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EDITORIAL

Epilepsy is a complex circuit disease with a cure

La epilepsia es una enfermedad compleja de circuitos con cura

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According to the World Health Organization, 50 million people were diagnosed with epilepsy until year 2017. About 90% of these were in under-served communities[1]. Although the global burden of disease in Latin America has decreased by 20%, mortality has risen in the past 20 years[2]. The main factors related to this increase in mortality and burden (mostly in the elderly) were found to be secondary to alcohol consumption and under-development. Although epilepsy is quite common, it is not uncommon that physicians fail to recognize it and promptly treat it. Most importantly, although its visibility has increased, the possibility of surgery is still thought of as a last resort[3]. If anyone needs convincing, the number of patients needed to treated with surgery for one additional patient to be seizure free is two[4]. This finding is a rarity in neurology practice!

Although classifications in epilepsy have changed a myriad of times over the years, clinical manifestations have not[5]. One of the pitfalls of epilepsy surgery is the complexity of its propagation patterns. For instance, Jimenez-Ruiz et al. depicts distinct manifestations in epilepsia partialis continua (continuous focal epilepsy according to new nomenclature)[6] associated with a single pathology, stroke, in a case series. Stroke is strictly anatomical and follows this anatomical location. We know that stroke-related epilepsy may often lead to mesial temporal sclerosis, even though the lesional zone is far away anatomically[7].

Epilepsy is a complex network disease[8]. The most common type of epilepsy, temporal lobe epilepsy, is characterized by a complex extratemporal network involving not only the mesial and neocortical regions but also extratemporal regions. Often, the symptomatogenic zone may be farther away from the epileptogenic zone[9]. In fact, in temporal lobe epilepsy, the seizure onset may arise from structures interconnected within the temporal lobe or other regions simultaneously[10]. Understanding this concept is key to achieve seizure freedom.

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ORIGINAL ARTICLE

Stroke-induced epilepsia partialis continua

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Abstract

Objective: *Focal status epilepticus requires timely diagnosis and treatment. Stroke is a common cause of epileptic seizures, but stroke-induced epilepsia partialis continua (SIEPC) is a rare type of focal status epilepticus with unknown management and prognosis. The aim of the study was to present a single-center case series of patients admitted to a third-level referral hospital diagnosed with SIEPC.* **Methods:** *We performed a retrospective review assessing all in-hospital consultations from July 2021 to July 2022 describing patients who presented with a diagnosis of SIEPC during hospital admission. Patients received standard diagnostic approaches (including electroencephalographic assessment) and treatment protocols. We defined EPC as focal, continuously repeated seizures with preserved consciousness lasting at least 1 h, confirmed with electroencephalography.* **Results:** *We identified 1054 patients seen by the neurology department as in-patient consultations. We found 268 patients with a diagnosis of stroke or epilepsy and then excluded 265 patients due to an alternate diagnosis. We finally identified three patients with (SIEPC).* **Conclusions:** *Although cerebrovascular disorders are a common cause of hospital admission, and SIEPC is rare, this condition is relevant to the practicing clinician. This study draws attention to this distinct clinical entity with variable presentation, diagnosis, treatment, and prognostic issues.*

Keywords: *Stroke. Focal status epilepticus. Epilepsia partialis continua. Stroke-induced epilepsia partialis continua.*

Epilepsia partialis continua inducida por ictus

Resumen

Objetivo: *El status epilepticus requiere un diagnóstico y tratamiento temprano. El ictus es una causa común de crisis epilépticas, pero la epilepsia partialis continua inducida por ictus es un tipo raro de status epilepticus focal con tratamiento y pronóstico desconocido. Presentar una serie de casos unicentrica de pacientes admitidos a un hospital de referencia de tercer nivel con diagnóstico de epilepsia partialis continua inducida por ictus.* **Métodos:** *Realizamos una revision retrospectiva, recopilando todas las interconsultas desde Julio del 2021 hasta Julio del 2022 que describieran pacientes quienes tuvieran un diagnóstico de epilepsia partialis continua inducida por ictus durante el ingreso hospitalario. Los pacientes recibieron abordajes diagnósticos (incluyendo realización de electroencefalograma) y terapéuticos estandar. Definimos epilepsia partialis continua como episodios convulsivos continuos focales con estado de consciencia preservado con duración mayor a una hora, confirmado por electroencefalografía.* **Resultados:** *Identificamos 1054 pacientes que fueron vistos por el*

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servicio de neurología como interconsultas hospitalarias. A partir de dichos pacientes, encontramos 268 con diagnóstico de ictus o epilepsia, y excluimos 265 pacientes debido a diagnósticos alternativos. Finalmente, identificamos tres pacientes con epilepsia parcialis continua inducida por ictus. **Conclusiones:** *A pesar de que las enfermedades cerebrovasculares son una causa frecuente de admisión hospitalaria, y la epilepsia parcialis continua inducida por infarto es rara, esta condición es relevante para el médico practicante. Este estudio llama la atención hacia esta distinta entidad clínica con presentación variable, y dificultades en el diagnóstico y tratamiento*

Palabras clave: *Ictus. Status epilepticus focal. Epilepsia partialis continua. Epilepsia partialis continua inducida por ictus.*

Introduction

Epilepsia partialis continua (EPC) is part of the focal status epilepticus spectrum. Standardized management for this condition remains unknown. Stroke-induced EPC (SIEPC) is a rare disorder with unknown frequency. We aim to describe a single-center case series regarding this uncommon condition, emphasizing clinical outcomes.

Methods

We considered consecutive adult patients (≥ 18 years) with a history of stroke or epilepsy admitted to the Hospital Civil Fray Antonio Alcalde (Guadalajara, Mexico) from July 1, 2021, to July 1, 2022. Inclusion criteria were: ≥ 18 years, with an admission diagnosis of previous or acute stroke, history of post-stroke epilepsy, and SIEPC. Exclusion criteria were generalized status epilepticus and epilepsy before stroke. We identified 1052 patients seen in-hospital consultation using the electronic health record. During this period, 268 patients presented with the diagnosis of stroke or epilepsy. We identified eight patients with post-stroke epilepsy and excluded five due to generalized epilepsy diagnosis. We finally included three patients with a diagnosis of SIEPC (Fig. 1).

Patients received standard diagnostic (including electroencephalographic assessment) and treatment protocols. A board-certified neurologist made the diagnosis on clinical grounds and supported by brain imaging and electroencephalogram (EEG). We defined EPC as continuously repeated motor seizures with preserved consciousness lasting at least 1 h, confirmed with an electroencephalogram. We analyzed the following sociodemographic variables: age, gender, stroke risk factors (dyslipidemia, hypertension, diabetes, and atrial fibrillation), clinical symptoms, EEG findings, radiological findings in computerized tomography (CT) or magnetic resonance imaging (MRI), stroke localization, pharmacological treatment, the use of mechanical ventilation, clinical outcome, and follow-up.

Results

After a systematic search, we identified eight patients with post-stroke epilepsy. Three of these presented with SIEPC (< 1% frequency [0.28%]) (Table 1). All three patients had clinical, radiological, and electrophysiological findings consistent with SIEPC.

Patient 1

A 49-year-old right-handed female experienced right hemifacial weakness. After 26 days of this event, she presented to the emergency room with repeated right hemifacial seizures, aphasia, and preserved awareness. Her medical history was relevant for Type 2 diabetes mellitus and hypothyroidism. Unenhanced brain computed tomography (CT) was unremarkable. MRI showed subacute infarction involving the left frontocortical and superior frontal gyrus (Fig. 2). The ictal standard scalp EEG reported the presence of continuous focal epileptiform discharges in the left centroparietal region and no secondary generalization. We treated her with levetiracetam, valproate, lacosamide, and carbamazepine (doses shown in Table 1). On 8-month follow-up, she remained seizure-free with levetiracetam and valproate. After extended workup, the stroke was classified as an embolic stroke of unknown source.

Patient 2

A 49-year-old right-handed female presented to the emergency room after experiencing lingual motor seizures with motor left faciobrachial progression. She had a history of hypertension, obesity, and dyslipidemia. CT scan revealed an intracerebral hemorrhage (ICH) in the right frontal lobe at the level of the precentral gyrus. Brain MRI showed a lesion at the same level (T2 hypointensity with isointense center and a “popcorn” appearance with associated perilesional edema) consistent with a cerebral cavernous venous malformation (cavernoma) (Fig. 3). The ictal standard scalp EEG showed right frontocentral discharges (F4-C4) with propagation to the contralateral

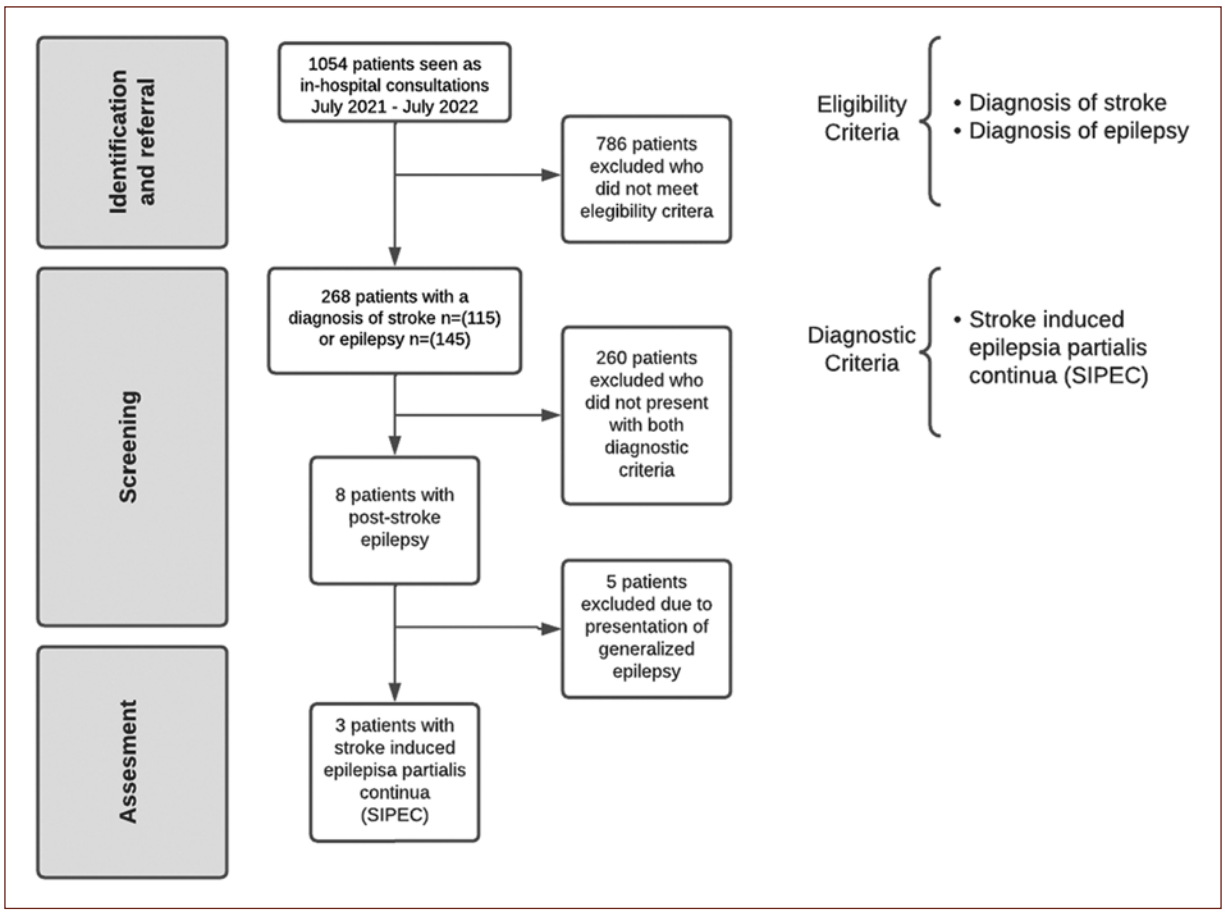

Figure 1. Flowchart.

hemisphere. At admission, we treated her with oxcarbazepine and levetiracetam (doses shown in Table 1). The patient responded well to pharmacotherapy.

The lesion was surgically removed, and the patient remained seizure-free on 2-month follow-up.

Patient 3

A 72-year-old right-handed male presented to the emergency department with left hemiparesis and rhythmic, ipsilateral, and clonic movements (synchronic, face-arm-leg). He had a history of type 2 diabetes, hypertension, and chronic kidney disease. A brain CT scan showed a right temporal-occipital gyrus infarction consistent with a posterior cerebral artery territory stroke (Fig. 4). The ictal standard scalp EEG showed irregular rhythm, right hemispheric slowing, and lateralized periodic discharges (LPDs). The abnormal left-sided movements stopped abruptly after a benzodiazepine challenge but reinitiated acutely after a few minutes. The patient remained awake throughout the hospital admission and was treated with a combination of levetiracetam, phenytoin, clonazepam, and valproic acid with marked improvement (doses shown in Table 1). The patient was discharged against medical advice and was lost to follow-up. This patient's stroke was classified as cryptogenic due to an incomplete workup.

Discussion

EPC was first described by Yakovlevich Kozhevnikov in 1894 but lacks a universally accepted definition[1]. It is a subtype of focal status epilepticus defined as continuous regular or irregular muscular clonic twitching affecting a limited body part for at least an hour[2]. Consciousness is typically preserved, and the twitching most commonly involves the face, arms, or both[3]. The diagnosis is usually supported with an EEG; however, it may be normal[4]. EPC is uncommon, but when identified, a common underlying cause is stroke[4-6].

Stroke is the most common cause of epilepsy in older adults, accounting for approximately 20% of the

Table 1. Demographic and clinical information of patients with stroke-induced epilepsia partialis continua

Case	Sex	Age	Medical history	Clinical presentation	Imaging	Radiologic diagnosis	Abnormal EEG	Treatment	Pharmaco resistant epilepsy	Death
1	F	49	Type 2 diabetes and hypothyroidism	Hemifacial seizures with accompanying aphasia	MRI	IS	+	Levetiracetam (2 g every 12 h), Valproate (600 mg every 8 h), Carbamazepine (200 mg every 6 h), Lacosamide (200 mg every 12 h)	+	-
2	F	49	Hypertension, obesity, dyslipidemia	Lingual seizures with accompanying motor faciobrachial progression	MRI	ICH	+	Levetiracetam (1 g every 12 h), Oxcarbazepine (600 mg every 12 h)	-	-
3	M	72	Type 2 diabetes, hypertension, and chronic kidney disease	Hemiparesis with accompanying rhythmic clonic movements (synchronic, face-arm-leg)	CT	IS	+	Levetiracetam (1 g every 12 h), Phenytoin (100 mg every 8 h), Clonazepam (0.25 mg every 8 h), Valproate (1 g every 8 h)	+	-

MRI: magnetic resonance imaging; CT: computed tomography; EEG: electroencephalogram; IS: ischemic stroke; ICH: intracerebral hemorrhage.

cases[7,8]. The incidence of post-stroke status epilepticus is 0.1-0.9%[9]. Stroke is also the most common cause of status epilepticus in people over 60 years[10]. The risk of seizures is highest in the first week after stroke[11]. Early seizures (< 14 days after stroke) have a 35% increased risk of later epilepsy, but the risk of epilepsy after late seizures (> 14 days after stroke) increases to 90%[12]. The stroke subtype is also a significant predictor of seizures and epilepsy. Hemorrhagic stroke patients have a higher incidence of seizures compared to ischemic stroke. A symptomatic post-stroke seizure has a > 60% probability of seizure recurrence[13]. Large infarcts with cortical involvement increase the risk of epilepsy, and the localization of the lesion determines seizure type[14].

SIEPC is rare, the frequency of this condition is unknown, and few studies have focused on determining its incidence. A prospective study conducted by Bentes et al. showed an incidence of 1.7% among 151 patients with stroke. However, the study sample was small, with no similar studies[15].

The differential diagnosis for this rare condition includes cluster seizures (> 3 seizures in 24 h) and other abnormal movement disorders such as hemiballismus and hemichorea[16]. A benzodiazepine challenge (clonic movement cessation after IV administration of short-acting benzodiazepine) may help distinguish these entities.

Management of EPC remains to be seen. Studies are highly heterogeneous, with variable clinical responses to antiseizure drugs[15]. However, anti-seizure medications (ASMs) such as levetiracetam, carbamazepine, and lacosamide have shown promising responses with seizure resolution. These results, although showing adequate responses, should be taken with caution, since only one patient was included for each study[17-19]. Other approaches such as vagus nerve stimulation, transcranial brain stimulation, and alcohol; performed in four, one, and one patient, respectively; have also been used in EPC unresponsive to medical therapy[20-22].

SIEPC response to ASMs is varied and presents a worse clinical response than EPC due to other etiologies. In a study conducted by Phabphal et al., all patients with EPC due to metabolic etiologies responded well to ASMs, but only 81% of the patients with SIEPC responded well to ASMs[3]. In our case series, all patients required two or more ASMs to archive clinical response. Levetiracetam was administered to all patients, with favorable outcomes; only one patient (Case 3) could not be evaluated in the follow-up but showed partial resolution within hospitalization. Previous studies have shown adequate clinical responses with the use of levetiracetam in SIEPC secondary to traumatic

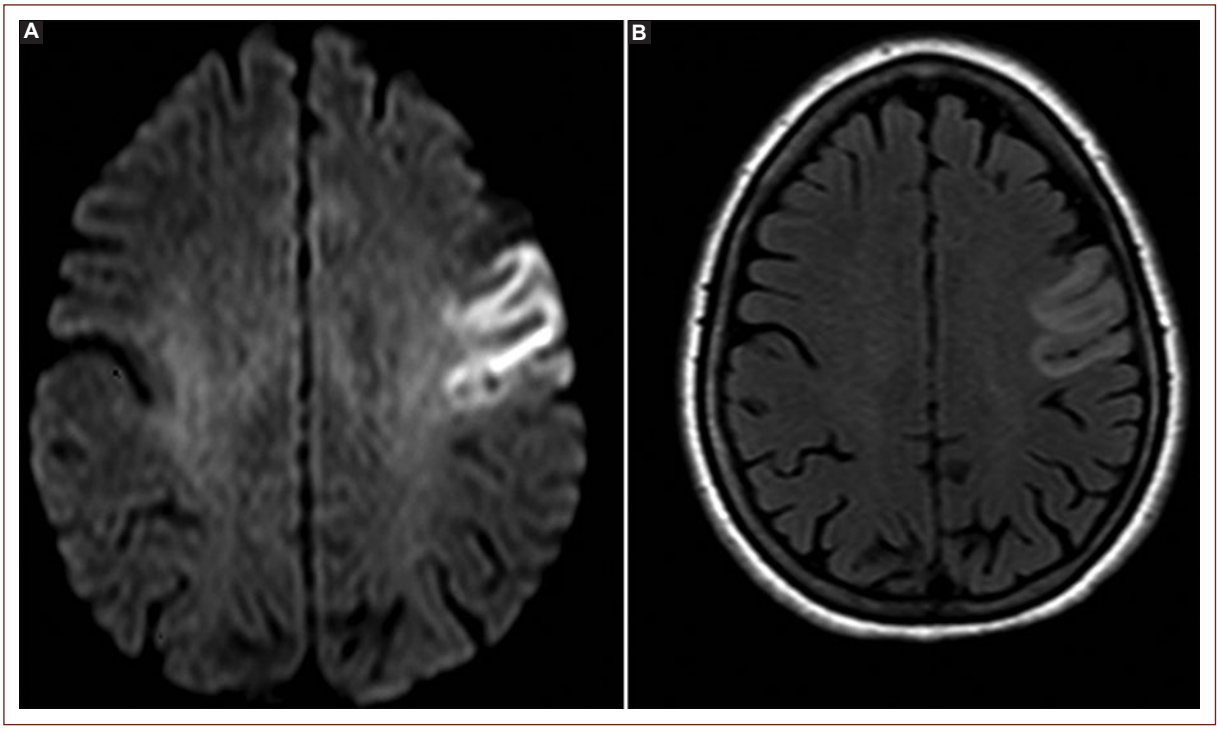

Figure 2. Diffusion-weighted image **(A)** shows diffusion restriction in the left superior frontal gyrus. Fluid-attenuated inversion recovery magnetic resonance imaging **(B)** confirms subacute infarction involving the left superior frontal gyrus.

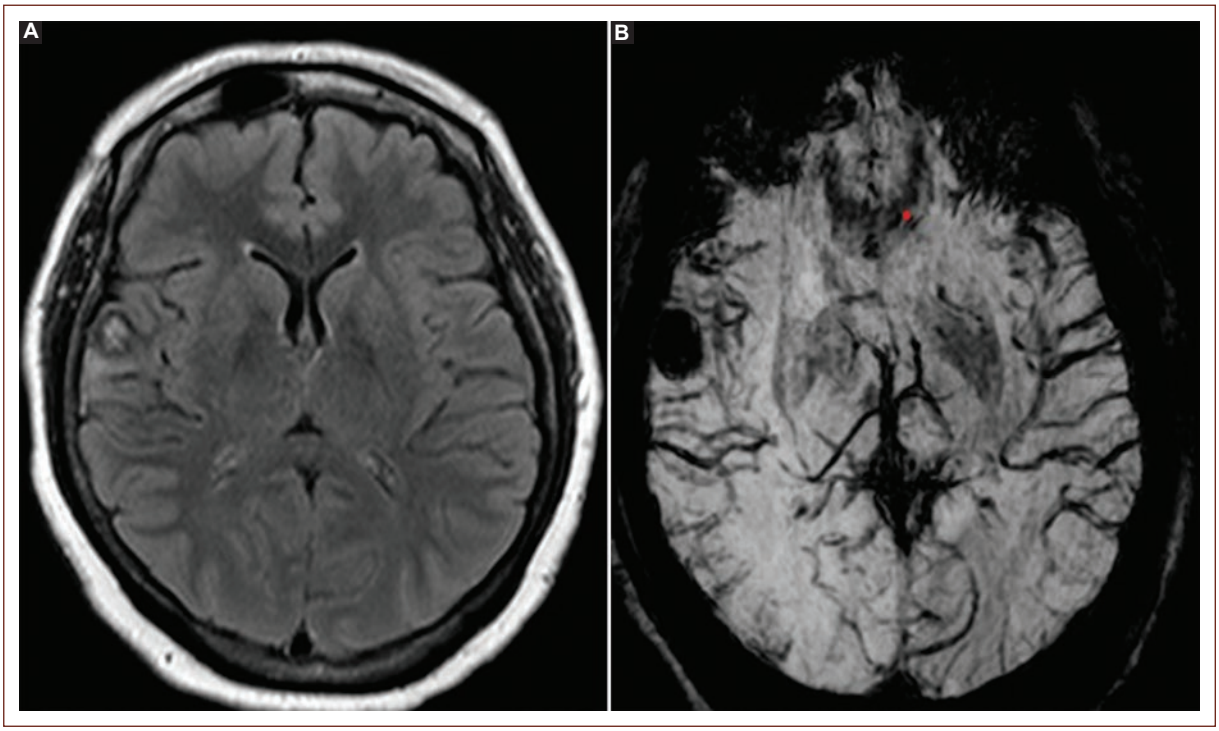

Figure 3. Fluid-attenuated inversion recovery magnetic resonance imaging (MRI) **(A)** shows a hypointense lesion with an isointense center (popcorn appearance) and perilesional edema in the right parietal operculum. Susceptibility-weighted angiography MRI **(B)** reveals a hypointense lesion in the right parietal operculum.

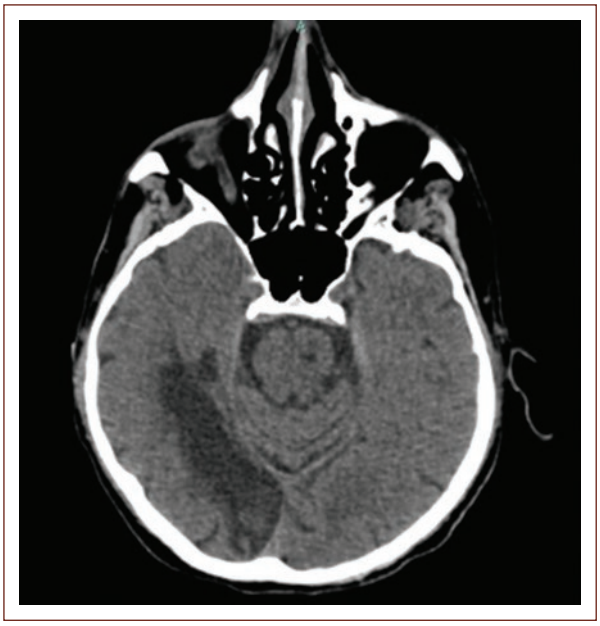

Figure 4. Brain computed tomography shows a hypointense lesion in the right temporo-occipital gyrus.

hemorrhagic intracerebral hemorrhage[23], venous sinus thrombosis[24], and ischemic stroke[25,26]. One of the limitations of these studies is that all were one patient-case reports; therefore, further studies should be conducted to confirm these findings. Other therapies used for SIEPC include fosphenytoin and clobazam[27]. The dose of ASMs could also impact the patient's outcome; in our series, we used either a dose of 1 g of levetiracetam every 12 h or 2 g every 12 h, similar to the doses used by Brigo et al[26]. and Haase et al[28]. Unfortunately, other case reports of SIEPC do not specify dosing.

In our case series, SIEPC secondary to ischemic stroke required more than two ASMs to archive clinical response, contrary, SIEPC secondary to ICH only required two ASMs to archive seizure resolution. Previously, Haase et al. showed similar results of seizure resolution of SIEPC secondary to ICH with the use of levetiracetam[23].

Timing between seizure onset and treatment administration could also impact the clinical response of the patients since previous studies have shown that delayed treatment is related to longer duration of the episodes[28]. This could be explained by the greater momentum gained with the longer duration of the episodes[6]. Hyperglycemia may also contribute to worse clinical outcomes[28,29]. However, more studies should be conducted to confirm this hypothesis.

Our study has strengths and limitations. We acknowledge that it was a single-center retrospective design, and the small sample size may be a substantial limitation of our study. As an in-hospital consultation department, most patients are admitted to the geriatric or internal medicine ward. Patients with subtle clinical manifestations in other departments may be unrecognized.

Stroke is a prevalent neurological disorder in in-hospital admissions, and this complication must be correctly identified. Our study includes many screened patients with epilepsy or stroke. All patients were treated directly by us, and we were directly involved in the diagnosis and treatment. In this study, the frequency of SIEPC was low. However, cerebrovascular disease is a common cause of hospital admission, making this disorder clinically relevant. The lack of diagnostic criteria and treatment protocols for SIEPC is striking.

Conclusion

Stroke-induced epilepsia partialis continua is rare. However, given the high prevalence of stroke as a common cause for hospital admissions, it is essential for practicing physicians to be aware of this condition. This study draws attention to this distinct clinical entity with variable presentation, diagnosis, treatment, and prognostic issues. We need a precise diagnostic strategy for this patient population, and more studies are required to guide adequate management.

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The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

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

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ORIGINAL ARTICLE

Location and morphology of cortical lesions in multiple sclerosis

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Abstract

Objective: *Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system. Diagnosis is based on the Mc-Donalds criteria, magnetic resonance imaging (MRI) studies, and the expanded disability status scale (EDSS) which assesses disease progression. These criteria do not include the recently described cortical lesions. The aim of the study was to describe the most frequent location and morphology of cortical lesions in patients with MS in Puebla, Mexico.* **Methods:** *A descriptive, retrospective, cross-sectional, and analytical study was conducted on patients with MS at a tertiary care hospital. Patients diagnosed with relapsing-remitting, secondary-progressive, and progressive-relapsing MS variants with cranial magnetic resonance imaging were included in the study. Age, sex, MS variant, EDSS score, cognitive impairment, annual relapse rate, morphology, location, and number of cortical lesions were evaluated. Descriptive statistics were used. To compare features between groups, the χ^2 test was used, and for correlations, the Spearman's Correlation Coefficient was used. A $p \leq 0.05$ was considered significant.* **Results:** *Twenty-five patients met the selection criteria. The most frequent location of cortical lesions was the parietal region 84%, and the second was the temporal region 16%. The most common morphology was juxtacortical at 64% and mixed at 36%. The most frequent variant of MS was relapsing-remitting, present in 92%, and 8% had the secondary progressive variant. In the EDSS scale, the scores most frequently observed were 0.0 and 3.5.* **Conclusions:** *The most frequent location of cortical lesions was in the parietal region, and the most common morphology was juxtacortical.*

Keywords: *Multiple sclerosis. Cortical lesions. Neurology. Magnetic resonance imaging.*

Localización y morfología de las lesiones corticales en la esclerosis multiple

Resumen

Objetivo: *La esclerosis múltiple es una enfermedad desmielinizante inflamatoria crónica del sistema nervioso central. El diagnóstico se basa en los criterios de Mc-Donalds, los estudios de Resonancia Magnética y la Escala Expandida del Estado de Discapacidad (EDSS) que evalúa la progresión de la enfermedad. Estos criterios no incluyen las lesiones corticales descritas recientemente. Describir la localización y morfología más frecuente de lesiones corticales en pacientes con esclerosis múltiple en Puebla, México.* **Métodos:** *Se realizó un estudio descriptivo, retrospectivo, transversal y analítico en pacientes con esclerosis múltiple en un hospital de tercer nivel de atención. Se incluyeron pacientes con diagnóstico de Esclerosis*

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Múltiple con variantes Remitente-Recurrente, Secundaria-Progresiva y Progresiva-Recurrente con resonancia magnética de cráneo. Se evaluó edad, sexo, variante de esclerosis múltiple, puntaje de EDSS, deterioro cognitivo, tasa de recaída anual, morfología, ubicación y numero de lesiones corticales. Se utilizó estadística descriptiva. Para comparar características entre grupos se utilizó χ^2, para correlaciones se utilizó Coeficiente de Correlación de Spearman. Una $p \leq 0.05$ se consideró significativa. **Resultados:** *25 pacientes cumplieron con criterios de selección. La localización más frecuente de lesiones corticales fue la región parietal 84% y la segunda temporal 16%. La morfología más frecuente fue la yuxtacortical en un 64%, y la mixta en 36%. La variante más frecuente de esclerosis múltiple fue Remitente-Recurrente presente en 92%, y 8% la variante Secundaria Progresiva. En la escala de EDDS la puntuación con mayor frecuencia fue 0.0 y 3.5.* **Conclusiones:** *La localización más frecuente de las lesiones corticales fue en región parietal y la morfología más frecuente la yuxtacortical.*

Palabras clave: *Esclerosis múltiple. Lesiones corticales. Neurología. Resonancia magnética.*

Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system. It is most common in adults and affects more than two million people worldwide. It follows a variable progression, leading to disability and high costs for healthcare systems[1,2]. Diagnosis is based on the Mc-Donalds criteria, the expanded disability status scale (EDSS) which assesses disease progression and magnetic resonance imaging (MRI). MRI plays an important role in clinical practice by enabling accurate diagnosis. It helps to understand the evolution of the disease and to evaluate treatments by monitoring response to treatment[3-5]. All of this is based on the McDonald criteria, but until now, these criteria have not included the cortical lesions that have been recently described[6-9].

Cortical lesions are more frequently observed in primary and secondary progressive forms, affecting the cerebral and cerebellar cortex, particularly in the hippocampus and cerebellum[10,11]. They are less common in acute and remitting forms but tend to be larger in size. Considered an additional pathological substrate, they contribute to cognitive decline in these patients. Cortical lesions are significant in the neurodegenerative phase of recurring variants[2,12,13]. Magnetic resonance imaging assessment of cortical lesions in MS patients improves disease monitoring and diagnosis and enables precise treatment targeting by providing a detailed understanding of lesion location and morphology[7,12,14-16].

The purpose of this study was to provide a description of the most common location and morphology of cortical lesions among MS patients receiving treatment at a tertiary care hospital at Puebla, Mexico.

Materials and methods

A retrospective, descriptive study was conducted on patients with MS who received treatment at a tertiary care hospital of the Mexican Social Security Institute (IMSS). Patients diagnosed with relapsing-remitting, secondary-progressive, and progressive-relapsing MS by cranial magnetic resonance imaging were included in the study.

The McDonald criteria are used by neurologists to make a diagnosis of MS[9,13]. Based on the current classification of progressive, non-progressive, activity-including, and activity-excluding variants, patients meeting the operational definitions outlined below were included in the study[13,17].

The MS subtypes were defined as:

- Relapsing-remitting: Clearly defined episodes of new or increasing neurological symptoms, such as vision problems, vertigo, generalized weakness, ataxia, and loss of bladder control, are followed by periods of recovery or remission[13,17].
- Secondary-progressive: characterized by evidence of disability accumulation over time, with or without relapses or new activity observed in MRI images[13,17].
- Progressive-relapsing: Deterioration in neurological function or accumulation of disability from the onset of symptoms, with initial periods of relapse and/or remission[13,17].

Procedure

The diagnosis of the subtype of MS was provided by the neurology service, in addition, age, sex, EDSS score, and annual relapse rate were evaluated, which were data collected during outpatient visits; the Montreal Cognitive Assessment (MOCA) was used to evaluate cognitive impairment, taking < 26 points as cognitive impairment, according to the recommendations of the MACFIMS consensus[18].

The morphology, location, and number of cortical lesions were taken from the final report of the radiodiagnostic and imaging service.

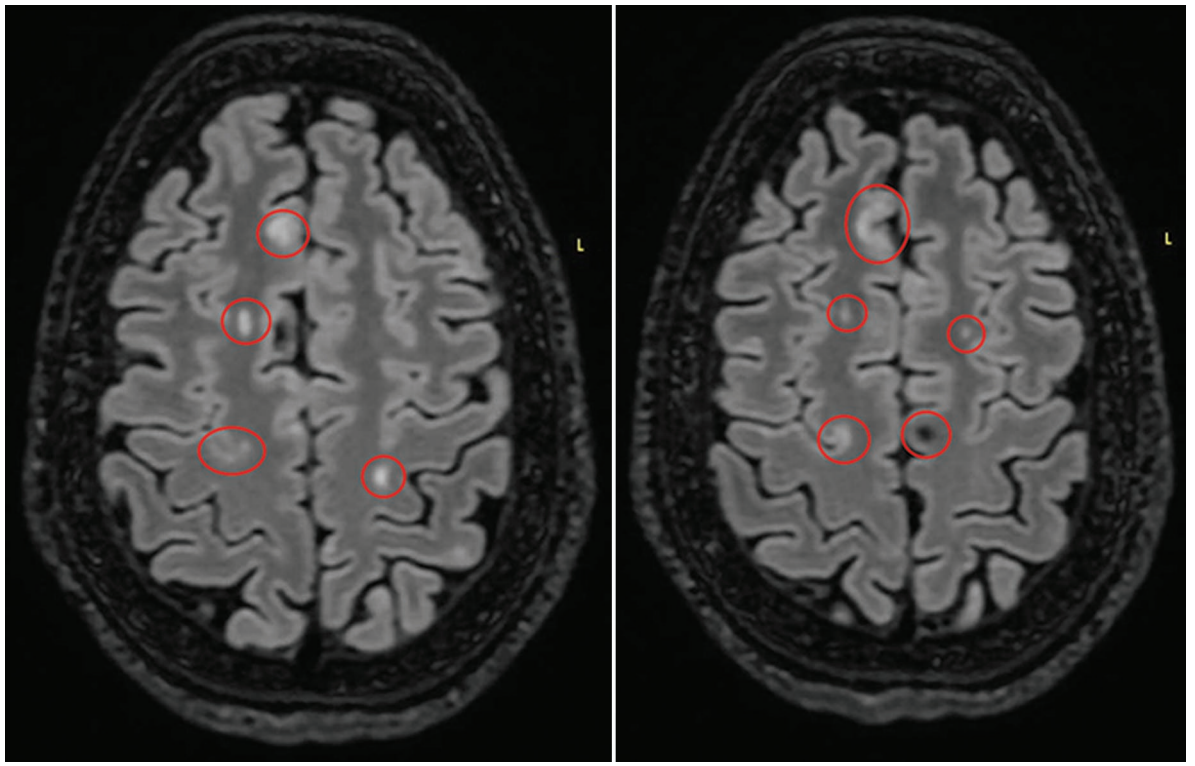

Figure 1. Fluid attenuated inversion recovery enhanced sequence, axial plane, subcortical, and juxtacortical frontoparietal demyelinating plaques.

Statistical analysis

Data analysis was conducted using descriptive statistics. The χ^2 test was used to compare features between groups of cortical lesions and morphology. Spearman's test was employed for correlations. A p-value of ≤ 0.05 was deemed significant.

Ethical aspects

The Local Health Research Committee No. 2101 of the IMSS has approved this study. All participants signed an informed consent chart, and their anonymity was preserved throughout the study. The data were utilized solely for scientific purposes and for this study.

Results

A total of 25 patients were included, 10 (40%) were men and 15 (60%) were women.

The most common MS subtype was relapsing-remitting, found in 23 (92%) patients, while secondary-progressive was less common, found in 2 (8%) patients. Cognitive impairment was observed in only 5 (20%) patients.

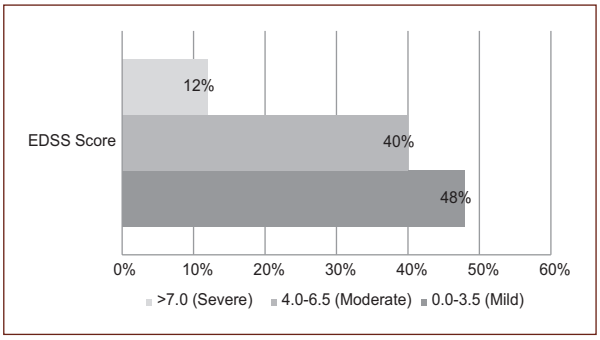

Figure 2. Disability in patients with multiple sclerosis (expanded disability status scale scale score) (n = 25).

The most common location of cortical lesions was the parietal region (Fig. 1), found in 21 (84%) cases, followed by the temporal location, found in 4 (16%) cases.

The most common morphology was juxtacortical (Fig. 1), found in 64%, and mixed, found in 36%. On the EDSS scale, the most frequently observed scores were 0.0 and 3.5 (Fig. 2). According to the number of cortical lesions, 4-6 (48%) were the most common (Fig. 3).

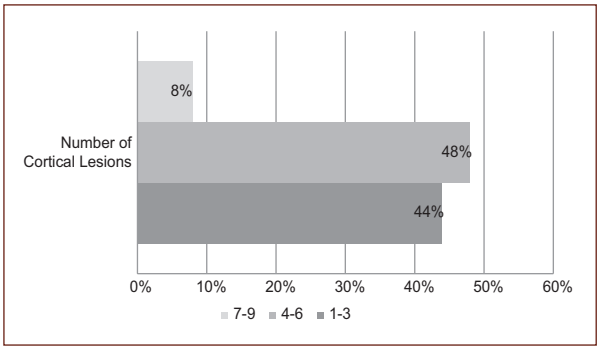

Figure 3. Number of cortical lesions in multiple sclerosis (n = 25).

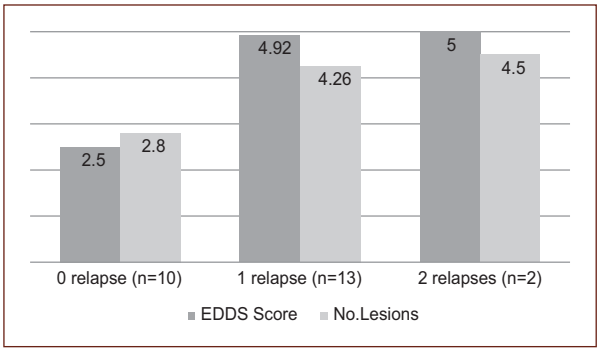

Figure 4. Distribution of number of lesions and disability (expanded disability status scale score) by number of relapses in patients with multiple sclerosis ($p < 0.0001$).

The predominant number of relapses was 1 (52%), followed by 0 relapses 40%, the correlation of the number of lesions with relapses and with EDSS was 0.58 ($p = 0.02$) and 0.678 ($p < 0.0001$), respectively. The association between lesion count and EDSS score showed statistically significant differences. (Fig. 4)

Cognitive impairment was more prevalent in women with 80% (n = 4) compared to men with 20% (n = 1) ($p = 0.6$).

The number of lesions and cognitive impairment did not showed a significative correlation, with an asymptotic Pearson Chi-squared value of 0.464 and a likelihood ratio of 0.391.

The association of lesion morphology with the EDSS scale did not show a correlation, with an asymptotic likelihood ratio of 0.112 and a Chi-squared of 0.311.

Discussion

The predominance of the variable sex, age, and type of MS is consistent with previous reports in the Mexican population[15].

It is noteworthy that the percentage of cognitive impairment does not agree with previously reported studies, in our study, it was only present in 20%, while in others, it is variable (40-70% and 42-52.5%)[19,20].

Cognitive impairment does not correlate with physical disability and can be present in early stages of the disease. The most frequently affected areas are information processing speed, working memory, visual and verbal memory, verbal fluency, learning, word retrieval, and executive functions[18,20]. Because a neuropsychological evaluation was not conducted to assess a baseline state of cognitive impairment or any previously established alterations in mental functions, these aspects remain unclarified[19,21].

The predominance in our study of the MS subtype was relapsing-remitting, having concordance with other previous imaging and histopathology studies[22,23].

The average number of lesions is relatively higher in our study (4.01) compared to the population of Harrison et al. (3.38)[24]. However, both coincide closely in the intrinsic gradual relationship with the presence of high EDSS scores. The greater the number of lesions, the higher the EDSS score.

Pareto et al. describe only the relationship of the presence of juxtacortical lesions in patients with relapsing remitting MS describing that there is cortical thinning and loss of subcortical gray matter[25].

This study complements the previous line of research by also describing the location and making correlations with other variables, finding that the most common morphology was juxtacortical lesions and the most common location was the parietal region. These findings cannot be compared because there is no existing literature that reports the morphology and location of lesions by brain lobe, making this the first studies of its kind in Mexico[26].

It was observed that the number of lesions was associated with the number of relapses, and in turn, if the patient presented one or more relapses, was associated with intermediate EDSS scores (both $p < 0.001$). This finding may be due to the small sample size. It is already known from previous literature that these variables are not always directly proportional[21,26,27].

Aldrete et al suggest that the number of lesions is associated with greater cognitive impairment; their study was also in Mexican population. In this study, no association was found between the number of lesions and cognitive impairment or between lesion morphology and EDSS scale. Several factors, including biological, medical, and psychosocial factors, may contribute to cognitive impairment in MS. These findings need to be investigated in future studies with larger sample sizes[21].

The use of high detail resonators is recommended for the identification of more cortical lesions, for this study, 3-T MRI was used[28].

Perhaps multicenter studies are needed to increase the sample size. This would allow us to draw conclusions. There is also a need for further monitoring of this research topic to identify areas for better utilization in both clinical and diagnostic settings.

Conclusions

The most common location of cortical lesions in MS was in the parietal region, and the most common morphology is juxtacortical. Studies with larger sample sizes are needed to improve the diagnosis, treatment, and prognosis of patients with MS.

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The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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 they have followed the protocols of their work center on the publication of patient data.

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.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

Parkinson's disease-associated pain in a Mexican Institute

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Abstract

Objective: *Parkinson's disease (PD) presents as a chronic condition with symptoms that worsen over time. Many PD patients experience pain at some point during their illness.This complaint is often overlooked because PD is primarily a motor disorder. The main objective is to assess the prevalence and the most frequent type of pain in this population, as well as its relation to common neuropsychiatric factors.* **Methods:** *A cross-sectional study was conducted including 196 patients diagnosed with PD. The variables analyzed included age, gender, smoking, alcohol consumption, anxiety, depression, antiparkinsonian treatment (levodopa, dopaminergic agonists, monoamine oxidase inhibitors, and amantadine), intake of antidepressants or antipsychotics, age of symptom onset, age of diagnosis, years of progression, total MDS-UPDRS 3.3 score, total MDS-UPDRS score, MDS-non-motor symptom scores, Hamilton depression and anxiety scales, and montreal Cognitive Assessment.* **Results:** *Our patient cohort consisted of 115 males (58.7%) and 81 females (41.3%), with a mean age of 63.56 ± 11.88. The mean disease duration was 7.18 ± 4.9 years. The most common type of pain was musculoskeletal pain, present in 66.7%, followed by radicular pain (24.2%), pain related to fluctuations (22.7%), chronic pain (20.7%), nocturnal pain (17.2%), discoloration, edema, or swollen pain (14.6%), and orofacial pain (5.6%).* **Conclusions:** *From the study carried out, it can be observed that the most common type of pain was musculoskeletal pain, followed by radicular pain. Pain patients had a significant association with depression and anxiety due to the intensity of pain.*

Keywords: *Parkinson's disease. Pain. Depression.*

Dolor asociado a la enfermedad de Parkinson en un Instituto Mexicano

Resumen

Objetivo: *La enfermedad de Parkinson (EP) se presenta como una enfermedad crónica con síntomas que empeoran con el tiempo. Muchos pacientes con EP experimentan dolor en algún momento de su enfermedad. Esta dolencia a menudo se pasa por alto porque la EP es principalmente un trastorno motor. El objetivo principal es evaluar la prevalencia y el tipo más frecuente de dolor en esta población, así como su relación con factores neuropsiquiátricos comunes.* **Métodos:** *Se realizó un estudio transversal que incluyó 196 pacientes diagnosticados de enfermedad de Parkinson. Las variables analizadas incluyeron edad, sexo, tabaquismo, consumo de alcohol, ansiedad, depresión, tratamiento antiparkinsoniano (levodopa, agonistas dopaminérgicos, inhibidores de la MAO, amantadina), ingesta de antidepresivos o antipsicóticos, edad*

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de inicio de los síntomas, edad de diagnóstico, años de evolución, puntuación total MDS-UPDRS 3.3, puntuación total MDS-UPDRS, puntuaciones MDS-NMS, escalas de depresión y ansiedad de Hamilton y MoCA. **Resultados:** *Nuestra cohorte de pacientes estaba formada por 115 varones (58.7%) y 81 mujeres (41.3%), con una edad media de 63.56 ± 11.88 años. La duración media de la enfermedad fue de 7.18 ± 4.9 años. El tipo de dolor más frecuente fue el musculoesquelético, presente en el 66,7%, seguido del dolor radicular (24.2%), el dolor relacionado con fluctuaciones (22.7%), el dolor crónico (20.7%), el dolor nocturno (17.2%), el dolor por decoloración, edema o hinchazón (14.6%) y el dolor orofacial (5.6%).* **Conclusiones:** *Del estudio realizado se observa que el tipo de dolor más frecuente fue el musculoesquelético, seguido del radicular. Los pacientes con dolor presentaron una asociación significativa con depresión y ansiedad debido a la intensidad del dolor.*

Palabras clave: *Enfermedad de Parkinson. Dolor. Depresión.*

Introduction

Parkinson's disease (PD) presents as a chronic, long-lasting, irreversible condition with symptoms that worsen over time[1]. PD is usually considered a motor disease; less known and explored are the non-motor symptoms (NMS). These are various and arise in part due to the accumulation of Lewy bodies in regions of the nervous system distinct from the substantia nigra, which can occur even before their detection in the substantia nigra. This explains the occurrence of some non-motor manifestations before the onset of cardinal disease symptoms[2]. In this context, pain is considered a non-motor symptom.

Many PD patients experience pain at some point during their illness. This complaint is often overlooked because PD is primarily considered a motor disorder. However, for a minority of patients, pain and discomfort can be so debilitating that they dominate the clinical picture[1]. It is estimated that approximately 10% of individuals have pain as an initial symptom preceding any movement disorder. Furthermore, recently published data suggest that up to 50% of patients experience painful sensations during the course of the disease[3].

Pain in PD is often a result of inadequate dopaminergic therapy. Individuals with PD in the "on" state, when the medication is at its maximum effectiveness, report less pain than those in the "off" state[1]. Individuals with pain and PD exhibit higher scores on depression assessment scales. Therefore, it is important that any assessment of pain in an individual with PD takes into account the possibility of depression contributing to the experience. Another factor to consider is cognitive disorders, which can influence the patient's perception of pain[3].

The objective of this study is to determine the prevalence and the most frequent type of pain, as well as its relation to different motor and neuropsychiatric symptoms.

Materials and methods

A cross-sectional study was conducted involving 196 patients diagnosed with PD according to the MDS criteria[4] seen at the Movement Disorders Clinic of the National Institute of Neurology and Neurosurgery. A structured questionnaire was administered to all participants after giving informed consent. Data collection spanned from 2021 to 2023, involving expert-led directed interviews during outpatient visits. The variables collected included age, gender, smoking habits, alcohol consumption, anxiety, depression, antiparkinsonian treatment (levodopa, dopaminergic agonists, monoamine oxidase [MAO] inhibitors, and amantadine), intake of antidepressants or antipsychotics, age at symptom onset, age at diagnosis, disease duration, MDS-Unified PD Rating Scale (MDS-UPDRS) item 3.3 score (rigidity item)[5], and total MDS-UPDRS score[6], where scores were assigned as follows: 0: Never, 1: Rarely (≤ 10% of the time), 2: Sometimes (11–25% of the time), 3: Frequently (26–50% of the time), and 4: Most of the time (≥ 51% of the time).

The MDS-UPDRS consists of four parts, namely I: Non-motor experiences of daily living; II: Motor experiences of daily living; III: Motor examination; IV. Each question is based on five responses that are linked to commonly accepted clinical terms: 0 = normal, 1 = mild, 2 = mild, 3 = moderate, and 4 = severe. The full MDS-UPDRS contains questions/assessments, divided into Part I (13), Part II (13), Part III (33 scores based on 18 items, several with right, left, or other body distribution scores), and Part IV (6). The MDS-UPDRS scores 65 items compared to 55 in the original UPDRS, 48 that had 0-4 options and 7 with yes/no responses.

The MDS Non-Motor Rating Scale (MDS-NMS) L1, 2, 3, and 4 scores (pain-related items)[7] were also applied; scores were assigned as follows: L1: muscular, joint, or back pain; L2: deep or dull pain; L3: pain due to abnormal twisting movements of arms, legs, or body; L4: other types of pain (e.g., nocturnal pain and orofacial pain).

The MDS-NMS instrument consists of 30 questions with dichotomous responses, items are grouped into nine domains: Gastrointestinal, urinary tract, sexual function, cardiovascular, apathy/attention/memory, hallucinations/delusions, depression/anxiety/anhedonia, sleep/fatigue, pain, and miscellaneous[7].

In addition, the following assessments were performed: QUICK questionnaire 18[8] for pain presence or improvement after medication dose, Montreal Cognitive Assessment (MOCA)[9], Hamilton Depression Scale, Hamilton Anxiety Scale (HAS), King's Parkinson's Disease Pain Scale (KPPS), MDS-UPDRS 4.3 (time in off, and MDS-UPDRS 4.6 (on-dystonia).

Regarding the HAD scale[10], scores were assigned as follows: 0-7 points: Normal, 8-13 points: Mild depression, 14-18 points: Moderate depression, 19-22 points: Severe depression, ≥ 23 points: Very severe depression.

For the HAS[11], the scores were as follows – 0-17 points: Mild anxiety, 18-24 points: Mild-to-moderate anxiety, 25-30 points: Moderate-to-severe anxiety, and 31-56 points: Very severe anxiety. For the Hamilton Depression and Anxiety scales, obtained scores were classified as follows: Scores < 8 as normal, scores < 14 as mild depression, scores < 19 as moderate depression, scores < 23 as severe depression, and scores > 23 as very severe depression. Similarly, for the anxiety scale, scores < 18 were categorized as mild anxiety, scores < 25 as mild-moderate anxiety, scores < 31 as moderate-severe anxiety, and scores < 57 as very severe anxiety. MOCA questionnaire scores were divided into < 26 for probable mild cognitive impairment and < 16 for probable severe impairment.

The Levodopa Equivalent Dose (LED) was calculated using the formula: (dose in mg of L-dopa × 1) (dose in mg of L-dopa × 0.33 (entacapone) or 0.5 (tolcapone or opicapone) to obtain the COMT inhibitor LED)) + (dose in mg of controlled-release L-dopa × 0.75) + (dose in mg of extended-release L-dopa × 0.5) + (dose in mg of pergolide × 100) + (dose in mg of cabergoline × 66) + (dose in mg of cabergoline × 66) + (dose in mg of cabergoline × 66) + (dose in mg of cabergoline × 66) + (dose in mg of cabergoline × 66. mg of cabergoline × 66. 77) + (dose in mg of bromocriptine × 10) + (dose in mg of pramipexole × 100) + (dose in mg of ropinirole × 20) + (dose in mg of lisuride × 100) + (dose in mg of dihydroergocryptine × 5) + (dose in mg of lisuride × 100) + (dose in mg of dihydroergocryptine × 5) + (dose in mg of bromocriptine × 5) × 5) + (mg dose of oral selegiline × 10 or sublingual × 80) + (mg dose of rasagiline × 100) +(mg dose of subcutaneous apomorphine × 10 or sublingual apomorphine × 1. 5) + (dose in mg rotigotine × 30) + (dose in mg rotigotine × 30)(dose in mg of piribedil × 1) + (dose in mg of amantadine immediate release × 1 or prolonged release × 1.25) = L-dopa daily dose equivalents[12].

The KPPS[13] is an evaluator-based scale that assesses pain in PD patients through an interview. It consists of 14 items divided into seven separate domains. Each item is scored for severity (from 0 [no pain] to 3 [very intense pain]) multiplied by frequency (from 0 [never] to 4 [all the time]), resulting in sub-scores ranging from 0 to 12. The sum of these sub-scores gives the total score with a theoretical range of 0-168. The domains and score ranges are as follows: (1) Musculoskeletal pain (range, 0-12); (2) chronic pain (range, 0-24); (3) fluctuation-related pain (range, 0-36); (4) nocturnal pain (range, 0-24); (5) orofacial pain (range, 0–36); (6) discoloration, edema/swelling (range, 0-24); and (7) radicular pain (range, 0-12)[14].

Statistical analysis

Patients were categorized according to the MDS-UPDRS item 1.9 (pain)[6], patients with pain (Group 1) and non-pain (Group 2). Normality testing was conducted using the Shapiro–Wilk test, resulting in a non-normal distribution. The categorical variables included smoking, alcohol consumption, current treatment, intake of antipsychotics or antidepressants, and self-perceived anxiety or depression, categorized with values of 0 (absence) or 1 (presence). The continuous variables encompass age of onset, age of diagnosis, years of progression, equivalent dose per medication group, equivalent dose of medications per day, NMS-UPDRS total, and NMS-UPDRS 3.3 total.

For the nominal variables, the Chi-squared test was used, and for continuous variables, the T-test or Mann–Whitney U test was used as needed. The statistical analyses were conducted using SPSS software. Statistical significance was set at $p < 0.05$.

Results

The final sample consisted of 115 males (58.7%) and 81 females (41.3%), with a mean age of 63.56 ± 11.88. The mean disease duration was 7.18 ± 4.9 years. All patients were receiving antiparkinsonian treatment, with 184 on levodopa, 27 on MAO inhibitors, 91 on dopaminergic agonists, and 26 on amantadine (Table 1). Regarding the intake of antidepressants or anxiolytics, 13 were taking anxiolytics and 56 were taking antidepressants.

Upon conducting the analysis, the following observations were made: Regarding the group of 139 patients with pain, 83 were male and 56 were female (p = 0.645). Group G1 had 92 patients with negative smoking status and 47 with positive smoking status, whereas G2 had 47 with negative smoking status and 10 with positive smoking status (p = 0.23). Positive alcohol consumption was observed in 13 patients and negative in 44 for G2 and 90 were negative with 49 positive for G1 (p = 0.89).

For the self-perceived anxiety variable, we found that in G1, 78 did not have anxiety and 61 did (p = 0.364). On the anxiety scale, for G1, 125 had mild anxiety, 10 had mild-moderate anxiety, and four had moderate-severe anxiety. For G2, 55 had mild anxiety, two had mild-moderate anxiety, and none had moderate-severe anxiety (p = 0.25).

In the self-perceived depression variable, we noted that 79 patients in G1 did not present anxiety and 60 did, whereas in G2, there were 20 patients with anxiety and 37 without it (p = 0.296). In the analysis of the depression scale, for G1, 59 had no depression, 61 had mild depression, 10 had moderate, five had severe, and four had very severe. In G2, 38 had no depression, 15 had mild, four had moderate, and no patient had severe or very severe depression (p = 0.20).

Regarding the analysis of the MOCA questionnaire score, for G1, 29 patients had no impairment, 90 had a mild impairment, and 20 had severe impairment. In G2, 15 had no impairment, 37 had mild impairment, and 5 had severe impairment (p = 0.464).

When performing the analysis of the MDS-UPDRS variable on dystonia and time off, no association was found between groups, detailed information is shown in Table 2. Out of the 139 patients who reported self-perceived pain at the time of the QUICK 18 questionnaire, 83 confirmed again that they were experiencing fluctuating pain. Regarding the improvement in pain with doses of medication, it was found that 55 patients mentioned improvement.

In the MDS-NMS variable L, the most frequently self-perceived types of pain reported by the patients were muscular/joint pain (p < 0.001) and deep/dull pain in the body (p < 0.001).

To compare the total score of the different scales between the groups, we used the Student's t-test where we obtained a significant relationship between depression, anxiety, and the presence of pain. More information is shown in Table 3.

The mean KPPS score was 8.62 ± 10.2. The most associated type of pain in our population was musculoskeletal pain, present in 66.7% of the population, followed by radicular pain (24.2%), pain related to

Table 1. Description of the type of drug in the sample

Medication type		G1 (n = 139)	G2 (n = 57)	p-value
Levodopa	Levodopa/ Carbidopa Levodopa/ benserazida	124 7	48 5	0.565
MAOI	Rasagiline	20	7	0.697
Dopaminergic agonist	Bromocriptine Pramipexole Rotigotine	3 45 19	2 14 8	0.805
Amantadine	Amantadine	21	5	0.235

G1: Parkinson's disease and pain; G2: Parkinson's disease with no pain; MAOI: Monoamine oxidase inhibitor.

Table 2. Comparison between groups about dystonia and time off

Variable	G1 (n = 139)	G2 (n = 57)	p-value
Dystonia			
No dystonia	126	52	0.316
Minimum	3	4	
Mild	5	2	
Moderate	4	0	
Serious	1	0	
Off time			
No periods	99	39	0.843
< 25%	22	10	
26-50%	12	4	
51-75%	6	4	

G1: Parkinson's disease and pain; G2: Parkinson's disease with no pain.

Table 3. Comparison of scales applied between groups

Variable	GROUP 1 (n = 139)		GROUP 2 (n = 57)		p-value
	Mean	SD	Mean	SD	
MDS-UPDRS 3.3	34.17	14.67	32.40	15.51	0.452
MDS-UPDRS TOTAL	61.08	25.69	57.82	28.41	0.436
MOCA	20.88	5.72	21.77	4.66	0.297
HAD	9.37	5.69	5.77	4.75	0.000
HAS	9.36	6.04	6.02	4.89	0.000

MDS-UPDRS: MDS-Unified Parkinson's Disease Rating Scale; MOCA: Montreal cognitive assessment; HAD: Hamilton depression scale; HAS: Hamilton anxiety scale; G1: Parkinson's disease and pain; G2: Parkinson's disease with no pain.

fluctuations (22.7%), chronic pain (20.7%), nocturnal pain (17.2%), discoloration, edema, or swollen pain (14.6%), and orofacial pain (5.6%).

The correlation coefficients for KPPS: Bivariate correlation of the total scores of the KPPS scale and anxiety yielded a Pearson correlation coefficient of 0.320, indicating a moderate correlation (p = 0.000). Similarly, when compared to the depression scale, the Pearson correlation coefficient was 0.381, also indicating a moderate correlation (p = 0.000).

Discussion

The mechanisms underlying pain in PD are unclear. Although some studies have reported that PD patients may have a low pain threshold and tolerance and that they tend to decrease as PD progresses, which may predispose to the development of pain, when we performed our analysis, there was no significant difference in the years of evolution[15]. Pain can occur at any time during the disease and may be present before diagnosis[16].

"KPPS" is a questionnaire with 14 questions covering seven domains: (1) Musculoskeletal pain; (2) chronic pain; (3) pain related to fluctuation; (4) nocturnal pain; (5) orofacial pain; (6) discoloration and edema/swelling; and (7) radicular pain. This is a new approach to pain in PD, which will allow for more in-depth testing in clinical trials for treatments for this aspect of PD[17].

It has been observed that all motor symptoms fluctuate, presenting more severe symptoms in the "off" state than in the "on" state but at the time of our analysis, no relationship was found because the patients did not spend so much time in off, although they did report that they noticed an improvement in pain with their medication doses according to the analysis carried out[18].

According to several studies, as well as in our population, musculoskeletal pain has been reported to be the most prevalent due to in our population was present in 98 patients[19,20]. All types of pain were more prevalent in patients with PD in advanced stages than in early stages[21], Although in our population, pain in early stages was seen more frequently, this may be due to the fact that patients in advanced stages are often difficult to follow-up.

No association between dystonic or non-dystonic pain has been found in other studies, nor was any association found in this one[22]. The risk factors for pain in PD include early age of onset, comorbid depressive symptoms, and associated diseases[23], we did not take into account the associated diseases but we can see that in the age of our population is no association with early age but there is an association with depressive symptoms.

Although most studies report that pain related to PD is significantly more common in women than in men[24], some articles state the opposite[25], and this was observed in our study since it was more common in men and no association was found.

Pain patients had significantly more severe depressive symptoms than pain-free patients and pain intensity was associated with more severe depression[26], in our study also had an association with depression and anxiety. Some studies mention that as pain intensity increases, quality of life decreases significantly in PD patients[27].

Diagnosing the cause of pain requires skill and clinical experience. The most important diagnostic tool is the patient's medical history. Perhaps, the most crucial task for individuals with Parkinson's who experience pain is to describe with the utmost precision whether medications induce, exacerbate, or alleviate their pain[1].

The limitations of this study were the lack of information on whether the patient was taking any treatment for pain, the sample was not so large, and most of our patients were in the intermediate stages of the disease so we do not know how it presents in advanced stages, the variables of education or socioeconomic level were not included.

Conclusions

In recent years, nonmotor symptoms in PD have received increasing attention from physicians and researchers. Pain is a heterogeneous symptom in PD. Pain is affected by several factors, e.g., age, sex, depression, severity or duration of illness. Of the disease From the conducted study, it can be observed a significant association between depression and anxiety due to the intensity of pain. In our analysis we found musculoskeletal pain to be the most frequent as seen in the literature. Increased awareness of pain symptoms in PD would provide greater understanding. Further research is needed assessing patients in advanced stages of the disease, including socioeconomic status, pain management, to give a specific analysis that will help us in the majority of PD patients.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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 they have followed the protocols of their work center on the publication of patient data.

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.

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REVIEW ARTICLE

Migraine in pregnancy. A narrative review

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Abstract

Migraine is one of the most common types of headaches, affecting almost all group ages and both sexes. Nevertheless, it is known that migraine can modify its characteristics during pregnancy and that nearly 60-80% of pregnant women with migraine will suffer attacks, especially during the first trimester. In this narrative review, we describe critical aspects of this frequent neurological pathology during pregnancy and provide a reference hallmark to guide diagnosis and treatment.

Keywords: *Migraine. Pregnancy. Migraine treatment. Migraine drugs.*

Migraña en el embarazo. Revisión narrativa

Resumen

La migraña es uno de los tipos de dolores de cabeza más comunes y afecta a casi todos los grupos de edades y a ambos sexos. Sin embargo, se sabe que la migraña puede modificar sus características durante el embarazo y que cerca del 60-80% de las mujeres embarazadas con migraña sufrirán ataques, especialmente durante el primer trimestre. En esta revisión narrativa, describimos aspectos críticos de esta patología neurológica frecuente durante el embarazo y proporcionamos referencias para guiar el diagnóstico y el tratamiento.

Palabras clave: *Migraña. Embarazo. Tratamiento de la migraña. Medicamentos para la migraña.*

Introduction

The term migraine originates from the Greek word hemicranias, which means “half of the head”[1]. Nevertheless, there are historical recordings of headaches dating back nearly 600 years. In the 17th century, a migraine was called a “hypoglycemic headache,” and the term “chronic migraine was coined during the early 20th century”[2].

Definition

Migraine is a chronic brain disease with episodic manifestations that typically involve unilateral headache of throbbing or pulsating quality, associated with complex sensory disturbances such as photophobia and phonophobia and neurovegetative symptoms such as nausea or vomiting. Migraine can occur in episodic or chronic forms, with or without aura[1,3,4].

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An aura consists of focal neurological symptoms with positive and negative manifestations, most commonly visual disturbances. Approximately one-third of patients will report an associated aura with their migraine[5].

Epidemiology

Migraine accounts for 20% of all outpatient neurology consultations[6] and thus is considered the most common cause of disability worldwide[7,8]. Yearly, it affects one billion people worldwide[9].

Migraine has racial disparities in its incidence, being more common among Caucasians[1], in its episodic form, it affects nearly 12-18.5% of adult subjects. In contrast, chronic migraine affects ~2% of the general population[4], particularly those younger than 50[6]. There is also an apparent sex disparity among females in a proportion 1:2 or 1:3 (20.2% to 24.4% vs. 9.4%)[4,5,10], but only in adults, in young childhood, the prevalence of migraine are marginally higher in boys than in girls. In contrast, in pre-pubertal populations**,** prevalence is similar among both genders. However, after menarche, migraine prevalence increases in girls (6.4%) compared with males (4.0%)[11-13]. The disparity in the incidence of migraine between men and women seems to be related to the hormonal differences between sexes; specifically, estrogens and progesterone appear to play a pivotal role in producing the disease[14,15].

The incidence of migraine in women between 30 and 39 years (the central period of reproductive age) is 24%[16]. Migraine symptoms also vary due to other hormonal states, such as hormonal contraception, pregnancy, and menopause[16-18]. During the reproductive age, migraine prevalence becomes 3 times higher in women than men[12]. Then, after age 60, prevalence decreases in both sexes (5.0% women, 1.6% men)[6].

The pathophysiologic mechanism by which menstruation favors the susceptibility to migraine attacks is not well understood, but sudden decreases in estrogen serum levels appear to be implicated. Still, similar drops in circulating estrogen during ovulation do not seem to provoke migraine attacks[19].

Migraine in pregnancy

Nearly 60-80% of pregnant women with migraine will suffer attacks, which can be especially burdensome during the first trimester. After the first trimester has passed, about half of the patients will improve; by the last trimester, up to 80% will have improved[16,20].

Two possible explanations exist for migraine symptoms decreasing after the first trimester of pregnancy. One is the physiological increase in estrogen and endogenous opioid levels, and the other is the disappearance of sudden fluctuation in hormone levels, a factor that usually triggers attacks[16]. Estrogens modulate neuronal excitability by upregulating serotonin, norepinephrine, dopamine, and endorphin levels and downregulating the endothelial nitric oxide synthase.

MacGregor and Hackshaw demonstrated that migraine attacks are more frequent during the late luteal and early follicular phase of falling estrogen; in contrast, attacks are less frequent during the increase of estrogen. Therefore, increased levels of estrogen protect women against migraine attacks[21].

The phenotype of migraine might be modified in pregnant women[20]. One of the most common changes is aura development[22]. In a retrospective hospital-based study, 70% of women diagnosed with migraine with aura had no prior history of aura[20].

Migraine without aura improves more frequently than other types of migraine during the first trimester; partial improvement is seen in 46.8% and remission in 10.6%. During the second trimester, remission rates increase to 53.2%, and in the third semester, the remission rate reaches 78.7%[16]. Pregnant migraineurs with aura also experience improvement in their symptoms. However, it is not as crucial as in women without aura.

Diagnosis

If the diagnosis of migraine does not precede the pregnancy, the International Classification of Headache Disorders, 3rd edition (beta version) (ICHD-3 beta)[23] diagnostic criteria for migraine can be applied regardless of the pregnancy state[24]. However, excluding other causes of headache in this particular population is vital since, especially in low-income countries, pregnant women are at a heightened risk of cerebral venous thrombosis (CVT), pre-eclampsia/eclampsia and posterior reversible encephalopathy syndrome, among several grave secondary causes of headache[25].

Differential diagnosis

There are several conditions that, such as migraine, also increase its frequency during pregnancy. The most important include[26]:

Table 1. Doses and risk class of medications used in pregnant women with migraine

Drug	Dose	Risk category
Aspirin	325-650 mg, oral, or rectal q4h	First and second trimester: C Third trimester: D
Ibuprofen	400 mg tablets 400-800 mg q3h, oral; maximum dose: 2400 mg/day	First and second trimester: B Third trimester: D
Diclofenac	100-200 mg tablets 75 mg, q12h, and oral 50 mg, q8h, and oral 100 mg, q12h, and oral	First and second trimester: B Third trimester: D
Naproxen	500/825 mg, oral	First and second trimester: B Third trimester: D
Ketorolac	Oral: 2 tablets q6h Intramuscular: 60 mg/2 mL; repeat in 4 h if needed	First and second trimester: B Third trimester: D
Acetaminophen	500 mg tablets 1 or 2 tablets q4h, oral. Do not exceed more than eight tablets per day	B
Acetaminophen/aspirin/caffeine	Tablets contain 250 mg of aspirin, 65 mg of caffeine, and 250 mg of acetaminophen 1-2 tablets q3h, oral; do not exceed more than four tablets per day	A (caffeine dose ≤ 200 mg daily)
Sumatriptan	Intranasal: 10 mg-20 mg Oral: 25, 50, 100 mg Subcutaneous: 4, 6 mg Dose Intranasal: 40 mg/d Oral: 50 and 100 mg q2h; maximum 200 mg/d Subcutaneous: 4-6 mg q3h maximum dosing: twice daily	C
Eletriptan	20 and 30 mg tablets 40 mg q4h, oral	C
Rizatriptan	5 and 10 mg tablets 10 mg q4h, oral	C
Almotriptan	6.25 and 12.5 mg tablets 12.5 mg q4h, oral	C
Frovatriptan	2.5 mg tablets 2.5 mg q4h, oral	C
Naratriptan	1 and 2.5 mg tablets 1 tablet q3h, oral; maximum three doses per day	C
Zolmitriptan	2.5 or 5 mg tablets 5 mg, q3h, oral, as needed	C
Dihydroergotamine	1 mg intramuscular or intravenous 0.33 or 0.50ml on its first administration	X
Opioids	Oral or intramuscular These are limited per day and month	C
Metoclopramide	5-10 mg tablets Migraine and nausea without vomiting: 10 mg/8 h, oral	A
Ondansetron	4-8 mg tablets 8 mg q3h, oral	B
Dexamethasone	4 mg q8h, oral, as needed. Maximum 8 mg/day	D
Prednisone	20 mg q8h, oral, as needed. Maximum 40mg/day	C
Ergotamine	0,5-1 mg, q6h -12h, oral	X

(Continues)

Table 1. Doses and risk class of medications used in pregnant women with migraine *(continued)*

Drug	Dose	Risk category
Lasmiditan	50-100 mg, oral, per event	NA
Amitriptyline	10-25 mg up to 400mg, oral every bedtime	C
Imipramine	10-25 mg up to 400mg, oral every bedtime	D
Topiramate	Titrate over 4 weeks until effect. Week 1: 25 mg, oral every bedtime Week 2: 25 mg, oral q12h Week 3: 25 mg, oral in the morning and 50 mg oral every bedtime Week 4: 50 mg, oral q12h	D
Sodium Valproate	250 mg, oral q12h for 1 week May increase up to 1000 mg/day if needed	D
Propranolol	80 mg/day, oral, divided q6-8h; may be increased by 20-40 mg/day every 3-4 weeks; not to exceed 160-240 mg/day split q6-8h	C
Flunarizine	5-10 mg, oral every bedtime	NA
Onabotulinum toxin A	The recommended total dose is 155 units, as 0.1 mL (5 units) of intramuscular injections per site divided across seven head/neck muscles q12 weeks. Frontalis: 20 units divided into four sites Corrugator: 10 units divided into two sites Procerus: 5 units in 1 site Occipitalis: 30 units divided into six sites Temporalis: 40 units divided into eight sites Trapezius: 30 units divided into six sites Cervical paraspinal muscle group: 20 units divided into four sites	C
Erenumab	70 mg, subcutaneous once monthly OR 140 mg subcutaneous once monthly (administered as two consecutive 70-mg subcutaneous doses)	NA
Galcanezumab	Loading dose: 240 mg subcutaneous once (i.e., two consecutive 120 mg subcutaneous injections) Maintenance dose: 120 mg subcutaneous monthly	NA
Fremanezumab	225 mg subcutaneous once monthly OR 675 mg every 3 months, administered as three consecutive 225 mg subcutaneous doses	NA
Eptinezumab	100 mg intravenous every 3 months OR 300 mg intravenous dose every 3 months	NA
Lidocaine nerve block	Every 2 or 4 weeks	B

Idiopathic intracranial hypertension

It can appear during the first half of the pregnancy; its physiopathology is related to pregnancy-related weight gain. The headache is continuous, holo cranial, progressive, and aggravated by the Valsalva maneuver. Abnormalities in the neurological examination can include papilledema, visual disturbances, tinnitus, or paresis of the VI cranial nerve[27].

Pre-eclampsia and eclampsia

It commonly occurs after the 20th week 20 of pregnancy and during the puerperium. The headache is bilateral, pulsatile, and aggravated by physical activity. Its course is toward progressive deterioration without response to symptomatic treatment until the end of pregnancy. Additional clinical features include significant visual disturbances, seizures, and confusion[26].

Table 2. Pregnancy risk category definitions

A	Commonly acceptable. Controlled studies in pregnant women show no evidence of fetal risk.
B	It can be acceptable. Either animal or human studies demonstrated no harm, human studies are unavailable, or animal studies demonstrated minor risks.
C	Use with precaution only if the benefits outweigh the risks. Animal studies have demonstrated fetal risk, but human studies have not been available or demonstrated no risk.
D	Only use in cases where life is compromised. There is evidence of human fetal risk. The benefits may outweigh the risks.
X	Contraindicated, do not use in pregnancy. Use alternatives as risks outweigh benefits.

NA: information not available

Cerebral Venous Thrombosis

It can occur during any stage of pregnancy and puerperium. The headache is the most common presenting symptom. It tends to be paroxysmal, severe, and throbbing. It can be holocephalic or unilateral and have migraine-like features. Accompanying focal neurological symptoms include seizures, blurred vision, nausea, and vomiting[28].

Central nervous system tumors

Although intracranial tumors do not have a higher incidence during pregnancy, tumors such as pituitary adenomas and meningiomas may grow during pregnancy. Therefore, the clinical presentation of brain tumors during pregnancy tends to occur in the second half of the pregnancy. Although headache is a common presenting feature of brain tumors, it is rarely its only manifestation, and focal neurological complaints and symptoms of increased intracranial pressure, such as nocturnal headache, nausea, vomiting, and blurred vision, are almost universally present[29].

Treatment

Treatment for acute migraine should be tied to the severity of the headache. For mild-to-moderate headaches, treatment is initially based on first-line drugs. Paracetamol is safe during pregnancy. However, long-term use has been recently associated with hyperactivity and behavioral disorders[30]. Metoclopramide is also considered safe if nausea is prominent and concomitant to the pain.

Non-steroidal anti-inflammatories are possibly safe to take under certain circumstances but have also been associated with premature closure of the ductus arteriosus and pulmonary hypertension. Ibuprofen, diclofenac, naproxen, and piroxicam during the second trimester have also been associated with low birth weight. Ibuprofen during the second and third trimesters was associated with asthma. During the third trimester, diclofenac was related to maternal vaginal bleeding. Finally, indomethacin has been associated with miscarriage[31].

Triptans are also classified as possibly safe to take during pregnancy but are mainly reserved for migraine with aura and severe migraine[32]. These 5-HT 1B/D agonists are safer during the first trimester of pregnancy. Still, during the second and third trimesters, a small association has been demonstrated between the risk of atonic uterus and post-delivery bleeding. Triptans are contraindicated in patients with poorly controlled hypertension, hemiplegic migraine, severe hepatic and renal impairment, basilar migraine, and coronary artery disease[33].

Lasmiditan, a 5-HT 1F receptor antagonist, might be a safer alternative for acute migraine in pregnant women with cardiovascular conditions[34]. Onabotulinum toxin A has been used for chronic migraine in Europe[1].

Calcitonin gene-related peptide (CGRP) antibodies monoclonal antibodies.

In recent years, the US FDA has approved CGRP monoclonal antibodies as a promising preventive treatment for migraine. Current options vary according to the route of administration and dose schedules and include erenumab, galcanezumab, fremanezumab, and eptinezumab[35]. Nevertheless, safety data on migraine preventive monoclonal antibodies targeting the CGRP system in pregnancy are limited[36].

No specific maternal, fetal, or neonatal toxicity patterns were observed in a pharmacovigilance assessment of the safety reports related to pregnancy associated with erenumab, galcanezumab, fremanezumab, and eptinezumab. Spontaneous abortion was not more frequently reported with CGRP monoclonal antibodies compared with the use of other prophylactic drugs (ROR 1.1, 95% confidence interval, CI, 0.8-1.5), and triptans (ROR 1.2, 95% CI 0.8-1.9)[33]. However, a relatively limited number of adverse drug reactions are reported, and long-term safety data is lacking. Therefore, its use in pregnant women is anecdotal and case-by-case. In the event of prescription, continuous surveillance is required in pregnant and lactating women exposed to these drugs[37]. Table 1 lists medications' doses and risk class with documented use during pregnancy. Table 2 shows the risk classification system in pregnancy and breastfeeding.

Conclusion

The treatment objective is to reduce the severity of headaches as possible, restore functioning ability, reduce the use of drugs, and promote management with minimal side effects. These goals are not different when treating pregnant women. Still, non-pharmacological treatment of migraine is preferable whenever possible, and preventive migraine drugs should be used only in severe and selected cases. After balancing risks and benefits, the lowest effective dose and frequency should be prescribed. Pregnant women should be counseled to avoid migraine triggers by having a regular sleeping schedule, avoiding missing meals, and practicing relaxation techniques such as mindfulness and yoga.

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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 appears in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

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