s life is <1:1000.

The main infectious agent reported in GBS outbreaks is Campylobacter jejuni. Other infections associated with GBS are: Cytomegalovirus, Epstein-Barr virus, influenza A virus, Mycoplasma pneumoniae, and Hae mophilus influenzae.
The clinical manifestations of the patient with classic GBS begin 2-4 weeks after an infectious episode (respiratory and/or gastrointestinal), presenting with acute weakness predominantly in the lower extremities, posterior caudocephalic dissemination, and in some cases compromise in bulbar or cranial nerves.

The diagnosis of GBS is clinical. However, it can be complex in the population of preschool children due to an atypical clinical presentation, so the neurological examination must be thorough. As mentioned, the clinical diagnosis is based on the latest update of the diagnostic criteria established by Asbury and Cornblath in 1990. There are also specific biomarkers but many of these are not positive in some variants of GBS.

The GBS is defined clinically, anatomo-pathologically, and electrophysiologically as an acute inflammatory demyelinating polyneuropathy (AIDP). According to the characteristics of nerve conduction studies it was observed that GBS is characterized by: slowing of driving speeds, driving blockage, delayed latencies and/or scattered responses; but over time the evidence from several studies indicated that there are several clinical, serological, and electrophysiological characteristics in each of the GBS variants.

The following describes in detail the pathological anatomy, the antibodies present, and the symptomatology of each of the GBS variants:

a. In the acute inflammatory demyelinating type variant; there is involvement of motor roots, notable segmental demyelination, infiltration of mononuclear cells predominantly T lymphocytes and macrophages in the peripheral nervous system, chains of sympathetic ganglia, and cranial nerves. In addition to the proliferation of Schwann cells as part of the repair mechanism. There is an antibody cross-reaction against ganglioside GM1, finding axonal epitopes similar to the gangliosides present in C. jejuni (serotypes 19 and 41), whose polysaccharides are similar to the gangliosides located in the nerve, which would explain direct axonal damage and demyelination.

The main characteristic symptom of GBS is symmetric weakness in the lower extremities, decreased or absent deep tendon reflexes (areflexia) and localized pain in the lower extremities or low back pain, which has been proven in 79% of the reported trials.

b. In the Miller Fisher syndrome (MFS) type variant; the findings found are very similar to those found in the PDIA. The main responsible is the ganglioside GQ1b, located in the myelin of cranial nerves, constituting the main ganglioside injured by specific antibodies cross-reactive by C. jejuni infections. The ganglioside GQ1b is considered a marker of ophthalmoplegia in SGB. The anti-GT1 antibody is also a compromise marker and translates bulbar cranial nerve injury in SGB. The classic triad of MFS is: ataxia, areflexia, and ophthalmoplegia in almost 50% of cases, diplopia, and/or facial paresis have been reported as the first clinical sign. In the case of external ophthalmoplegia, the first affected muscle is the superior rectus muscle, followed by paralysis of the lateral rectus muscle and finally the inferior rectus muscle is affected. It is characteristic in patients with MFS to appreciate the clinical phenomenon of bell.

c. In the axonal type variant, no inflammatory changes are seen; only a discrete primary lesion is found at the Ranvier nodes explaining the axonal degeneration. The anti-GD1a antibody is specific in this variant; the clinical picture is not severe and depends on the extent of axonal injury. Unlike the classic variant of GBS, tendon reflexes are preserved and may even have hyperreflexia. In addition, if there is distal involvement, recovery is rapid and complete.

Clarifying that, regardless of the variants of GBS, axons are the main target for autoimmune injury.

The effect of immunotherapy in GBS has been studied for several years, based on several randomized controlled trials, establishing that the use of intravenous immunoglobulin (IVIG) and plasma exchange (plasmapheresis) is effective.

The use of IVIG or plasmapheresis should be performed as soon as possible, ideally, start before there is irreversible nerve damage.

The cornerstone of the treatment of GBS in pediatric patients is based on the use of IVIG. The treatment guidelines are divided according to the dose; 1st guideline (most effective therapy): immunoglobulin dose (2 g/kg of body weight) administered in 2 days at 1 g/kg/day, and the 2nd pattern: dose of immunoglobulin at 0.4 g/kg of body weight administered in 5 days.

The administration of IVIG at 0.4 g/kg in 5 days decreases the risk of cases of side effects. However, the use of IVIG at a dose of 1 g/kg/dia for 2 days, effectively decreases the subsequent clinical complications with greater limitation of damage neuronal present in GBS, constituting the ideal treatment in pediatric patients.

The specific indications for the use of IVIG are the following; rapid progression of muscle weakness, respiratory insufficiency or mechanical ventilatory support, bulbar or cranial nerve involvement and inability to ambulate.
In case of therapeutic use with plasmapheresis, five sessions will be required, each exchange will include 2-3 L of plasma according to the patient’s body weight with a treatment duration of 2 weeks, confirming the therapeutic benefit when treatment is initiated in the first 4 weeks (preferably in the first 2 weeks) from the start of SGB.

Plasmapheresis has shown the same efficacy as immunoglobulin but is a more invasive treatment, being reserved only for cases of intolerance or poor response to the administration of IVIG.

Therapy that was previously used based on corticosteroid doses does not show effectiveness in SGB.

The clinical evolution of GBS is usually limited. Symptoms reach their maximum expression in the first 4 weeks after an infectious episode and a recovery period after months or years (secondary to the decrease in the immune response and the period during which the peripheral nerve performs an endogenous repair with limited of the box).

The prognosis of GBS in children is generally good. More than 90% of the cases of the acute inflammatory demyelinating variant and all cases of MFS recover completely. Cases of emergencies are when there is a delay in the diagnosis of GBS especially in young children.

The severity of the clinical picture is important as a prognostic factor in GBS. About 40% of affected children have the inability to ambulate during the acute phase. In severe cases, approximately 25% of patients will require special support in intensive care units due to the need for support with artificial ventilation secondary to dysautonomias.

After the natural evolution of the disease, it has been shown that 20% of patients with GBS will not be able to walk without support after 6 months of starting the clinical picture of GBS. Therefore, it is important to establish predictive measures clinic, to improve care and establish an opportune treatment in patients with GBS.

In this way, it constitutes the fundamental role of rehabilitation therapy as a coadjuvant treatment of patients with GBS. With which, it is allowed to reduce the cases of thrombophlebitis (mobilization and use of elastic bandages) and the subsequent damage of joints (using orthoses and splints). Muscle stimulation is essential to prevent or reduce the degree of muscle atrophy in patients with GBS.

The support established by respiratory and motor physiotherapy will aim to reduce the severity of muscle atrophy due to the prolonged paralysis present in GBS, with the final goal of having an early restoration of motor function with the reintegration of the patient to their autonomy and improve their quality of life.

Because there are currently few studies on GBS in pediatrics, constituting a national public health problem (since it affects thousands of Mexican patients), the present work was aimed at; to describe the clinical severity and associated complications in pediatric patients with GBS in a concentration hospital in Mexico City.

**Methods**

The study carried out is descriptive and retrospective. Data were collected from the clinical files of patients admitted to Legaria Pediatric Hospital with a diagnosis of GBS, in a period of 3 years (January 2015-December 2017).

**Considering as inclusion criteria**

a. Complete clinical records of pediatric patients of male and female sex, with an age between 1 and 18 years of age.
b. Previously healthy pediatric patients with a history of gastrointestinal and/or previous respiratory infection (2 weeks-1 month) before the onset of neurological symptoms (according to the clinical criteria of GBS established by Asbury).
c. Pediatric patients with clinical criteria characteristic of GBS (clinical criteria of GBS established by Asbury) and comprehensive assessment by the pediatric neurology service.
d. Pediatric patients with an integral approach to GBS (laboratory and/or cabinet studies).

**Considering as exclusion criteria**

a. Complete clinical records of pediatric patients with previous neuropathy or lower motor neuron lesion, not compatible with GBS.
b. Pediatric patients who do not have an adequate comprehensive approach to GBS (incomplete clinical file, laboratory studies, and/or incomplete cabinet).

d. Pediatric patients who moved to another hospital unit during their hospitalization.

**Finally, the elimination criteria**

Complete clinical records of patients who met the inclusion criteria on admission to the emergency department were evaluated by a pediatric neurologist, verifying that they met the...
clinical criteria of Asbury and Cornblath to be diagnosed with GBS.

All pediatric patients were requested to enter the hospital unit, as part of the comprehensive diagnostic protocol, the following laboratory studies; complete blood count, serum electrolytes (Na, K, Cl, Ca, Mg, and P), creatine kinase (CK) and CK-MB levels, liver function tests (alanine aminotransferase, aspartate aminotransferase, and lactic acid dehydrogenase [LHD]), general urinalysis, and cerebrospinal fluid (CSF) study during your inpatient stay.

Complementary electrophysiological studies (neuroconduction studies) were also requested to classify each of the present clinical variants of GBS: acute inflammatory demyelinating, motor axonal, motor and sensitive, plus some axonal pattern as established by the International Federation Standards of Clinical Neurophysiology.

The evaluation of motor conduction was performed in the median, ulnar, tibial, and peroneal nerves, including the F wave analysis. Sensory antidromic conduction studies were performed on the median, ulnar, and sural nerves. The patients were classified into three categories according to the electrophysiological criteria of Asbury and Cornblath: (1) AIDP; (2) acute motor axonal neuropathy (AMAN), when in the absence of demyelination parameters, amplitudes of distal composite muscle action potentials < 80% of the lower normal limit in two or more motor nerves were recorded; and (3) acute motor-sensory axonal neuropathy, when with the AMAN pattern there was also a decrease in the amplitude of the sensory nerve action potentials < 50% of the lower normal limit in two or more nerves.

During the study, each of the following variables were analyzed: age, sex, preceding factors (previous gastrointestinal and/or respiratory infections, surgery, toxins, and vaccination), and time elapsed since the event or previous pathology and the onset of symptoms, manifestations clinics, analysis of laboratory studies, CSF study, ventilatory mechanical support and duration of the same, length of in-hospital stay, degree of severity at admission and discharge, clinical variant of the disease, in-hospital clinical evolution, and medical treatment established (steroids, immunoglobulin, plasmapheresis, etc.).

Subsequently each of the pediatric patients were examined and classified according to the functional disability scale for GBS of Winer and Hughes (0: normal; 1: minor signs or symptoms, able to run; 2: can walk 5 m without help, independently; 3: can walk 5 m with a walker or similar support; 4: cannot walk, stays in bed, or wheelchair; 5: requires mechanical ventilation, and 6: death). CSF analysis was performed, with determination of cells, glucose, total proteins, and presence of protein-cytological dissociation.

The descriptive statistical analysis was carried out, where media and standard deviation (SD) are used for the quantitative variables (days of stay), and for the qualitative ones (assisted mechanical ventilation) frequencies and percentages are used.

In the inferential statistical analysis, the Chi-square was determined to establish whether there is an association between the degree of clinical severity of GBS and the support of mechanical assisted ventilation. The percentage of patients was determined according to the association between the degree of clinical severity and the support of mechanical ventilation.

The student's t-test was applied to compare the means of the continuous quantitative variables of normal distribution and to determine the relationship between the degree of clinical severity of GBS on admission with respect to the degree of clinical severity of GBS at discharge.

Regarding the continuous quantitative variables, they will be described as arithmetic mean and SD, as well as the rank that corresponded to a normal distribution or a non-parametric distribution, respectively.

Contingency tables were made to determine the association between the degree of clinical severity of GBS on admission and discharge with respect to the ideal medical treatment (IVIG 1 g/kg/day for 2 days).

All p-values for comparisons were calculated to two tails and considered significant when p < 0.05. The statistical package SPSS v 20.0 was used in all calculations.

Results

During a period of 3 years (January 2015-December 2017) in the Legaria Pediatric Hospital of Mexico City, a referral hospital for neurological pathologies, 24 patients met the inclusion criteria established for this research work (criteria based on in guidelines and/or international protocols for the diagnostic and therapeutic approach of GBS in pediatrics).

Of the 24 cases that met the inclusion criteria, the frequency according to sex was 18 cases of the male gender and six of the female gender. The percentage according to sex was 75% of the male sex and 25% of the female sex. The average age was 7.33 years. The age range was 15 years, the youngest patient was 1-year-old, and the largest patient was 16-years-old.
The group of patients most affected with GBS according to age was that of school children (5-11 years) with a frequency of 11 patients and an average of 45.8%.

Of the 24 cases, 15 (62.5%) had a history of respiratory infection; 5 (20.8%) had gastrointestinal infection, 4 (16.7%) had no history of the previous infection, and 0 (0%) received previous vaccination (immunization).

The average time between the preceding factors (respiratory, gastrointestinal infection, no previous infection, or vaccination) and the onset of the clinical symptoms of GBS was 8.71 days (range of 27 days, minimum 1 day, and maximum 28 days).

In patients who had a previous respiratory infection, the period of time elapsed at the onset of symptoms of GBS was 10.13 days (range 27 days, minimum 1 day, and maximum 28 days).

Patients with a history of gastrointestinal infection, during the period of time elapsed at the onset of symptoms of GBS was 9.60 days (range 7 days, minimum 7 days, and maximum 14 days).

In the case of patients with no history of the previous infection, the period of time elapsed at the onset of symptoms of GBS was 2.25 days (range 5 days, minimum 1 day, and maximum 6 days).

The main clinical signs that appeared in the patients on admission to the hospital unit were: weakness in the lower extremities 22/24 (91.66%) and diminished tendon reflexes in the lower extremities 22/24 (91.66%).

The time elapsed between the onset of the symptoms of GBS and the clinical diagnosis of GBS was on average 1.88 days (range 5 days, minimum 1 day, and maximum 6 days).

The most frequent clinical variant of GBS, in our group of patients, was the acute inflammatory demyelinating with 15 cases (62.5%), the axonal motor syndrome variant with 7 cases (29.2%), and finally the MFS syndrome variant with 2 cases (8.3%).

The cranial nerves that suffered the most affection were the III, IV, and VI cranial nerve, occurring in up to two patients (8.32% of cases).

Within the in-hospital clinical evolution, four patients (16.7%) presented with dysautonomies characterized by tachycardia or bradycardia.

The average number of days of in-hospital stay was 16 days (range 50 days, minimum 4 days, and maximum 54 days).

All the patients underwent laboratory studies as part of the comprehensive protocol and approach.

The studies carried out were blood count, blood chemistry, serum electrolytes, liver function tests, CK and CK-MB exhaust enzymes, general urinalysis, and acute phase reactants.

In 100% of the laboratory studies, normal results were reported.

In 50% of the patients, when lumbar puncture was performed, they presented albuminocytological dissociation (hyperproteinorrachia or proteins > 50 mg/dl and/or cells < 10 mm³).

The average days between the beginning of the GBS and the lumbar puncture were with an average of 3.13 days, with a range of 13 days. The earliest lumbar puncture was on the 1st day of hospitalization and the later one at 14 days of hospitalization.

Regarding the neuroconduction study (study of support for the confirmation of the clinical variant of GBS), the average time between the time of the initial clinical manifestations of GBS and the performance of the neuroconduction study was on average 9.46 days (range 56 days, minimum 1 day, and maximum 57 days).

According to the neuroconduction study, the most frequent clinical variant of GBS was the acute inflammatory demyelinating type with a frequency of 15 (62.5%), followed by the axonal motor variant with a frequency of 7 (29.2%) and finally the Miller Fisher variant with a frequency of 2 (8.3%).

The degree of clinical severity more frequent in patients on admission to the hospital unit was Grade IV (confined to bed) based on the Hughes scale, with 13 patients being affected (54.2%) (Fig. 1).

The degree of clinical severity more frequent in patients on discharge from the hospital unit was Grade II (walk more than 5 m without help or support but not jump or perform daily activities) based on the Hughes scale, eight patients being affected (33.3%) (Fig. 1).

The average of the different medical treatments used according to availability in the hospital unit were: 1 = steroid (methylprednisolone (dose 30 mg/kg/dia for 3 days) 2/24 (8.3%), 2 = IVIG (dose 1 g/kg/dia for 2 days) 10/24 (41.7%), 3 = IVIG (400 mg/kg/dia dose for 5 days) 3/24 (12.5%), 4 = IVIG (suboptimal dose < 2 kg/kg/dia or < 400 mg/kg/dia) 6/24 (25%), 5 = plasmapheresis 0/24 (0%), and 6 = supports measures 3/24 (12.5%) (Fig. 2).

The average time between the onset of clinical manifestations of GBS and the start of hospital treatment with a steroid (methylprednisolone 30 mg/kg/dia for 3 days) was on average 7 days (range 2 days, minimum 6 days, and maximum 8 days).

The average time between the onset of the clinical manifestations of GBS and the start of hospital treatment with IVIG (1 g/kg/dia for 2 days) was on average...
Figure 1. Percentage of patients according to the Hughes severity scale of Guillain-Barré syndrome at hospital admission (A) and hospital discharge (B) (source: Clinical record. Legaria Pediatric Hospital. Secretariat of Health of Mexico City).
4 days (range 10 days, minimum 1 day, and maximum 11 days).

The average time between the onset of clinical manifestations of GBS and the start of hospital treatment with IVIG (400 mg/kg/dia for 5 days) was on average 4 days (range 4 days, minimum 2 days, and maximum 6 days).

The average time between the onset of the clinical manifestations of GBS and the start of inpatient treatment with IVIG (suboptimal dose) was on average 2.5 days (range 6 days, minimum 1 day, and maximum 6 days).

The time between the onset of GBS and the start of hospital treatment with supportive measures was on average 1 day.

According to the clinical evolution during the inpatient stay, 16.7% of the patients (4/24) required assisted mechanical ventilation, reporting an average of 2.25 days between the onset of the clinical manifestations of GBS and the need for support with mechanical ventilation according to the patient’s clinical conditions (range 4 days, minimum 1 day, and maximum 5 days).

Of the four patients who needed assisted mechanical ventilation, the average duration of ventilatory support was 29.75 days (range 13 days, minimum 23 days, and maximum 36 days).

According to the clinical evolution, the four patients that required assisted mechanical ventilation (16.7%) presented respiratory muscle and/or bulbar involvement, this being an absolute indication for it (Phase III mechanical ventilation).

Of the four patients who required mechanical ventilatory support; one-fourth (25% of cases) required orotracheal intubation without requiring tracheostomy and/or gastrostomy due to clinical improvement, presenting adequate suction and swallowing reflex and absence of respiratory distress. One-fourth (25% of the cases) required a tracheostomy but no gastrostomy, presenting an adequate clinical evolution and weaning of mechanical ventilatory support. Two-fourth (50% of cases) required surgical intervention with tracheostomy and gastrostomy due to poor clinical evolution, with subsequent weaning of the ventilator, but in all three cases...
of patients requiring tracheostomy (75%) all required support of supplemental oxygen at home discharge.

During the hospital stay, five patients (20.8%) developed nosocomial infection characterized by pneumonia associated with health care and 19 patients did not develop intrahospital infection (79.2%).

It was determined whether the degree of clinical severity of GBS constitutes a risk factor for assisted mechanical ventilation.

Of the 24 patients, eight were classified in the group with the highest degree of severity of GBS (Grades IV, V, or VI established by the Hughes severity scale), and 16 patients belonged to the group with the lowest degree of severity of GBS (Grades 0, I, II, and III established by the Hughes severity scale).

Of the eight patients with greater degree of severity of GBS, 4 (50%) required assisted mechanical ventilation, and the remaining 4 (50%) did not require assisted mechanical ventilation (Fig. 3).

The 16 patients with a lower degree of severity of GBS did not require assisted mechanical ventilation. We obtained a Chi-square 9.60 p < 0.01, establishing that there is a significant difference; there is an association between the degree of clinical severity and the assisted mechanical ventilation (Table 1).

Regarding the degree of clinical severity of GBS at admission related to the degree of clinical severity of GBS at discharge, a Student’s T-test of 5.933 was obtained, with p < 0.001; there is a statistically significant difference between the degree of severity at admission versus patient discharge (Table 2 and Fig. 4).

The association between the degree of clinical severity of GBS on admission and the ideal medical treatment (IVIG 1 g/kg/dia for 2 days) was obtained; and the existing association between the degree of clinical severity of GBS at discharge and ideal medical treatment (IVIG 1 g/kg/day for 2 days).

It was determined that there are 3.8 times higher risk of clinical severity in those patients who do not receive the ideal medical treatment (IVIG dose of 1 g/kg/day for 2 days).

Discussion

In the present study, we found predominance of patients with GBS, an inflammatory demyelinating variant, as has been demonstrated in international studies.

Of the 24 patients, according to the clinical evolution during the in-hospital stay, 16.7% (4 patients) required assisted mechanical ventilation due to respiratory and bulbar muscle involvement, reporting an average of 2.25 days between the onset of the manifestations clinics of GBS and the need for support with mechanical ventilation.

**Figure 3.** Frequency of patients according to the association between the degree of clinical severity of Guillain-Barré syndrome and the support of mechanical assisted ventilation (source: Clinical record. Legaria Pediatric Hospital. Secretariat of Health of Mexico City).

**Figure 4.** Comparison of the degree of severity at the patient’s admission and discharge. Student’s t = 5.933, with p < 0.01, there is a significant difference (source: Clinical record. Legaria Pediatric Hospital. Secretariat of Health of Mexico City).

**Table 1.** Association between the degree of clinical severity of GBS and the support of mechanical assisted ventilation

<table>
<thead>
<tr>
<th>Association between degree of severity of GBS and mechanical ventilation</th>
<th>Mechanical ventilation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Degrees of severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greater</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Minor</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>16</td>
</tr>
</tbody>
</table>

Chi-square 9.60; p < 0.01, there is significant difference.
The degree of clinical severity of GBS is associated with the need for assisted mechanical ventilation support.

GBS: Guillain-Barré syndrome.

Source: Clinical record. Legaria Pediatric Hospital. Secretariat of Health of Mexico City.
ventilation according to the patient’s clinical conditions (range 4 days, minimum 1 day, and maximum 5 days).

Of the four patients who needed assisted mechanical ventilation, the average duration of ventilatory support was 29.75 days (range 13 days, minimum 23 days, and maximum 36 days).

Of the four patients who required mechanical ventilatory support, one patient required orotracheal intubation without requiring tracheostomy and/or gastrostomy due to clinical hospital improvement after administration of IVIG, presenting adequate suction and swallowing reflex and absence of respiratory distress.

Another patient required a tracheostomy due to the respiratory condition but without needing gastrostomy since the clinical evolution was favorable and allowed her to wean from the mechanical ventilatory support. In this way, two patients required surgical intervention with tracheostomy and gastrostomy due to poor clinical hospital evolution, with subsequent weaning of the ventilator after a long inpatient stay. Therefore, of the four patients, only three patients who required a tracheostomy (75%) required additional oxygen support at home.

Nearly 20.8% of pediatric patients with GBS (five patients) developed hospital-acquired infection characterized by pneumonia associated with health care.

The degree of clinical severity of GBS as a risk factor for assisted mechanical ventilation was determined in the study. Of the 24 patients, eight patients (33.3%) were classified in the group of greater degree of severity of GBS (Grades IV, V, or VI established by the Hughes severity scale) and 16 patients (66.6%) belonged to the group of degree of minor severity of SGB (Grades 0, I, II, and III established by the Hughes severity scale).

Of the eight patients with greater severity of GBS, only 50% of them required assisted mechanical ventilation. Being that the 16 patients with a lower degree of severity of GBS, did not require any type of assisted mechanical ventilation. Establishing that there is a significant difference; there is an association between the degree of clinical severity and assisted mechanical ventilation (Table 1).

In addition, the existing association between the degree of clinical severity of GBS on admission and ideal medical treatment (IVIG 1 g/kg/dia for 2 days) was obtained; and the existing association between the degree of clinical severity of GBS at discharge and ideal medical treatment (IVIG 1 g/kg/day for 2 days). With an estimated risk of 3.8 times greater clinical severity in those patients who do not receive the ideal medical treatment (IVIG dose of 1 g/kg/day for 2 days) in a timely manner and warrants more mechanical ventilatory support and subsequent complications.

The results of the present study could not be analyzed with results of other works performed in pediatric patients with GBS, since in Mexico there are only studies focused on the study of GBS in adult patients, for which we have no previous reference to integrate an opportune analysis.

This study has certain limitations, since it is of a retrospective and observational type, but with the

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**Table 2.** Relationship between the degree of clinical severity of GBS on admission and hospital discharge (A) and test of matched samples according to the degree of clinical severity of SGB on admission and hospital discharge (B)

<table>
<thead>
<tr>
<th>(A)</th>
<th>Mean</th>
<th>n</th>
<th>Standard deviation</th>
<th>Standard error average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of severity on entry</td>
<td>3.83</td>
<td>24</td>
<td>0.761</td>
<td>0.155</td>
</tr>
<tr>
<td>Degree of severity at discharge</td>
<td>2.58</td>
<td>24</td>
<td>1.412</td>
<td>0.288</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(B)</th>
<th>Paired differences</th>
<th>T</th>
<th>gl</th>
<th>Sig. (bilateral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>Standard deviation</td>
<td>Standard error average</td>
<td>95% confidence interval of the difference</td>
<td>Lower</td>
</tr>
<tr>
<td>Degree of severity on entry-degree of severity at discharge</td>
<td>1.250</td>
<td>1.032</td>
<td>0.211</td>
<td>0.814</td>
</tr>
</tbody>
</table>

GBS: Guillain-Barré syndrome.
Source: Clinical record. Legaria Pediatric Hospital. Secretariat of Health of Mexico City.
obtained results, it is a matter of encouraging in each one of the health professionals, in the realization of new investigations of the GBS in pediatric patients with a prospective nature. To establish which clinical variant is most prevalent in the Mexican population studied and establish the associated complications, making an opportunity diagnosis that influences the prognosis and management of GBS, since the treatments recommended by international guidelines, with plasmapheresis or IVIG, they have a high economic cost and a therapeutic efficiency not yet demonstrated in the Mexican pediatric population.

The present work was carried out with the purpose of describing clinical severity in pediatric patients with GBS, since at the national level; there are no studies that allow us to know an adequate statistics of this disease.

The Legaria Pediatric Hospital in Mexico City is a second-level center for health care and a reference for pediatric patients with neurological diseases.

The GBS is a national health problem that requires costly treatment in addition to generating large sequelae and complications subsequent to the discharge of medical care.

Conclusions

In most hospitals in Mexico, the main limitation is the lack of availability of the ideal treatment in several diseases. Therefore, it would be transcendental to have the necessary resources to offer adequate diagnosis and treatment of GBS, to reduce subsequent complications of the underlying pathology, improving the quality of life and prompt reintegration of patients to their daily activities.

Conflicts of interest

The authors declare that in this study, there are no relevant conflicts of interest.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Carotid free-floating thrombus treated with apixaban: report of a case and review of literature

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Abstract

Free-floating thrombus of the internal carotid artery is infrequent (< 1% of strokes), although its diagnosis is straightforward, its treatment represents a challenge. Based mostly on case reports, standard treatment consists of therapeutic anticoagulation, while waiting for carotid endarterectomy. Both unfractioned heparin and Vitamin K antagonists have been reported as efficacious; nevertheless, due to its rarity, clinical trials with novel oral anticoagulants are lacking. We report a patient with cardioembolic stroke and a free-floating carotid thrombus successfully treated with apixaban.

Key words: Free-Floating Thrombus. Stroke. Novel oral anticoagulants.

Trombo libre flotante de la arteria carótida tratado con apixaban: revisión basada en un caso

Resumen

Los trombos libres flotantes de la arteria carótida interna son infrecuentes (menos del 1% de los ictus), y representan un desafío terapéutico. El tratamiento actual, basado en series de casos, consiste en anticoagulación terapéutica en espera de endarterectomía. Tanto la heparina no fraccionada, como los antagonistas de vitamina K, han sido reportados como eficaces. Sin embargo, dada la escasez de casos, no se dispone de ensayos clínicos con nuevos anticoagulantes orales. Reportamos el caso de un paciente con ictus cardioembólico y un trombo libre flotante de la carótida, tratado exitosamente con apixaban.

Palabras clave: Trombo libre flotante. Ictus. Nuevos anticoagulantes orales.

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Introduction

A free-floating thrombus (FFT) of the carotid artery is defined as "an elongated thrombus attached to the arterial wall with circumferential blood flow at its distal most aspect with cyclical motion relating to cardiac cycles"1. They are infrequently found in patients with stroke and are associated with large artery atherosclerosis, in which the rupture of an unstable plaque results in an intraluminal thrombus that in most of the cases dislodges and embolized causing ischemia on distal arterial beds; however, there are cases in which the thrombus remains attached to the plaque, giving origin to the FFT. The absence of randomized clinical trials due to scarcity of cases makes acute treatment and secondary prevention a challenge. We describe one patient with cardioembolic stroke and a FFT of the carotid artery, successfully treated with apixaban. We describe a patient with cardioembolic stroke and large artery atherosclerosis with a FFT of the carotid artery, successfully treated with apixaban.

Clinical case

A 69-year-old male of Mexican descent, active smoker (7 pack-per-year), with 20-year history of uncontrolled diabetes mellitus and hypertension is admitted to the neurovascular care unit for etiological assessment of left anterior choroidal artery and middle cerebral artery ischemic stroke, with a NIHSS 14. Treatment with aspirin, atorvastatin, and prophylactic unfractionated heparin (UFH) is started. Etiology is ascertained as cardioembolism (paroxysmal atrial fibrillation with left-atrial appendage thrombus echocardiogram); and extracranial large-artery atherosclerosis (left internal carotid artery occlusion of 70%) confirmed with Doppler sonogram and computed tomography angiography (CTA) which revealed a FFT attached to an heterogeneous plaque, with a “doughnut sign” (Fig. 1). Due to distal embolization concerns, endarterectomy is delayed; and 7 days after stroke-onset, UFH is suspended, and after consensus with the neurovascular unit team, apixaban (5 mg bid) started as secondary prevention measure. After 4 days, control CTA shows no evidence of FFT (Fig. 2); absence of neurological worsening and additional strokes on imaging, ruled out distal embolization. Incidentally, a pituitary prolactinoma was found, along with thyroid papillary neoplasia; hormonal profile was normal, which ruled out multiple endocrine neoplasia.

Discussion

We present the first case of a FFT treated with apixaban, a novel oral anticoagulant, acting as direct Xa factor inhibitor. FFT is an uncommon entity, reported in < 1% of stroke patients (0.004%-0.9%)2,3, and its appearance on axial projections has been referred to in the literature as the “doughnut sign” (Fig. 1). Although digital-subtraction angiography is considered the diagnostic gold standard, there are no formal diagnostic criteria, and the FFT can be identified on CTA4, and we agree with the definition by Bhatti et al.1 Pathophysiology that explains FFT is lacking; however, we hypothesize that it is a two-hit mechanism, needing a ruptured unstable atherosclerotic plaque on the carotid artery, and a hypercoagulable state (as a cardiac source of embolism) that fosters thrombus adherence and elongation. This hypothesis is supported by the fact that
FFT has been reported in association with procoagulant factors as lupus anticoagulant.

Given its scarcity, there are no guidelines for therapeutic management. The most commonly reported protocol is therapeutic anticoagulation with either UFH or Vitamin K antagonists (VKA) while waiting for endarterectomy. Nevertheless, therapeutic anticoagulation alone has been reported effective in up to 85% of cases with thrombus recurrence after discontinuation of anticoagulants. There are no randomized trials to demonstrate superiority of...
either UFH or VKA, and until our report, novel oral anticoagulants (like apixaban) had not been used for this entity. Whether temporary or definitive, anticoagulation is needed, and typically is withdrawn when a cause for long-term therapy is ruled out, and thrombus resolution is demonstrated; although the optimal time to repeat imaging is uncertain, carotid ultrasound could be used as screening method. Monotherapy with antiplatelet agents is not recommended, as it has been associated with carotid occlusion\(^3\). Furthermore, novel endovascular therapeutic approaches have been reported as effective in the treatment of FFT\(^7\).\(^8\).

Although dislodgment and distal embolization of thrombus could explain thrombus disappearance, the absence of clinical and radiological worsening, speak in favor of apixaban-related resolution. Thrombus disappearance has been scarcely documented, with 35 cases reported to date\(^1,3,5,6,9-13\) (Table 1). Nevertheless, we must acknowledge there are other potential confounding factors, such as prophylactic UFH contribution, which could suggest apixaban was not the sole responsible; yet, until better evidence is available, our case report speaks in favor of direct Xa factor inhibitors as an alternative to UFH and VKA.

**Conclusion**

Carotid FFT is an uncommon entity that can be successfully treated with novel oral anticoagulants.

**Contributorship statement**

CASR contributed to the conception and design of the manuscript, data acquisition and drafting of the first manuscript. SACT contributed to design of the manuscript, data analysis and interpretation and critical review of the first manuscript. AGA contributed to conception and design of the manuscript, data acquisition and drafting of the first manuscript. ICFN contributed to conception and design of the manuscript, data analysis and interpretation and critique of intellectually relevant content the manuscript. BECL contributed to design of the manuscript, data analysis and interpretation, and critique of intellectually relevant content the manuscript. FGR contributed to conception and design of the manuscript, data analysis, and interpretation and critique of intellectually relevant content the manuscript, providing the expert’s opinion on the use of novel oral anticoagulants in difficult cases. All authors agreed on the final form of the manuscript.

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- **Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

**References**

Circadian variations of neurotransmitters in the brain – Its importance for neuroprotection

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Abstract

Circadian rhythms are expressed at the biochemical, physiological, and behavioral level; they help to maintain the internal temporal order of an organism and allow adaptation to a cyclical environment. Circadian rhythms have a substrate at the genetic level and are synchronized to geographical cycles, as well as to other external factors, of which the main one is the light-dark cycle. Cerebral functions present circadian rhythms, which influence the neuroprotective response to acquired brain damage, such as a traumatic brain injury (TBI). Knowing the moments of greatest vulnerability to such events will allow us to offer elements to develop better study models and therapeutic objectives. Here, we present a review on diurnal variation in the levels of noradrenaline, histamine, orexin, glutamate, gamma-aminobutyric acid, serotonin, acetylcholine (ACh), and dopamine, as well as in the expression of their receptors in the brain, neurotransmission systems that may be involved in neuroprotective responses to a TBI.

Key words: Diurnal variation. Traumatic brain injury. Biological rhythms. Neuroprotection.

Variciones circadianas de los neurotransmisores en el cerebro. Su importancia para la neuroprotección

Resumen

Los ritmos circadianos se expresan a nivel bioquímico, fisiológico y conductual; ayudan a mantener el orden temporal interno de un organismo y permiten la adaptación a un entorno cíclico. Los ritmos circadianos tienen un sustrato a nivel genético y están sincronizados con los ciclos geográficos, así como con otros factores externos, de los cuales el principal es el ciclo luz-oscuridad. Las funciones cerebrales presentan ritmos circadianos, que influyen en la respuesta neuroprotectora al daño cerebral adquirido, como un traumatismo craneoencefálico (TCE). Conocer los momentos de mayor vulnerabilidad a tales eventos nos permitirá ofrecer elementos para desarrollar mejores modelos de estudio y objetivos terapéuticos. Aquí presentamos una revisión sobre la variación diurna en los niveles de noradrenalina (NA), histamina, orexinas, glutamato, ácido gamma-aminobutírico (GABA), serotoninina (5-HT), acetilcolina (ACh) y dopamina (DA), también como en la expresión de sus receptores en el cerebro; sistemas de neurotransmisión que pueden estar involucrados en respuestas neuroprotectoras a un TCE.


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Introduction

In the main biological processes, periodic oscillations are observed at all levels of organization, from isolated cells to complete organisms. This periodicity represents a fundamental phenomenon in biological systems conferring functional advantages in a cyclical external environment.

These oscillations have a wide range of periods that can cover fractions of a second, such as the firing of a neuron, or cycles of 1 or more days and up to a year, such as in hibernation or the seasonal reproduction of some animals.

Some oscillations are synchronized with environmental phenomena such as the light–dark cycle, result of rotation, and terrestrial translation. Other oscillations occur even in the absence of external synchronizers, indicating that internal clocks regulate them. These are known as biological rhythms. The most studied are the circadian rhythms whose cycle is approximately 1 day.

Circadian rhythms in mammals are generated by the circadian system, a group of oscillating tissues directed by an internal clock, the suprachiasmatic nucleus (SCN). However, different tissues and even isolated cells can oscillate and express periodic changes in their function. These structures, external to the SCN with their own rhythms, have been called peripheral oscillators and exist in practically all the tissues studied, including the liver and the lungs.

Circadian rhythms in health and pathology

The circadian system transmits signals of the time to the whole organism, and consequently, all the internal processes exhibit maximum and minimum values over a period of 24 h. These rhythms allow adaptation to a cyclical environment, making the body more efficient at times when circumstances demand it and saving effort in others. When the rhythmicity is lost or altered, there are disorders and alterations in the internal functions and in the responses of the individual to their environment, which increases the vulnerability to develop various diseases and chronic diseases. If the chronobiological alteration is corrected, the condition or damage decreases.

Experimentally, it has been observed that the response of mice exposed to pathogens is influenced by the time at which this exposure occurs, which suggests that both the infectious capacity of the microorganisms and the immune response of the host have a circadian rhythmicity. The vital role of the sleep-wake cycle in these interactions has also been described. For example, during slow-wave sleep, the activation of the immune system is more efficient to counteract bacterial infections and increases resistance to pathogens since it is presumed that during this period, there is higher production of some pro-inflammatory cytokines such as tumor necrosis factor-alpha or interleukin-2 that are inducers of this type of sleep.

Experimental evidence suggests that the circadian regulation of some of the antioxidant systems influences the response to oxidative stress and, therefore, DNA damage, lipoperoxidation, and the oxidation of proteins. It is also known that superoxide dismutase is expressed rhythmically. Likewise, when the circadian rhythms are altered, the state of oxidative stress increases, which can impact on the state of health-disease. This rhythmicity in antioxidant systems can be used specifically as a therapeutic target for the modulation of reactive oxygen species and, therefore, for the protection of cells.

Another clear example of the importance of circadian rhythms in the health-disease relationship is presented when analyzing the start time of a stroke, which, similar to the attack to the myocardium, has a marked diurnal rhythm. Numerous studies have shown that the time of onset of a stroke, as well as the transient ischemic attacks, occur more frequently between 6:00 and 12:00 AM, that is, when the subject initiates its activities. In the rat, which is a nocturnal animal, ischemia causes more significant damage, if it is induced in the hours of darkness, which is when it begins its stage of greatest activity. We analyzed the severity of a traumatic brain injury (TBI) in relation to the time of day using the rat as a model, finding that the recovery from a TBI has diurnal variations, recovery being better if the trauma occurs in the hours of darkness compared to the hours of light.

During an acquired brain injury, as in a TBI, two types of responses are presented: those that generate damage and those that generate neuroprotection. Among the former, the excitotoxicity produced by the excessive release of glutamate, which allows the entry of calcium, the activation of caspases promoting apoptosis, stands out. While in the neuroprotective response, the release of gamma-aminobutyric acid (GABA) inhibits the excitability and therefore, the activation of the apoptotic pathways, minimizing cell death and brain damage. This shows that both glutamate and GABA have great interference in injury processes. The balance between damage and neuroprotection responses depends on circadian variations where the intensity and efficiency of the synaptic neurotransmission plays a preponderant role.
fundamentally that of the glutamatergic and GABAergic systems.

In this work, we review the existing knowledge of the influence of circadian rhythms in the neuroprotection processes emphasizing the relevance of the diurnal and/or circadian variations present in the release of noradrenaline (NA), histamine, orexin, glutamate, GABA, serotonin (5-HT), and dopamine (DA), as well as in the expression of its receptors.

Circadian variations in neurotransmission systems that affect the response to a TBI

**The noradrenergic system as an example of diurnal variation**

A classic example of diurnal variation is observed in the noradrenergic system in the pineal gland. One of the best-documented rhythms is the secretion of melatonin, generated by the rhythmic activity of serotonin N-acetyltransferase. This rhythm is regulated by the SCN which stimulates the cyclic release of NA from the upper cervical ganglion according to the light–dark cycle. NA binds to beta-adrenergic receptors that stimulate cyclic adenosine monophosphate (cAMP) synthesis. In the pineal gland, diurnal variations have been reported in the expression of beta-adrenergic receptors, as well as adenyate cyclase type I and cAMP. In contrast, the alpha-adrenergic receptors of the pineal gland do not present diurnal changes (Fig. 1 and Table 1).

Concerning the neuroprotective role of NA, its potent anti-inflammatory effect is known in glial cell cultures protecting dopaminergic cells and reducing oxidative stress. There is no reference to any NA rhythms involved in this process.

**Diurnal variations of the histaminergic system**

Histamine, a wake-promoting neurotransmitter shows diurnal variation in the hypothalamus of many species with higher levels during the waking period and lower levels during sleep; in mice, the number of neurons containing histidine decarboxylase (HDC), the key enzyme for histamine production, is higher in the dark than in the light; even in the human hypothalamus, the diurnal variation of HDC mRNA has been documented. Concerning the possible neuroprotective role of histamine, several clinical trials using agonists for histamine receptors, in particular for H3, are in process for the treatment of some neuronal diseases, such as sleep-wake disorders, neuropathic pain, attention deficit hyperactivity disorder, Alzheimer’s disease, schizophrenia, and Parkinson’s disease. Besides, recent studies in animal models have shown that histamine protects hippocampal neurons from excitotoxic damage induced by kainic acid and increases the neuroprotective effect of astrocytes.

**Diurnal variations of the orexinergic system**

The orexin, hypothalamic peptides that regulate the waking state, presents diurnal variations in several species. In mice, more orexin neurons are seen in the night compared to the day, and diurnal variation of their levels in cerebrospinal fluid has been described even in humans. Regarding the neuroprotective role of orexin, it has been described that they reduce neuroinflammation and infarct volume in stroke animal models; recently, it has been reported that intranasal orexin administration as post-cardiac arrest treatment in rat facilitates arousal from a coma.

**Diurnal variations of the glutamatergic system**

Virtually, all the excitatory cells in the nervous system are glutamatergic, and it is estimated that more than 50% of the synapses in the brain release glutamate.
There are few studies on the diurnal variability of the glutamatergic system and most only analyze its variation in the SCN. Some reports indicate a higher concentration of glutamate in the SCN of hamsters during the latter part of the night, a pattern that is preserved under conditions of continuous darkness. Furthermore, it has been observed that mRNA for glutamate decarboxylase (GAD65), one of the isoforms of GAD, which catalyzes the decarboxylation of glutamate to form GABA, presents diurnal variations in the SCN, which disappears when the animals are subjected to continuous darkness19,20 (Table 1).

In the SCN, there is also a diurnal variation in the expression of the NR2B, NR1, and NR3 subunits of the N-methyl-D-aspartate (NMDA) receptor, with the lowest expression at 0 h and the highest at 20 h21 (Table 1). While the Ca²⁺ currents evoked by α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), present a wide distribution in the SCN, and a diurnal rhythm with a peak during the night. Michel establishes that the communication between the right and left SCN, as well as the degree of synchronization of the neurons of this nucleus, depends on the AMPA receptor since they are lost when it is blocked22.

Outside the SCN, it has been described that mRNA for the kainate receptor KA2 presents diurnal variations in GnRH-ergic neurons in females whose maximum level of expression depends on the age of the rat23. Furthermore, the transporter the VGLUT1, the isoform that is mainly expressed in cerebral cortex, presents diurnal variations in synaptic vesicles obtained from mouse brain; this rhythm does not seem to depend on the synthesis of VGLUT1, but rather on the vesicular turnover24.

At the level of the olfactory bulb, recently identified as a circadian oscillator, a diurnal variation in the expression of the GluR1 subunit of the AMPA receptor has been reported. This finding could be the basis of the circadian synchronization of the action potential in the bulb and modify the synaptic interactions expected to impact olfactory coding25 (Table 1).

NMDA receptors have been considered fundamental in brain memory and plasticity processes, in which the energetic factor could be playing an important role; in

### Table 1. Maximum and minimum values of some neurotransmitters and their receptors in the brain

<table>
<thead>
<tr>
<th>Neurotransmitter/receptor (species)</th>
<th>Day</th>
<th>Night</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulating melatonin (human, rat)</td>
<td>↓</td>
<td>↑</td>
<td>Solís and Sánchez-Barceló, 201011</td>
</tr>
<tr>
<td>Noradrenaline in the innervation of the cervical ganglion superior to the pineal gland (rat)</td>
<td>↓</td>
<td>↑</td>
<td>Wirz-Justice, 19871</td>
</tr>
<tr>
<td>Expression of beta-adrenergic receptors in the pineal gland (rat)</td>
<td>↓ (mRNA)</td>
<td>↑ (mRNA)</td>
<td>Wirz-Justice, 19871</td>
</tr>
<tr>
<td>Histamine in hypothalamic tuberomammillary region (rat)</td>
<td>↓</td>
<td>↑</td>
<td>McGregor et al., 201715</td>
</tr>
<tr>
<td>Glutamate in SCN (hamster)</td>
<td>↓</td>
<td>↑</td>
<td>Glass et al., 199319</td>
</tr>
<tr>
<td>Expression of GAD65 in SCN (rat)</td>
<td>↑ (mRNA)</td>
<td>↓ (mRNA)</td>
<td>Huhman et al., 199620</td>
</tr>
<tr>
<td>Expression of NR1-NMDA in SCN (rat)</td>
<td>↑ (RNAm)</td>
<td>↓ (Protein)</td>
<td>Bendová et al., 200921</td>
</tr>
<tr>
<td>Expression of GLUR1-AMPA in olfactory bulb (rat)</td>
<td>↓ (mRNA)</td>
<td>↑ (mRNA)</td>
<td>Corthell et al., 201225</td>
</tr>
<tr>
<td>Expression of NR1-NMDA in motor cortex (rat)</td>
<td>↑ (Protein)</td>
<td>↓ (Protein)</td>
<td>Estrada-Rojo et al., 20189</td>
</tr>
<tr>
<td>GABA in SCN (rat)</td>
<td>↓</td>
<td>↑</td>
<td>Aguilar-Roblero et al., 199327</td>
</tr>
<tr>
<td>GABA in striatum (rat)</td>
<td>↓</td>
<td>↓</td>
<td>Choma et al., 197928</td>
</tr>
<tr>
<td>Expression of α2-GABAa in median eminence (hamster)</td>
<td>↑</td>
<td>↑</td>
<td>Naum et al., 200139</td>
</tr>
<tr>
<td>Serotonin binding in brain membrane fraction (rat)</td>
<td>↓ (inactive phase)</td>
<td>↑ (active phase)</td>
<td>Wesemann et al., 198636</td>
</tr>
<tr>
<td>Brain activity of the cholinergic system (rat, hamster, mouse)</td>
<td>↓ (inactive phase)</td>
<td>↑ (active phase)</td>
<td>Hut and Van der Zee, 201139</td>
</tr>
<tr>
<td>Dopamine in striatum (rat)</td>
<td>↓</td>
<td>↑</td>
<td>Castañeda et al., 200427</td>
</tr>
</tbody>
</table>

GABA: gamma-aminobutyric acid, SCN: suprachiasmatic nuclei, NMDA: N-methyl-D-aspartate, AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazole propionate.
this sense, it has recently been reported that orexin-A inhibits the activation of these receptors by NMDA, in rat hippocampus in a time-dependent manner.

Recently, we described a diurnal variation in the expression of the NR1 subunit of NMDA in motor cortex with a peak in the hours of light, this correlated with greater behavioral damage in rats subjected to TBI during the light phase (Table 1).

Although limited, the available knowledge of the diurnal variation of the glutamatergic system is of great importance. Deepening its role in different areas of the brain will make it possible to increase neuroprotective responses to a brain injury and create more effective therapeutic windows.

**Diurnal variations of the GABAergic system**

GABA is found in most inhibitory synapses of the brain and spinal cord.

Several authors report diurnal variations in the GABAergic system in the SCN. Even some studies indicate that GABA, in SCN, can be excitatory during daytime and inhibitory at night (Table 1).

Outside the SCN, a diurnal variation of GABA levels has been reported in the pons, the striatum, the nucleus accumbens, the hypothalamus, in addition to the median eminence of lactating rabbits and the expression of the GABAA receptor, in rat cerebral cortex. In the hamster, a variation in the turnover of GABA in the brain has been reported, as well as the a2 subunit of the GABAA receptor in the median eminence and the Kd of the GABAA receptor in the cerebral cortex (Table 1). Even in humans, a diurnal variation in GABAergic modulation of the motor cortex inhibition has been described.

Therefore, before a brain injury process, the neuroprotection response would be modulated by the relationship between GABA and glutamate, which varies throughout the day.

**Diurnal variations of the 5-HT system**

Several studies report a diurnal rhythm in the levels of 5-HT in plasma, hippocampus, hypothalamus, striatum, cerebellum, pineal gland, and SCN, as well as for the binding of 5-HT to rat brain membranes, for the 5-HT2 receptor in the frontal cortex and the lateral hypothalamus (Table 1).

It should be noted that the serotonergic system is phylogenetically the oldest of the neurotransmission systems, and although only a few thousand neurons release 5-HT, there is a considerable amount of target neurons so that 5-HT acts as a thermostat that regulates internal variations with those of the environment and participates in complex processes of emotions and thoughts. It also stabilizes neuronal circuits and regulates the response of other neurotransmitters.

Regarding the relationship of 5-HT with acquired brain injury, there are reports suggesting that inhibitors of its recapture increase neuroplasticity after a focal injury. In the motor recovery of a TBI, the role of 5-HT is not so clear, but its participation in post-traumatic processes such as depression, mood swings, and even Alzheimer’s disease has been confirmed.

Several studies have shown circadian fluctuations in the release of acetylcholine (ACh), in the activity of choline acetyltransferase, and in the expression of its receptors that vary notably between species and even between strains. In general, the circadian rhythmicity of the cholinergic system is characterized by a high release of ACh during the active phase of the individuals. In SCN, its rate of secretion does not appear to be endogenous but rather depends on exposure to light (Table 1). The superior cervical ganglion of the rat, analyzed in vitro, releases ACh with a circadian rhythm, with a maximum peak in the middle of the nocturnal phase. Regarding the muscarinic receptors in rat brain, it has been reported that their number is higher when the ACh levels are lower (inactive phase of the animal), and they are found in less quantity at night when the animal is more active.

ACh has an essential role in the regulation of the sleep-wake cycle. It is considered a neurotransmitter of wakefulness, is released from basal forebrain nuclei during wakefulness and rapid eye movement (REM) sleep, and its release is dramatically reduced during slow-wave sleep (SWS). The neurons responsible for the SWS are located in the ventrolateral preoptic nucleus of the hypothalamus. They receive input from the SCN, and the retina and their firing are necessary for the maintenance of SWS. During wakefulness, their activity must be inhibited by norepinephrine from locus coeruleus nuclei and by ACh from the cholinergic nuclei of the basal forebrain.

In rat TBI models, cognitive deterioration is associated with cholinergic system damage since its activation provides improvement during the recovery period of the
brain injury. Excessive activation of muscarinic receptors in areas CA2 and CA3 of the hippocampus in post-TBI rats has also been reported, which contributes to the pathophysiological sequelae; however, it is not ruled out that this activation could be modulated by the time the injury occurs.

The role of ACh in neuroprotection processes requires more studies; the fact that its receptors show differential expression during the day could provide a therapeutic window in the recovery of cognitive processes that are regulated in the cerebral cortex and hippocampus.

**Diurnal variations of the dopaminergic system**

The release of DA follows a circadian rhythm, in structures such as the nucleus accumbens and the striatum, its rhythm is maintained under constant light conditions, but it is lost in constant darkness (Table 1).

At the level of the olfactory bulb, the concentration of DA varies according to the time of day, but it has not been established whether its receptors vary as well. In the striatum, several authors have shown diurnal variations in the dopaminergic receptors (Table 1).

At the level of the substantia nigra, it has been documented that the circadian disruption of DA produces motor abnormalities additional to those classically described for Parkinson’s disease; it is not known if this deregulation also involves its receptors.

From the clinical point of view, various dopaminergic drugs have been used to treat successfully cognitive deficits after a TBI.

**Other neurotransmission systems**

Finally, circadian rhythms have been demonstrated in other neurotransmitters, for example, opioids, adenosine, and endocannabinoids; all of them have been involved in neuroprotection processes. Specifically, our group has described diurnal variations in the CB1 cannabinoid receptor in pons, hippocampus, and cerebral cortex. Both adenosine and opioids are considered as neuroprotective, and the cannabinergic system has been identified as one of the most directly involved in neuroprotection.

**Limitations**

It is worth noting that most of the studies referred to in this review were carried out in animal models, *in vivo* or *in vitro*. However, we try to refer to studies that present data from human patients. In all cases, we indicate whether the reported data were obtained from animal models or human patients.

**Perspectives**

Knowing the relationship between the sleep-wake cycle, the diurnal or circadian rhythms and the neurotransmission systems involved in the acquired brain damage open a window in their study as potential biomarkers or therapeutic targets. With this approach, it will probably benefit a more significant number of patients with acquired brain damage.

Our group has published that both total sleep deprivation and REM sleep for short periods have favorable consequences in the recovery of a TBI. We believe that 5-HT, NA, and several other neurotransmitters and neuromodulators may be participating in this effect. Proposing them as therapeutic objectives is beyond the scope of this review.

**Conclusion**

The knowledge of rhythmic variations at the brain level of neurotransmission systems is essential to establish more effective neuroprotection processes in the face of acquired brain damage. This knowledge is gaining importance; however, it is still necessary to investigate whether this variation takes place only in the release or also in the expression of the receptors of the different neurotransmitters. This information will allow us to know better the normal functioning of the brain and in general of the nervous system.

In this review, we have provided evidence that neurotransmission systems show rhythmic variations.

In acquired brain damage, whether due to an ischemic process or a TBI, knowledge of circadian rhythms will determine the most appropriate time to apply therapeutic targets, drugs, and neuroprotective strategies.

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**Conflicts of interest**

There are no potential conflicts of interest for any of the authors in this scientific report.
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Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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