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Corrigendum

Jiménez-Ruiz A, Toledo BV. Topografía de lesiones cerebrales tratadas con cirugía estereotáctica mediante Gamma Knife en un Centro de Referencia. Rev Mex Neuroci. 2017;18(3):24-33.

We hereby corroborate that the study was performed between January 2005 and December 2007. This must be taken into consideration in pages 24-26 and 28.

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EDITORIAL

Editorial, January 2021: COVID-19 is here. What comes next?

Editorial, Enero 2021: COVID-19 está aquí. ¿Qué sigue?

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Medicine, especially neurology, are always challenging. Regardless of the expertise we might assume to possess in the various high specialties that comprise it, new findings and knowledge are generated every day, and it is our job to keep up to speed.

The 2019 coronavirus disease (COVID-19) pandemic emerged in Wuhan, China, as an acute respiratory syndrome. More than a third of the patients develop neurological disorders, which cause direct damage to the nervous tissue, finding edema, and neuronal degeneration, in addition to the presence of the virus itself in the cerebrospinal fluid (CSF). Many viral infections seem to be neurotrophic and this is not the exception, damaging macrophages, microglia, and astrocytes and causing polyneuropathy, encephalitis, and ischemia (among the most common manifestations). It is essential to point out that many patients may not have a respiratory condition but a neurological one. The virus entry is possible through an airway, passing to the olfactory system and arriving at the circulatory system, then to the motor nerve endings, through the rupture of encephalic barriers secondary to hypoxia and edema. The immune response favors the virus with the release of interleukins, cytosines, and tumor-necrosis factor, alterations in the angiotensin-converting enzyme, among other alterations caused by the same virus or the response of the host[1].

Viruses that infect the central nervous system (CNS) of mammals can have severe consequences and can result in chronic and persistent infections. Murine CNS CoV infection shows that T cells in the acute virus invasion mediate the immune response, and then host regulatory mechanisms appear, many aimed at protecting the CNS integrity. However, sometimes the virus is not eradicated. Both glia and neurons could be a sanctuary for the virus, and the host's defense response could eventually be more harmful to it than to the virus.

The neurological alterations caused by COVID-19 have not been thoroughly studied. Attempts to isolate Severe Acute Respiratory Syndrome CoV-2 (SARS-CoV-2) from spinal fluid and autopsies of victims of COVID-19 can play an essential role in understanding precisely what is happening in the affected patient, especially the deeply affected one.

Human CoV can spread from the airways to the CNS by transneuronal and hematogenous routes. On March 4, 2020, in Beijing, China, the virus' presence was demonstrated in the CSF, making the neuroinvasion associated with the virus unquestionable. Considering that encephalitis is associated with high mortality and morbidity, early diagnosis and treatment can improve prognosis. Brain imaging and CSF study are essential if neurological symptoms are present[4].

A great deal of fear appears in those who have faced the neurological problems associated with the neurotropism and pathogenesis of SARS-CoV-2 related to the infection's acute and long-term consequences. Strategies to

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combat these issues must be developed. An acute problem is the loss of the hypothalamus' regulatory capacity, with alteration in glucocorticoid levels associated with neutrophilia and lymphopenia, with a state of hypercoagulation, multiple organ failure, in addition to encephalopathy, encephalitis, cerebral infarction, and Guillain-Barré[5].

From the well-known relationship between virus and tumors and neurodegenerative problems, the question has arisen whether this neurotropic virus can undoubtedly be associated with these possibilities. The human T cell leukemia virus type 1, for example, is well known to favor a proliferation that leads to adult T-cell leukemia and to a neurodegenerative process that affects the white substance of both the spinal cord and the brain[6].

Other viruses, such as the hamster neurotropic strain of measles, cause non-inflammatory encephalopathy in mice, with neuronal loss in the CA1 and CA3 areas of the hippocampus with indirect neurodegenerative effects on the brain due to the activation of the N-methyl-D-aspartate receptors[7].

Alterations in the cytoskeleton can be induced by herpes simplex virus type 1 (HSV-1) and axonal injury results in significant neuronal damage and neuronal death. Altered microtubule dynamics and tau hyperphosphorylation are possible links between HSV-1 infection and altered neuronal cytoskeleton and may be associated with the neurodegenerative diseases known as tauopathies[8].

Several viruses are associated with different neurodegenerative diseases, mainly related to neurotropic viruses that can induce neuronal dysfunction and damage, leading to direct death, cell lysis, and induce apoptosis. Regardless of the route of entry, viruses activate both innate and adaptive immune responses. Viral antigens preferentially activate toll-like receptors 3, 7, and 8, which drive innate and adaptive immune responses by causing neuronal destruction, by direct damage, with the release of free radicals, cell activation, and inflammation; although the immunocompetent host for that virus could eliminate it[9].

Recently, there is a consideration of the fundamental need to implement programs to monitor people who survive SARS-CoV-2 infections over time, given the possibility that it is a factor that favors the presence of neurodegeneration associated with a viral infection[10].

DNA viruses such as herpes (HSV, HHV and, EBV, and VZV9 polyomavirus [JCV]), as well as RNA viruses (influenza, measles, rabies, WNV, poliovirus, Echo, Entero, and of course HIV), have been associated with neurodegeneration[9]. Therefore, SARS-CoV-2 may also be associated with a problem that concerns us, given the high prevalence that has been growing as life expectancy has increased.

Even though, life is too short no matter how long it may seem to be, the neurologist's curiosity to continue learning leads us to look for a different future where we can face this new challenge. We must come prepared with new weapons and new prevention, protection, treatment, rehabilitation, and social reintegration measures, given the consequences that this unfortunate pandemic we are facing will surely leave.

References

1. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun. 2020;87:18-22.
2. Bergmann CC, Lane TE, Stohlman SA. Coronavirus infection of the central nervous system: host-virus stand-off. Nat Rev Microbiol. 2006;4:121-32.
3. Asadi-Pooya AA, Simani L. Central nervous system manifestations of COVID-19: a systematic review. J Neurol Sci. 2020;413:116832.
4. Sun T, Guan J. Novel coronavirus and the central nervous system. Eur J Neurol. 2020;27:e52.
5. Iadecola C, Anrather J, Kamel H. Effects of COVID-19 on the nervous system. Cell. 2020;183:16-27.e1.
6. Barmak K, Harhaj E, Grant C, Alefantis T, Wigdahl B. Human T cell leukemia virus Type I-induced disease: pathways to cancer and neurodegeneration. Virology. 2003;308:1-12.
7. Andersson T, Schultzberg M, Schwarcz R, Löve A, Wickman C, Kristensson K. NMDA-receptor antagonist prevents measles virus-induced neurodegeneration. Eur J Neurosci. 1991;3:66-71.
8. Zambrano A, Solis L, Salvadores N, Cortes M, Lerchundi R, Otth C. Neuronal cytoskeletal dynamic modification and neurodegeneration induced by infection with herpes simplex virus Type 1. J Alzheimers Dis. 2008;14:259-69.
9. Zhou L, Miranda-Saksena M, Saksena NK. Viruses and neurodegeneration. Virol J. 2013;10:172.
10. Outeiro TF, Krisko A. SARS-CoV-2 as a trigger of neurodegeneration: thinking ahead. Mov Disord. 2020;5:1106-7.

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ORIGINAL ARTICLE

Wallenberg syndrome and isolated lateral bulbar infarction: Clinical characteristics and prognosis in a cohort of Mexican patients

José L. Ruiz-Sandoval[1,2], Fernando Barinagarrementeria-Aldatz[3], Carlos Cantú-Brito[4], Antonio Arauz-Góngora[5], Germán López-Valencia[1], Amado Jiménez-Ruiz[4], Patricia Laguna-Cruz[5], Jesús A. Aldana López[1], Sergio Cerpa-Cruz[1], and Christian Menchaca-Gutiérrez[1]*

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Abstract

Background: *Wallenberg syndrome (WS) is a classic neurologic disorder secondary to vascular pathology of the vertebrobasilar circulation.* **Methods:** *Consecutive patients > 18 years with WS and isolated lateral medullary infarction syndrome were included from two Mexican hospitals. Risk factors, initial signs, symptoms, radiological findings, and acute treatment were evaluated; the prognosis was assessed using the Glasgow Outcome Scale.* **Results:** *Twenty-six patients were studied in a 26-year period (1988-2014); 17 patients were men (67%); and the average age was 45 years (range 19-77). Fourteen patients were under 45 years old (54%). The most common risk factors were dyslipidemia (41%) and hypertension (37%). The main initial symptoms were vertigo-dizziness (89%) gait ataxia (70%), and crossed-sensory deficit; and the main signs were crossed-sensitive deficit (93%), Horner syndrome (85%), and nystagmus (82%). In the bivariate analysis, age under 45 years was associated with a vertebral arterial dissection (p = 0.001), and age > 45 with atherothrombotic etiology (p = 0.01). About 96% of patients presented good recovery at an average of 17 months follow-up.* **Conclusion:** *Non-atherosclerotic vasculopathy was the main cause of WS-ILBI in young people. The clinical characteristics were similar to those reported in other series with a usually benign prognosis.*

Key words: *Postero-lateral bulbar infarct. Stroke. Vertebral artery dissection. Wallenberg's syndrome.*

Síndrome de Wallenberg e infarto bulbar lateral aislado: características clínicas y pronóstico en una cohorte de pacientes mexicanos

Resumen

Antecedentes: *El síndrome de Wallenberg (SW) es un diagnóstico clásico en neurología, generalmente secundario a patología vascular de la circulación vertebro-basilar.* **Métodos:** *Se incluyeron a pacientes mexicanos consecutivos mayores de*

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18 años de edad con síndrome de SW e infarto bulbar lateral aislado (SW-IBLA) en dos hospitales mexicanos. Se evaluaron los factores de riesgo, signos y síntomas iniciales, hallazgos radiológicos, tratamiento agudo y pronóstico mediante el Glasgow Outcome Scale (GOS). **Resultados:** *Se estudiaron 26 pacientes en un periodo de 26 años (1988-2014); Diecisiete pacientes fueron hombres (67%); el promedio de edad fue de 45 años (rango 19-77). Catorce pacientes fueron menores de 45 años (54%). Los factores de riesgo más frecuentes fueron dislipidemia (41%) e hipertensión arterial (37%). Los principales síntomas al inicio fueron vértigo-mareo (89%) y ataxia para la marcha (70%), así como déficit sensorial cruzado (93%), síndrome de Horner (85%) y nistagmo (82%) a la exploración neurológica. En el análisis bivariado, la edad menor a 45 años se asoció a disección arterial vertebral (p = 0.001), y la edad > 45 a etiología aterotrombótica (p = 0.01). El 96% de los pacientes presentaron buena recuperación en un seguimiento promedio de 17 meses.* **Conclusión:** *La vasculopatía no ateroesclerosa fue la principal causa de SW-IBLA en jóvenes. Las características clínicas para esta localización fueron similares a lo reportado en otras series con un pronóstico habitualmente benigno.*

Palabras clave: *Circulación vertebro-basilar. Disección arterial vertebral. Enfermedad vascular cerebral. Ictus. Infarto bulbar. Síndrome de Wallenberg.*

Introduction

Twenty percent of brain infarctions occur in the vertebrobasilar territory, usually affecting the medulla[1-3]. In bulbar infarctions, the lateral or posterolateral topography is mainly compromised, causing a constellation of signs and symptoms encompassed in the Wallenberg syndrome (WS)[4-7]. The WS has been described throughout history from various perspectives. It began with clinical and clinical-pathological descriptions, followed by neurophysiological studies, as well as vascular findings (due to the use of cerebral angiography), culminating in precise clinical-radiological correlates after the advent of sophisticated magnetic resonance imaging (MRI)[8,9]. The prognosis for WS is usually favorable, and the sequelae, although frequent, are usually mildly disabling with complete remission in most cases[9-11]. We describe the clinical, radiological, and prognostic findings in a cohort of Mexican patients with WS and isolated lateral bulbar infarction (WS-ILMI) in two consecutive hospital records.

Patients and methods

Consecutive patients older than 18 years with WS confirmed with MRI admitted to the Neurology Department of the Instituto Nacional de Neurología y Neurocirugía “Manuel Velasco Suárez” (Mexico City, Mexico) from 1988 to 1998 were considered, as well as those admitted to the Neurology and Neurosurgery Department of the Hospital Civil de Guadalajara “Fray Antonio Alcalde” (Guadalajara, Jalisco, Mexico) from 1999 to 2014. Acute, ambulatory cases with these same diagnostic criteria attended in the outpatient clinic were also included in both cohorts. Socio-demographic variables, risk factors for stroke, symptoms at the onset of the infarct, and clinical signs on neurological examination, as well as antithrombotic management in the acute phase and secondary prevention strategies, were also analyzed.

Medullary infarctions were classified according to their location as rostral, caudal o rostrocaudal using MRI (FLAIR/DWI in the most recent cohort). Cerebral angiography, extracranial or transcranial Doppler of vertebrobasilar territory as well as magnetic resonance angiography (MRA) of the brain – individually or in combination – were considered to define the site of vascular stenosis or occlusion: vertebral, basilar, or the posteroinferior cerebellar artery (PICA).

The clinical condition at discharge was evaluated according to the Glasgow Prognostic Scale (GOS), where 1 = death; 2 = persistent vegetative state, without evident cortical activity; 3 = severe disability, with dependency; 4 = moderate disability in which he is independent but unable to return to his trade; and 5 = good recovery, returning to previous activities[12]. During outpatient follow-up, the clinical condition and sequelae in the last evaluation were recorded. Likewise, two age groups were considered: a young group (< 45 years) and an older group (> 45 years). For the registry of the information regarding clinical, radiological, therapeutic, and prognostic data, the same format was used for all patients.

Demographic data are presented as simple relative frequencies. Age is presented and analyzed as median with minimum and maximum. Pearson’s × 2 or Fisher’s test was used for nominal variables in the univariate analysis, when values with n > 5, or n < 5 were distributed in the boxes of the contingency tables, respectively. The T-student test was used to compare normally distributed continuous variables, and the Mann–Whitney U-test was performed when an ordinal or

non-parametric numerical variable was distributed between two groups (e.g., comparison of medians). The analyses with $p < 0.05$ were considered significant. The analyses and "p" value were calculated at two tails. All cases were captured for analysis in the SPSS Statistics Bass 20.0 program (IBM SPSS Inc. Chicago, IL). Ethics Committees were aware of the study and agreed to its development.

Results

A total of 73 patients with "medullary infarction," "medullary-cerebellar infarction," or "WS" were initially considered. Of these, 36 patients were excluded: ten due to cerebellar involvement, six because they had simultaneously affected multiple structures of the vertebrobasilar territory, and another 13 because they corresponded to medullary infarcts of anteromedial (2 cases) or postero, and posterolateral (11 cases) location. Sixteen cases were excluded due to incomplete clinical or radiological information. Twenty-six patients with WS-IBLI were included for the present analysis.

Of the total of 26 patients, 17 (65%) were men and 9 (35%) women with an average age of 44 years (range of 19-77 years). There were 14 (54%) young patients (younger than 45 years). The main risk factors were: dyslipidemia (42%), high blood pressure (38%), alcoholism (35%), and smoking (27%). Two patients (8%) had a history of ischemic stroke in another territory (Table 1). According to the location of the WS-IBLI, 18 (69%) were caudal, five (19%) rostral, and three (12%) rostrocaudal.

The most frequent symptoms at WS-IBLI presentation were: vertigo or dizziness (92%), gait ataxia (77%), headache (73%), dysphagia (65%), and body (62%) or facial (58%) hypoesthesia (Table 2), with no significant differences regarding sex or age groups. According to location, dysphagia and dysarthria were less frequent in WS-IBLI with caudal location (all with $p < 0.05$). Facial hypoesthesia was more common in infarcts with a caudal location, while facial paralysis was more frequently documented in those with a rostrocaudal location.

At neurological examination, the main signs were ipsilateral or contralateral abnormalities of sensation (96%), nystagmus (81%), palatal weakness (81%), Horner syndrome (73%), and gait ataxia (73 %) (Table 2). Gait ataxia was more frequent in young subjects and facial paralysis in rostrocaudal infarcts ($p < 0.05$).

To identify the mechanism of the stroke, several studies were used, including MRA in 18 patients (69%), transcranial Doppler ultrasound in 9 (35%), transesophageal echocardiogram in nine (35%), and digital subtraction angiography in eight cases (31%). The vascular abnormalities included: vertebral stenosis in ten cases (37%), vertebral artery occlusion in six (22%), PICA occlusion in two (7%), and PICA stenosis in one (4%) (Tables 1 and 2). These findings did not show a significant association with the age, sex, or location of the IBLI.

The primary etiology of the WS-IBLI corresponded to non-atherosclerotic vascular disease, including arterial dissection in 12 patients (46%). In eight patients, the cause was classified as atherothrombotic (31%), and in four, it was classified ad cardioembolic (15%). Two of the patients (8%) were classified as cryptogenic. Two cases with thrombophilia were included: one patient with systemic erythematosus lupus (with positive antiphospholipid antibodies and factor V Leiden) deficiency and another with Protein C deficiency.

Of the potentially cardioembolic sources reported, patent foramen ovale was identified in three cases (in one patient associated with an intra-atrial septum aneurysm) (Tables 1 and 2).

The clinical condition at the time of hospital discharge according to the GOS reported: one death (4%)-associated with sudden respiratory arrest; 16 patients were discharged with minor non-disabling sequelae (61%), eight with moderate sequelae (38%), and one patient with severe sequelae (dysphagia) (4%). Regarding antithrombotic treatment in the acute phase and as a subsequent secondary prevention measure: 21 (80%) patients were treated with antiplatelet agents (17 with aspirin, three with clopidogrel, and two with ticlopidine). Five patients (20%) were anticoagulated (four extracranial dissections and one cardioembolic).

Follow-up was available with an average of 17 months (range 1-72) with a median 16 months in 25 patients, with a GOS of 5 at the time of the last evaluation in 24 patients (96%). The one remaining patient continued with severe dysphagia requiring the use of a permanent nasojejunal tube. In our series, no recurrence of stroke was observed at long-term follow-up.

Regarding the etiology, arterial dissection was significantly associated with age younger than 45 years, since it occurred in ten of 12 cases ($p = 0.001$), while atherothrombotic etiology predominated among those older than 45 years in 8 of eight patients ($p = 0.001$). No other significant differences were observed between arterial findings or prognosis concerning age, sex, and location of the infarction (findings not shown in the table).

Table 1. General characteristics of patients with Wallenberg syndrome and isolated medullary infarction (WS-IBLI) n = 26

N	S/A	Risk factors	Etiology	Topography (MRI)	Arterial findings	Treatment	Follow-up (M)	Sequelae (GOS)
1	M/36	Alcohol	Spontaneous dissection	C-L- Right	A: V4 Right occlusion.	Aspirin	72	Facial pain (GOS) = 4
2	M/29	----	Spontaneous dissection	C-L- Right	A-MRI: V3 Right	Anticoagulation	12	Facial hypoesthesia (GOS) = 5
3	F/40	AH, Dyslip.	Spontaneous dissection	C-L- Right	D: V3 Right stenosis A (2 month) normal.	Aspirin	2	Horner/Nystagmus (GOS) = 4
4	M/33	Alcohol, Dyslip, Migraine	Spontaneous dissection	C-L- Right	A: V3-4 Right stenosis and ACPI occlusion	Aspirin	22	No (GOS) = 5
5	M/46	Sm, Alcohol, PCD	Traumatic dissection	C-L- Right	RM: V3 Right dissection.	Aspirin	9	Facial hypoesthesia (GOS) = 4
6	M/40	Dyslip. Sm	Traumatic dissection	C-L- Right	A: V3 Right occlusion.	Anticoagulation	14	None (GOS) = 5
7	M/33	AH	Traumatic dissection	C-L- Left	A: V4 Left stenosis.	Aspirin	5	None (GOS) = 5
8	F/28	----	Spontaneous dissection	RC-L- Left	A: V3-4 Left occlusion.	Aspirin	24	None (GOS) = 5
9	M/46	Alcohol, Dyslip.	Traumatic dissection	C-L-I Left	A: V4 bilateral stenosis	Aspirin	24	None (GOS) = 5
10	M/30	----	Traumatic dissection	R-L- Right	A: V3 Right occlusion.	Anticoagulation	65	None (GOS) = 5
11	M/34	Sm, Alcohol	Traumatic dissection	R-L- Right	A: V3 Right stenosis.	Anticoagulation	6	None (GOS) = 5
12	M/29	Sm, Dyslip.	Spontaneous dissection	RC-L- Right	A: V4 bilateral stenosis.	Aspirin	7	None (GOS) = 5
13	F/48	Estenosis mitral, Dyslip.	Cardioembolic	C-L- Right	A: V3-4 Right occlusion.	Clopidogrel	12	Severe dysphagia (GOS) = 3
14	M/52	AH, PFO	Cardioembolic	C-L- Right	A: PICA stenosis	Aspirin	3	No (GOS) = 5
15	F/37	PFO	Cardioembolic	C-L- Left	A: PICA distal occlussion	Clopidogrel	8	Vrtigo (GOS) = 4
16	M/33	PFO, Dyslip, ISA, FVL, AFL, SLE.	Cardioembolic	R-L- Left	A: normal	Anticoagulation	17	Dysarthria, dysmetria, nystagmus (GOS) = 4
17	M/60	Alcohol, Dyslip, DM.	Cardioembolic	C-L- Right	A: PICA occlusion	Ticlopidine	13	No (GOS) = 5
18	M/60	AH, Alcohol, Sm., Dyslip.	Cardioembolic	C-L- Left	A-RMI: V4 Left stenosis.	Aspirin	2	No (GOS) = 5
19	M/63	AH, Alcohol, DM, Dyslip.	Cardioembolic	C-L- Left	A: V4 Left stenosis.	Ticlopidine	36	No (GOS) = 5
20	F/47	AH	Atherothrombotic	C-L- Right	A: V4 Right stenosis.	Clopidogrel	12	No (GOS) = 5
21	F/49	Ah, Sm., Dyslip.	Atherothrombotic	C-L- Right	A: V4 Right stenosis. PICA stenosis	Aspirin	2	Dysarthria, facial hypoesthesia (GOS) = 4

(Continues)

Table 1. General characteristics of patients with Wallenberg syndrome and isolated medullary infarction (WS-IBLI) n = 26 (*Continued*)

N	S/A	Risk factors	Etiology	Topography (MRI)	Arterial findings	Treatment	Follow-up (M)	Sequelae (GOS)
22	M/68	Previous Stroke, AH	Atherothromboembolic A-A	C-L- Left	D, MRI: V1 Left stenosis.	Aspirin	6	Vertigo (GOS) = 4
23	F/77	Previous Stroke, AH, DM	Cryptogenic	R-C-L	----	Aspirin	0	Death (GOS) = 1
24	F/77	AH	Cryptogenic	R-L- Right	----	Aspirin	36	Dysphonia (GOS) = 4
25	F/37	Sm, Alcohol	Cryptogenic	C-L- Right	A: normal	Aspirin	2	No (GOS) = 5
26	M/19	----	Cryptogenic	C-L- Right	A: normal	Aspirin	15	No (GOS) = 5

PFO: patent foramen ovale; ISA: interatrial septum aneurysm; PCD: protein C deficiency; APL: antiphospholipid; SAPL: secondary antiphospholipid; C-L: caudal-lateral; R-L: rostral-lateral; RC-PL: rostral-caudal-postero-lateral; CP-L: caudal-postero-lateral; A: angiography; A-MRI: angio-magnetic resonance; D: Doppler neck/transcranial; Sm: smoking; AH: arterial hypertension; DM: diabetes mellitus; Dyslip: dyslipidemia; SLE: systemic lupus erythematosus lupus; PICA: posteroinferior cerebellar artery; S: sex; A: age (years); M: months; MRI: magnetic resonance imaging; CT: computerized tomography; A-A: arterio-arterial; FVL: Leiden V factor.

Table 2. Clinical manifestations, etiology, and prognosis of Wallenberg syndrome with isolated medullary infarction (WS-IBLI), n = 26

Symptoms		Signs		Etiology	n = 26
Vertigo/dizziness, n (%)	24 (92)	Body hypoesthesia n (%)	25 (96)	Arterial dissection, n (%)	12 (46)
Gait ataxia, n (%)	20 (77)	Nystagmus, n (%)	21 (81)	Atherothrombotic, n (%)	8 (31)
Headache, n (%)	19 (73)	Palate weakness, n (%)	21 (81)	Cardioembolism, n (%)	4 (15)
Dysphagia, n (%)	17 (65)	Horner, n (%)	19 (73)	Cryptogenic, n (%)	2 (8)
Body hypoesthesia, n (%)	16 (62)	Gait Ataxia, n (%)	19 (73)	30-days prognosis (GOS)	n=26
Vomiting, n (%)	15 (58)	Facial hypoesthesia, n (%)	19 (73)	(GOS 5) Good outcome, n (%)	16 (61)
Facial hypoesthesia, n (%)	15 (58)	Nauseous abolished, n (%)	17 (65)	(GOS 4), n (%)	8 (30)
Nausea, n (%)	15 (58)	Dismetry, n (%)	14 (54)	(GOS 3), n (%)	1 (4)*
Horner, n (%)	14 (54)	Facial paralysis, n (%)	11 (42)	(GOS 2), n (%)	------
Diplopia, n (%)	12 (46)	Corneal reflex loss, n (%)	7 (27)	(GOS 1) Death, n (%)	1 (4)
Dysmetry, (%)	11 (42)	------		Functional prognosis (17 months average)	n = 25
Dysphonia or hoarseness, n (%)	11 (42)	------		(GOS 5) Good outcome, n (%)	24 (96)
Dysarthria, n (%)	11 (42)	------		(GOS 4), n (%)	------
Weakness, n (%)	9 (35)	------		(GOS 3), n (%)	1 (4) *
Hiccups or singultus, n (%)	8 (31)	------		(GOS 2), n (%)	-----
Facial paralysis, n (%)	6 (23)	------		(GOS 1) Death, n (%)	-----

*Dysphagia, GOS: Glasgow Outcome Scale.

Discussion

From the original clinical description made by Alex Marcet more than two centuries ago, and the first clinicopathological characterization made by Adolph Wallenberg at the beginning of the last century, WS syndrome is one of the most studied disorders throughout the history of neurology[4,6,13].

In our setting, WS has been analyzed on more than one occasion, with isolated clinical-radiological reports[14-17]. Despite this, there is no precedent for a relatively large cohort of patients with SW and IBLA that provides the clinical, radiological, etiological, and prognostic information as in the present study.

In our cohort, the patients with WS-IBLI were mostly men (2:1 ratio), similar to other reported series[18-23]. The average age of our patients was 45 years, a much lower average compared with the previous by other authors (55 years)[18-23]. This may be due to the selection bias inherent in our reference hospital centers.

Traditional risk factors, including high blood pressure, diabetes, and dyslipidemia, were observed less frequently, due to the lower average age in our cohort. This observation is also supported by a higher frequency of alcoholism and smoking, more frequent in young patients[24].

The caudal location of the ILMI predominated over the rostral topography in a 4:1 relationship. This finding is repeatedly reported by other series and is probably associated with the higher frequency of proximal vertebral artery involvement (due to stenosis or occlusion) observed in our study[9,11].

Regarding the symptoms and signs of WS-ILMI, our patients did not show substantial differences with other reports[19,20,23]. The most common symptom was vertigo in comparison with others studies reporting dysphonia and dyshagia as the main clinical findings[25]. Headache was observed in 73% of cases with no difference regarding age, sex, or infarct location. This frequency is higher than other WS series, where it is reported in 30-52% of patients[19,23,26]. A plausible explanation is the association of arterial dissection with a presenting headache.

However, in the signs and symptoms analysis of symptoms according to the location (not shown in tables), the group of patients younger than 45 years presented more significant gait ataxia ($p = 0.01$); while dysarthria, dysphagia, and peripheral facial paralysis were observed more frequently in the WS-IBLI of rostral location (all with $p < 0.05$). This difference can be explained by the presence or absence of involvement of the ambiguous nucleus[5,7]. In rostral infarcts, this nucleus is affected, since these are narrower lesions that tend to affect the most ventral portion of the medulla[7]. Although the existence of facial paralysis is rare and its origin is unclear, in our series, this deficit occurred in a third of patients. It has been postulated that, in patients with facial paralysis, the injury could also affect the pons[27]. However, none of our patients had apparent involvement at this level. Kim, observed a greater involvement of the facial nerve fascicles and the corticobulbar fibers in relation to facial paralysis in rostral bulbar infarcts[9].

In our cohort, the most frequent cause of WS-IBLI was arterial dissection (in < 45 years-old patients), unlike other series where it is reported as the second or third cause in frequency[28,29]. Vertebral dissection has also been reported as one the most common etiologies in young patients in some series[30,31]. Large vessel disease (atherothrombotic or atherothromboembolic) was the second cause associated with an age > 45 years. A probable explanation for the higher incidence of arterial dissections in young patients is the higher frequency of high-risk physical and occupational activity (violent or abrupt) compared to older age groups. Of the infrequent causes, two cases with prothrombotic status were found as associated conditions: one patient with systemic erythematosus lupus (with positive antiphospholipid antibodies and factor V Leiden deficiency) and one with Protein C deficiency, which is an uncommon association in the literature[32,33].

The vascular abnormalities in our series coincide with those reported in the literature: vertebral artery stenosis was the most frequent, followed by vertebral artery occlusion, in 44% and 21%, respectively. Only two patients had PICA involvement[34,35].

Regarding complications, prognosis, and sequelae, our data are similar to that provided by the literature. WS usually has a benign prognosis with a low percentage of moderate and severe long-term complications and a 5-year survival > 50%[36]. Since our long-term follow-up was heterogeneous (range from 1 to 72 months), we were unable to perform a 5-year survival statistical analysis.

Most of the symptoms and signs of WS tend to improve rapidly, as occurred in our work. In contrast to other series, the most frequent sequela was sensory (cross-body paresthesia) followed by residual Horner syndrome; the only severe sequel was dysphagia[37-39]. In our series, only one patient died suddenly due to probable bronchoaspiration. Respiratory failure is usually the most common cause of death reported in WS[39].

During follow-up, 61% of the patients had good recovery (GOS of 5) at 30 days and 96% in the long-term, confirming the benign prognosis of this syndrome.

Conclusion

Our study contributes to the clinical characterization of WS with a strictly lateral and isolated location

(WS-IBLI), in addition to offering a new perspective on the functional prognosis in the medium term. A non-atherothrombotic etiology of SW should be considered in young patients with no other associated risk factors. Close monitoring and antithrombotic or anticoagulant therapy are essential in patients with SW to prevent stroke recurrence and to detect complications associated with this syndrome, which usually presents a benign course. The main limitation of this study was the selective sample of cases obtained from high concentrations centers which can lead to information biases. Further multi-center studies are needed in the future to complement the information presented in this manuscript.

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Con□icts of interest

None to report.

Ethical disclosures

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

Con□dentiality 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

1. Savitz S, Caplan LR. Vertebrobasilar disease. N Engl J Med. 2005;352:2618-26.
2. Tatu L, Moulin T, Bogousslavsky J, Duvernoy H. Arterial territories of human brain: brainstem and cerebellum. Neurology. 1996;47: 1125-35.
3. Caplan LR. Vertebrobasilar territory ischemia: an overview. In: Posterior Circulation Disease: clinical Findings, Diagnosis, and Management. Cambridge, England: Blackwell Science Ltd.; 1996. p. 179-97.
4. History of a singular nervous or paralytic affection, attended with anomalous morbid sensations. Med Chir Trans. 1811;2:217-35.
5. Wallenberg A. Acute bulbar affection. Arch Psychiatry Nervenheilkd 1895;27:504-40.
6. Wallenberg A. Anatomischer Befund in einem als Acute Bulbäraffection (Embolie der art. Cerebellar. Post. Inf. sinistr.). Beschriebenem falle. Arch Fr Psychiatr. 1901;34:923.
7. Currier RD, Giles CL, DeJong RN. Some comments on Wallenberg's lateral medullary syndrome. Neurology. 1961;11:778-91.
8. Roig C, Barraquer-Bordas LL. Historia del síndrome de Wallenberg. Rev Neurol (Barc). 1996;24:96-100.
9. Kim S. Pure lateral medullary infarction: clinical and radiological correlation of 130 acute, consecutive patient. Brain. 2003;8:1864-72.
10. Norrving B, Cronqvist S. Lateral medullary infarction: prognosis in an unselected series. Neurology. 1991;41:244-8.
11. Fukuoka T, Takeda H, Dembo T, Nagoya H, Kato Y, Deguchi I, et al. Clinical review of 37 patients with medullary infarction. J Stroke Cerebrovasc Dis. 2012;7:594-9.
12. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet. 1975;1:480-4.
13. Escobar-Izquierdo A. Nota biográfica de Adolf Wallenberg. Rev Mex Neuroci. 2007;8:296-8.
14. Roldán-Valadez E, Juárez-Jiménez H, Corona-Cedilloa R, Martínez-López M. Síndrome de Wallenberg: hallazgos en resonancia magnética con correlación clínica. Gac Méd Méx. 2007;143:420-32.
15. Estañol B, Juárez H, Díaz-Zambrano S, Boada FV, Ramos GG. Horizontal appendicular dysmetria in four patients with a typical Wallenberg's síndrome. Rev Invest Clin. 2000;52:415-7.
16. Estañol B, Lopez-Rios G. Neuro-otology of the lateral medullary infarct syndrome. Arch Neurol. 1982;39:176-9.
17. Castillo AL, Barahona-Garrido J, Criales S, Chang-Menéndez S, Torre A. Wallenberg's syndrome: an unusual case of dysphagia. Case Rep Gastroenterol. 2007;1:135-43.
18. Kitis O, Calli C, Yunten N, Kocaman A, Sirin H. Wallenberg's lateral medullary syndrome: diffusion-weighted imaging findings. Acta Radiol. 2004;45:78-84.
19. Kim J. Pure lateral medullary infarction: clinical-radiological correlation of 130 acute, consecutive patients. Brain. 2003;126:1864-72.
20. Cnyrim C, Rettinger N, Mansmann U, Brandt T, Strupp M, Central compensation of deviated subjective visual vertical in Wallenberg's síndrome. J Neurol Neurosurg Psychiatry. 2007;78:527-8.
21. Lee MJ, Park YG, Kim SJ, Lee JJ, Bang OY, Kim JS. Characteristics of stroke mechanisms in patients with medullary infarction. Eur J Neurol. 2012;19:1433-9.
22. Oshima F, Yokozeki M, Hamanaka M, Imai K, Makino M, Kimura M, et al. Prediction of dysphagia severity: an investigation of the dysphagia patterns in patients with lateral medullary infarction. Intern Med. 2013;52:1325-31.
23. Kameda W, Kawanami T, Kurita K, Daimon M, Kayama T, Hosoya T, et al. Lateral and medial medullary infarction a comparative analysis of 214 patients. Stroke. 2004;35:694-9.
24. Encuesta Nacional de Salud y Nutrición. Insituto Nacional de Salud Publica, Secretaria de Salud; 2012. Available from: https://www.ensanut.insp.mx/encuestas/ensanut2012/doctos/informes/ENSANUT2012ResultadosNacionales.pdf.
25. Rigueiro-Veloso MT, Pego-Reigosa R, Brañas-Fernández F, Martínez-Vázquez F, Cortés-Laíño JA. Síndrome de Wallenberg: revisión de 25 casos. [Wallenberg syndrome: a review of 25 cases]. Rev Neurol. 1997;25:1561-4.
26. Ogawa K, Suzuki Y, Oishi M, Kamei S. Clinical study of 46 patients with lateral medullary infarction. J Stroke Cerebrovasc Dis. 2015;24:1065-74.
27. Fisher CM, Tapia J. Lateral Medullary infarction extending to the lower pons. J Neurol Neurosurg Psychiatry. 1997;50:620-4.
28. Sacco RL, Fredo LF, Bello JA, Odel JG, Onesti ST, Mohr JP. Wallenberg's lateral medullary syndrome: clinical-magnetic resonance imaging correlations. Arch Neurol. 1993;50:609-14.
29. Mokri B, Wayne HO, Sandok BA. Spontaneous dissection of the vertebral arteries. Neurology 1988; 38: 880-5.
30. Inamasu J, Nakae S, Kato Y, Hirose Y. Clinical characteristics of cerebellar infarction due to arterial dissection. Asian J Neurosurg. 2018;13:995-1000.
31. Park MG, Choi JH, Yang TI, Oh SJ, Baik SK, Park KP. Spontaneous isolated posterior inferior cerebellar artery dissection: rare but underdiagnosed cause of ischemic stroke. J Stroke Cerebrovasc Dis. 2014;23:1865-70.
32. Shimomura T, Takahashi S, Tamura K, Nozaki A, Akiho N. A case of Wallenberg's syndrome with systemic lupus erythematosus and antiphospholipid syndrome. Nihon Naika Gakkai Zasshi. 1993;82:588-9.
33. Stutzer G. Lupus erythematodes acutus with Wallenberg's syndrome. Z Haut Geschlechtskr. 1967;42:329-34.
34. Kim JS, Lee JH, Choi CG. Patterns of lateral medullary infarction: vascular lesion-magnetic resonance imaging correlation of 34 cases. Stroke. 1998;29:645-52.
35. Vuilleumier P, Bogousslavsky J, Regli F. Infarction of the lower brainstem. Clinical, etiological and MRI-topographical correlations. Brain. 1995;118:1013-25.
36. Caplan LR, Pessin MS, Scott RM. Poor outcome after lateral medullary infarctions. Neurology. 1986;36:1510-3.
37. Rigueiro-Veloso MT, Pego-Reigosa R, Brañas-Fernández F, Martínez-Vázquez F, Cortés-Laíño JA. Síndrome de Wallenberg: revisión de 25 casos. Rev Neurol. 1997;25:1561-4.
38. Kim JS, Choi-Kwon S. Sensory sequelae of medullary infarction: differences between lateral and medial medullary syndrome. Stroke. 1999;30:2697-703.
39. Bogousslavsky J, Khurana R, Deruaz JP, Hornung JP, Regli F, Janzer R, et al. Respiratory failure and unilateral caudal brainstem infarction. Ann Neurol. 1990;28:668-73.

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ORIGINAL ARTICLE

Preservation of sural nerve in classic forms of Guillain-Barré in a Mexican health institution

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Abstract

Background: *The term sural sparing (SS) consists of the early finding in the nerve conduction studies (NCS) of patients with Guillain-Barré syndrome (GBS) of the preservation or normality of the sural nerve with abnormality in sensory nerves of thoracic limbs. Its pathophysiology lies in the greater vulnerability to demyelinating sensory damage in distal segments of the hand than proximally in the calf. The SS is highly specific of acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and is occasionally found in acute motor/sensory axonal neuropathy (AMAN/AMSAN).* **Objective:** *We aim to describe the prevalence of SS among the forms of GBS in patients hospitalized in our institute.* **Materials and methods:** *We reviewed 61 cases of confirmed GBS (19 demyelinating, 25 axonal, and 17 unclassified forms) corresponding to the 1999-2017 period. Exclusion criteria were as follows: NCS report not available or performed 21 days after the onset of symptoms, chemotherapy in the past 2 years, and/or previous polyneuropathy. SS was defined as the preserved amplitude in sensory action potentials (SAPs) of the sural nerve with abnormal findings in median and/or ulnar nerve SAPs.* **Results:** *Thirty patients (21 men, mean 45.5 ± 21.2 years) met the selection criteria, distributed in 12 AIDP, 3 Miller-Fisher syndromes, 9 AMAN, and 6 AMSAN. The NCS was performed 9.1 ± 6.0 days from debut. There were no significant differences in demographic variables or in the amplitude of SAPs between demyelinating and axonal forms. Two patients with AIDP presented SS (16.7%), which was not observed in any other form of GBS.* **Conclusion:** *We conclude that, despite the high specificity of SS for AIDP, its low prevalence and the high prevalence of axonal forms in Mexican population suggest that SS is not a suitable electrophysiological screening parameter for differentiating forms of GBS.*

Key words: *Sural nerve. Guillain-Barré. Sural sparing. Acute inflammatory demyelinating polyradiculoneuropathy.*

Preservación del nervio sural en formas clasicas de Guillain-Barré en una institución de salud en México

Resumen

Antecedentes: *La preservación sural (PS) es muy específica de la polirradiculoneuropatía desmielinizante inflamatoria aguda (PDIA) y se encuentra de modo ocasional en la neuropatía axonal motora/sensorial aguda (NAM/NASA).* **Objetivo:** *Describir la prevalencia de PS entre las formas del síndrome de Guillain-Barré (SGB) en pacientes hospitalizados en la institución*

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de los autores. **Material y métodos:** *Se revisaron 61 casos de SGB confirmados (19 formas desmielinizantes, 25 axonales y 17 no clasificadas) correspondientes al período 1999-2017.* **Resultados:** *No se observaron diferencias significativas en las variables demográficas o la amplitud de los potenciales de acción sensorial (PAS) entre las formas desmielinizantes y axonales. Dos pacientes con PDIA presentaron PS (16.7%), que no se observó en ninguna otra forma del SGB.* **Conclusión:** *A pesar de la alta especificidad de PS para PDIA, su baja prevalencia y la elevada prevalencia de formas axonales en la población mexicana sugieren que la PS no es un parámetro de detección electrofisiológico adecuado para diferenciar las modalidades del SGB.*

Palabras clave: *Nervio sural. Síndrome de Guillain-Barré. Preservación sural. PDIA.*

Introduction

Guillain-Barré syndrome (GBS) is classically presented by acute areflexic tetraparesis, which is potentially fatal because it compromises respiratory musculature and it is associated with autonomic dysfunction. The pathophysiology of GBS lies in the immune damage caused by autoantibodies production against myelin, and the axonal membrane of spinal roots and peripheral nerves, which, depending on the predominant pathophysiologic mechanism, classically cause two types of abnormalities: slowing of conduction speed and nerve conduction blockages, when primary demyelination occurs, or Wallerian degeneration, in relation to primary axonal damage[1].

The neurophysiological diagnosis of GBS includes the application of criteria, aimed at demonstrating phenomena of primary demyelination in motor nerves, such as delayed distal latencies, slowing of conduction, and conduction blocks[2,3].

The presence of some of these criteria, and the typical clinical picture, supports the diagnosis of GBS. For axonal forms, it is considered a diagnosis that does not meet criteria for primary demyelination and that the clinical picture is compatible. However, it has recently been shown that even in the axonal variants, antibodies directed against the components of the node and paranodal region can also generate conduction blocks, at axonal level[4]. However, alterations in sensory nerves are not commonly part of the established diagnostic criteria, despite the fact that sensory symptoms are prevalent in GBS.

The spinal roots and terminal segments of peripheral nerves are anatomical sites susceptible to autoimmune damage in GBS[5].

In fact, it is not unusual to find in nerve conduction studies (NCSs) performed early during the evolution of the clinical picture of GBS, abnormality in sensory nerves in upper extremities with normality conduction in the lower extremities, a phenomenon commonly known as “sural nerve preservation” (SS, from the English sural sparing)[3]. It is possible explanation lies in two technical aspects related to the pathophysiology of GBS: first, the recording of the sensory action potentials (SAPs) of the sural nerve is performed in segments that are not as distal, as it is done in the upper extremities, where they are less susceptible to demyelinating damage and, second, in the longer time required in longer sensory nerves (for example, sural nerve) to observe reduction in the amplitude of the SAP when Wallerian degeneration occurs due to axonal damage in the spinal roots[5].

Although the sensitivity reported for SS as a marker of GBS is low (~ 20%), its presence is usually considered to be highly specific for acute inflammatory demyelinating polyradiculoneuropathy (AIDP)[6], although in axonal forms, cases have been reported exceptionally. The present study aims to describe the prevalence of SS among the classic forms of GBS in patients hospitalized in our institute.

Materials and methods

We retrospectively reviewed a total of 103 clinical files with diagnosis of presumptive discharge of GBS corresponding to the period 1999-2017 of the National Institute of Medical Sciences and Nutrition Salvador Zubirán (INCMNSZ), evaluating the presence of Hadden criteria for SGB, as well as the clinical presentation, such as the presence of neuropathy associated with another disease, data of carpal tunnel syndrome, dysesthesia, or dysautonomia, which preliminarily excluded 42 of these patients, in whom GBS was ruled out, or had serological alterations, that is, they presented uncontrolled diabetes mellitus, storage diseases, electrolyte alterations, use of neurotoxic drugs, and/or an alternative diagnosis was found.

On the other hand, a total of 61 patients with the diagnosis of GBS were included, according to the clinical picture, evolution, and the neurophysiological criteria.

Table 1. Electrophysiological values found in our patients, and proposed by Hadden classification, in brackets

	Sural nerve						Ulnar nerve				Median nerve			
	Amp uV	VdeC m/s	NR n (%)	Amp uV	VdeC m/s	NR n (%)	Amp uV	NR n (%)	Amp uV	NR n (%)	Amp uV	NR n (%)	Amp uV	NR n (%)
	Right			Left			Right		Left		Right		Left	
All	11.0 (9.6)	47.8 (7.5)	10 (29)	10.8 (10.1)	47.2 (8.1)	12 (35)	20.8 (17.8)	8 (23)	20.2 (17.1)	8 (23)	25.7 (27.4)	10 (29)	26.4 (26.4)	10 (29)
AIDP	9.9 (8.7)	48.4 (8.5)	6 (35)	9.5 (9.4)	46.0 (9.6)	7 (41)	16.6 (15.4)	5 (29)	16.0 (14.1)	5 (29)	20.3 (26.1)	6 (35)	20.9 (25.8)	7 (41)
AMAN	19.3 (8.3)	48.9 (7.2)	0 (0)	19.3 (8.7)	49.3 (6.9)	0 (0)	38.7 (14.4)	0 (0)	37.7 (15.4)	0 (0)	49.9 (24.9)	0 (0)	48.5 (22.8)	0 (0)
AMSAN	1.9 (2.6)	45.0 (7.1)	3 (66)	2.6 (5.8)	24.0 (33.9)	4 (88)	7.0 (9.0)	2 (44)	7.3 (7.5)	2 (44)	5.9 (10.0)	3 (66)	8.6 (12.5)	2 (44)

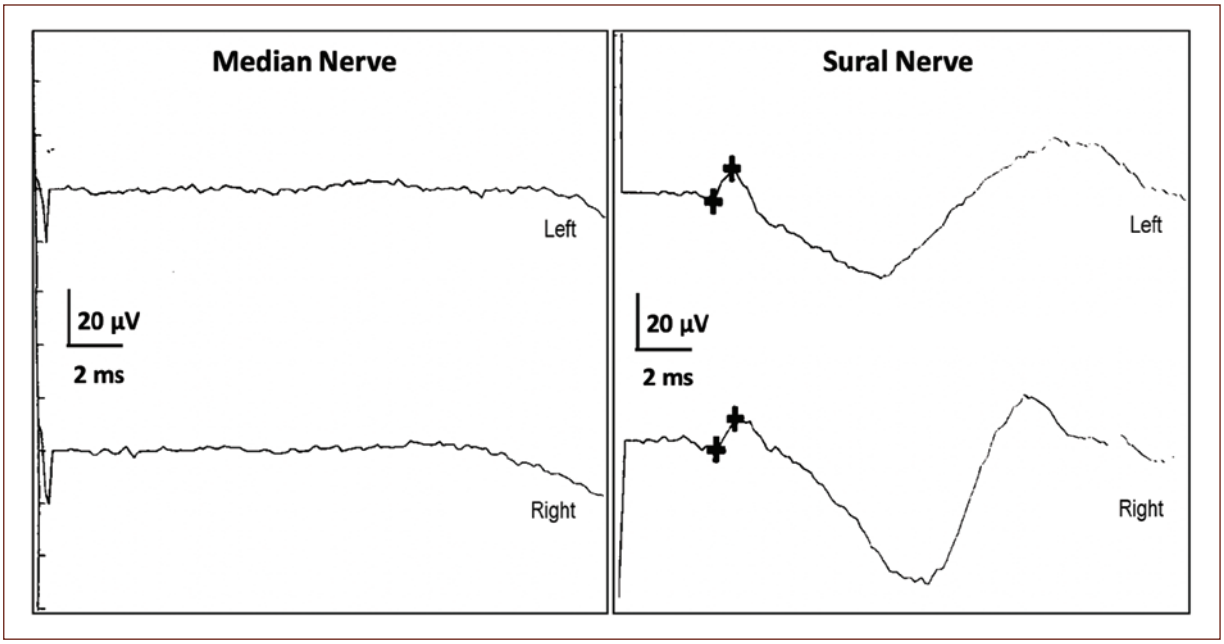

Figure 1. Presentation of the sural sparing phenomenon in the sural nerve, compared to normal median nerve.

Once the true cases of GBS were identified, we identified each of them according to the clinical presentation subtype, differentiating them from demyelinating (AIDP), axonal, pure motor (acute motor axonal neuropathy [AMAN]) or sensory motor (acute sensory axonal neuropathy [AMSAN]) forms, as well as Miller-Fisher (MF) variant. Subsequently, we analyzed the electrophysiological variants such as amplitude and speed of conduction of sural, ulnar, and median nerves, establishing values of normality according to the criteria of Hadden and Rajabally (Table 1).

SS was defined as normality in the amplitude or relative preservation of the sensory nerve action potential (SNAP) of the sural nerve with abnormality of the SNAPs of the median and/or ulnar nerve[5], excluding from the final analysis, the cases according to previously defined criteria[1] (Fig. 1).

We performed the statistical analysis with the statistical package SPSS 20, considering statistically significant differences with $p < 0.05$.

Results

Thirty-four patients met the selection criteria for SGB, which presented the following characteristics. Neurophysiological parameters showed a lower amplitude of the PANS and a high frequency of NR in AIDP and AMSAN compared to AMAN (Table 2).

Table 2. Relationship between the clinical presentations of GBS and the variables of age, sex, time of evolution, and presence of diabetes

	All	AIDP	AMAN	AMSAN
Age (years)	44.2 ± 20.0	48.5 ± 21.8	35.8 ± 19.0	42.0 ± 10.1
Gender (n, female, (%))	13 (28)	7 (41)	4 (44)	1 (20)
Time evolution (days)	10.4 ± 6.1	10.5 ± 6.5	8.9 ± 6.5	10.6 ± 5.0
Diabetes (n, (%))	4 (10)	2 (5)	0 (0)	1 (2)

Seven patients with AIDP showed SS (17.6%) (which was not observed in the other forms of GBS), two of them corresponding to "extreme" SS (absent median nerve PANSs).

Discussion

Our study has the limitation that it is a retrospective study, in addition to using only the Hadden criteria for the diagnosis of GBS. Historically, neurophysiological criteria for the diagnosis of GBS are applied to motor nerves and not to sensory nerves. This is partly because the demonstration of the phenomena of primary demyelination in sensory nerves is technically more difficult, for example, mainly related to the high degrees of temporal dispersion of their potentials when stimulated in more than 1 point. However, some authors consider SS to be a useful tool in the diagnostic support of acquired demyelinating polyneuropathies, including GBS and chronic inflammatory demyelinating polyneuropathy[5].

The previous studies have shown that SS has a sensitivity of 38% in the diagnosis of AIDP, with a specificity of 90.9% using the Hadden criteria, while a sensitivity of 36.8% and specificity of 69.6% have been found for AIDP with the Rajabally's criteria[7]. It is necessary that the neurophysiological study be performed with some precocity during the evolution of the disease (typically before 21 days from the onset of symptoms), since in later stages, phenomena of secondary axonal degeneration of the sural nerve can obscure its presence.

On the other hand, the terminology "sural nerve preservation" (SS) in GBS depends on the definition that is used, for example, that normality is considered versus the preservation of the PANS of the sural or of the sensory nerves that are explored in upper extremities (median, ulnar, or radial nerve) to be confronted with the sural. Classically, the SS seems to be specific of the demyelinating forms that imply the absence of a median nerve response, independently of the criteria used for the classification of the GBS subtype. However, some authors consider that the use of the median nerve can increase the false positives of SS for GBS considering the high prevalence of compression of the median nerve in the carpal channel in the general population.

Histopathologically, in patients who have presented SS, generalized inflammation, demyelination, and axonal degeneration of the spinal nerves have been observed, although the sural nerve is usually relatively preserved, which correlates with the absence of electrophysiological alterations[7]. In addition, the SS can be explained based on the fact that the nerve is registered near the lateral malleolus, somewhere between the spinal roots and its distal end in the foot, where there seems to be a lower predisposition to focal demyelinating damage[5].

The frequency of SS has been reported in different variants of GBS, being more frequent in the AIDP forms, followed by the MF syndrome (MFS) and occasionally found in patients with AMAN. It is not strange to observe this in the MFS that is mostly shown as a demyelinating form of GBS. However, due to the low prevalence found in SS and the high frequency of axonal forms described in our setting, it seems evident that SS is not applicable in electrophysiological screening to differentiate forms of GBS[8].

Conclusion

In conjunction with the clinical picture and other typical neurophysiological findings, the preservation of the sural nerve in the GBS seems to be a diagnostic support tool, which also adds to the fact that it is easy to obtain in the practical electrodiagnostic environment. In an isolated way, it provides information on the physiopathology of the phenomenon in the classic forms of GBS, mostly demyelinating. In the Mexican population, where axonal forms prevail, it is assumed that routine SS screening should not provide diagnostic support related to the low frequency in which it has been found in this study (17.6% of cases), so it should be considered in populations with predominance of the axonal form as complementary diagnostic method.

Conflicts of interest

None.

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.

References

1. van Doorn PA, Ruts L, Jacobs BC. Clinical features, pathogenesis, and treatment of guillain-barré syndrome. Lancet Neurol. 2008;10:939-50.
2. Hadden RD, Cornblath DR, Hughes RA, Zielasek J, Hartung HP, Toyka KV, et al. Electrophysiological classification of guillain-barré syndrome: clinical associations and outcome. Ann Neurol. 1998;44:780-8.
3. Hiew FL, Rajabally YA. Sural sparing in guillain-barré syndrome subtypes: a reappraisal with historical and recent definitions. Clin Neurophysiol. 2016;127:1683-8.
4. Al-Shekhlee A, Robinson J, Katirji B. Sensory sparing patterns and the sensory ratio in acute inflammatory demyelinating polyneuropathy. Muscle Nerve. 2007;35:246-50.
5. Umapathi T, Li Z, Verma K, Yuki N. Sural-sparing is seen in axonal as well as demyelinating forms of guillain-barré syndrome. Clin Neurophysiol. 2015;126:2376-80.
6. Grimm A, Oertl H, Auffenberg E, Schubert V, Ruschil C, Axer H, et al. Differentiation between Guillain-Barré syndrome and acute-onset chronic inflammatory demyelinating polyradiculoneuritis-a prospective follow-up study using ultrasound and neurophysiological measurements. Neurotherapeutics. 2019;16:838-47.
7. Bromberg MB, Albers JW. Patterns of sensory nerve conduction abnormalities in demyelinating and axonal peripheral nerve disorders. Muscle Nerve. 1993;16:262-6.
8. Derksen A, Ritter C, Athar P, Kieseier BC, Mancias P, Hartung HP, Sheikh KA, and Lehmann HC. Sural sparing pattern discriminates Guillain-Barré syndrome from its mimics. Muscle Nerve. 2014;50:780-4.

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ORIGINAL ARTICLE

Giant visual evoked potentials and their related factors in Mexican patients

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Abstract

Background: *In the analysis of electrical signals evoked through the application of appropriate stimuli to special sensory systems, the prolongation of latency and the incremented amplitude of the components studied are generally considered fundamental anomalies. However, the exaggerated increase in amplitude can also be an indicator of dysfunction in the central nervous system.* **Objective:** *The objective of the study was to evaluate giant visual evoked potentials (VEPs) and their related factors in patients at the Centro Médico Nacional (CMN) 20 de Noviembre.* **Materials and methods:** *At the CMN 20 de Noviembre, a descriptive, observational, and cross-sectional analysis of patients was performed at the Clinical Neurophysiology service, which found giant VEPs in the period from 2012 to 2018. The information obtained was from the clinical record of patients who met the selection criteria of the population to be studied. The IBM SPSS version 22.0 program was used for the statistical analysis.* **Results:** *A total sample of 36 patients was collected; the average age of the patients included in the study was 25.61 months. To improve and standardize the management of information, the population was divided into six categories according to the age group to which they belonged. The most frequent comorbidity of the patients was prematurity, observed in 63.9% (n = 23). No statistically significant difference was observed in the distribution of findings found in the different amplitudes and latencies regarding the age of the patient.* **Conclusions:** *There are greater latency and less amplitude in patients with giant visual evoked potentials.*

Key words: *Evoked potentials. Amplitude. Latency.*

Potenciales visuales gigantes evocados y sus factores relacionados en pacientes mexicanos

Resumen

Antecedentes: *En el análisis de las señales eléctricas evocadas mediante la aplicación de estímulos apropiados a sistemas sensoriales especiales, la prolongación de la latencia y la disminución de la amplitud de los componentes estudiados se consideran generalmente anomalías fundamentales. Sin embargo, el aumento exagerado de la amplitud también puede ser indicador de disfunción del sistema nervioso central (SNC).* **Objetivo:** *Evaluar potenciales evocados visuales gigantes y*

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factores relacionados en pacientes en el Centro Médico Nacional (CMN) 20 de Noviembre. **Materiales and métodos:** *Se realizó un análisis descriptivo, observacional y transversal en el CMN 20 de Noviembre de pacientes del Servicio de neurofisiología clínica en quienes se encontraron potenciales evocados visuales gigantes en el período 2012-2018. La información obtenida procede del expediente clínico de los pacientes que cumplieron los criterios de selección de la población a estudiar. Para el análisis estadístico se utilizó el programa IBM SPSS versión 22.0.* **Resultados:** *Se recogió una muestra de 36 pacientes; la edad media de los pacientes incluidos en el estudio fue de 25.61 meses. Para mejorar y estandarizar el manejo de la información, la población se dividió en seis categorías según el grupo de edad al que pertenecía. La comorbilidad más frecuente de los pacientes fue nacimiento prematuro, observada en 63,9% (n = 23). No se observaron diferencias estadísticamente significativas en los hallazgos de distribución de las amplitudes y latencias con respecto a la edad del paciente.* **Conclusiones:** *Hay una mayor latencia y una menor amplitud en los pacientes con potenciales evocados visuales gigantes.*

Palabras clave: *Potenciales evocados. Amplitud. Latencia.*

Introduction

Visual evoked potentials (VEPs) are visually evoked electrophysiological signals extracted from electroencephalographic activity in the visual cortex, recorded on the scalp[1]. Giant evoked potentials (poly(ethylene glycol) [PEGs]) are cortical evoked potentials that were initially described by Dawson in 1947 in patients with sensory stimulus reflex myoclonus[2,3]. They have also been described in many other disorders, primarily related to cortical myoclonus associated with progressive myoclonic epilepsy, idiopathic epilepsy, as well as toxic, metabolic, and infectious myoclonus. However, its clinical significance is not clearly defined, and its presence does not necessarily imply a pathology of the central nervous system (CNS)[2-5].

The amplitude of an evoked component can be measured from the baseline to the maximum peak or from the peak of one component to the peak of the next component with inverted polarity[6]. Multiple nosological entities have a common factor: the genesis of cortical evoked responses of great amplitude. These have been commonly called giant evoked potentials (PEG). In most cases, these are conditions that have the common clinical characteristic of the presence of myoclonus of cortical origin, such as progressive myoclonic epilepsy[7] and myoclonus of toxic origin[8].

VEPs are of particular clinical utility in determining a physiological abnormality where neurological and ophthalmological examinations are normal. VEPs are extremely sensitive and can detect a non-discernible dysfunction at the level of a neurological, ophthalmological examination, or another type of revision. The primary measurement of clinical interest is the latency of P100 after stimulus application. The abnormality is particularly clear if the P100 is normal after stimulation of the other eye, more posterior and chiasmatic lesions or a generalized cerebral dysfunction can cause a bilateral prolongation of the P100, usually with similar prolongation when testing each eye separately[9].

Methods

At the Centro Médico Nacional (CMN) 20 de Noviembre, a descriptive, observational, and cross-sectional analysis of patients was performed at the Clinical Neurophysiology Service, which found giant VEPs in the period from 2012 to 2018. The information obtained was from the clinical file of the patients that met the selection criteria of the population to study. The inclusion criteria were: patients of all ages, patients with identification of giant VEPs in at least two replicas for each side studied, and that they had a complete record with all the variables to study (age, gender, latency, and amplitude of the VEPs, signs, and symptoms on the occasion of shipment, the time elapsed from the beginning of the symptomatology to the realization of the VEPs, diagnoses at the time of the study of the VEPs, the pharmacological treatment used at the time of the study). VEPs were defined as (N75-P100) > 18 μV. The exclusion criteria were patients who did not strictly comply with the definition of giant evoked potentials and in whom there is not a minimum of two replicas with giant evoked potentials on each side studied. The elimination criterion was that there was incomplete information in the clinical file.

In the descriptive analysis, central tendency and dispersion measurement were handled, as well as proportions. For the statistical analysis, the IBM SPSS version 22.0 for Windows program was used. The resulting variables will be compared using the Student's t-test when they are measured in ratio scale and with Fisher's square or exact test when they are variables in the

Table 1. Comparison of the patient's age with the findings noticed in poly(ethylene glycol) at the Centro Médico Nacional 20 de Noviembre from 2012 to 2018

	Interpretation	N	Age (months)	p
Right amplitude	Normal	14	29.64	0.52
	Incremented	22	24.05	0.55
Left amplitude	Normal	9	23	0.66
	Incremented	27	27.3	0.65
Right latency	Normal	23	29.22	0.34
	Prolonged	13	20.92	0.25
Left latency	Normal	24	28.71	0.40
	Prolonged	12	21.25	0.30

Table 2. Comparison of the patient's sex with the findings noticed in poly(ethylene glycol) at the Centro Médico Nacional 20 de Noviembre from 2012 to 2018

	Interpretación	Male (%)	Female (%)	p
Right amplitude	Normal	11 (61.1)	3 (16.7)	0.008
	Incremented	7 (38.9)	15 (83.3)	
Left amplitude	Normal	1 (5.6)	8 (44.4)	0.009
	Incremented	17 (94.4)	10 (55.6)	
Right latency	Normal	13 (72.2)	10 (55.6)	0.24
	Prolonged	5 (27.8)	8 (44.4)	
Left latency	Normal	13 (72.2)	11 (61.1)	0.36
	Prolonged	5 (27.8)	7 (38.9)	

nominal scale. A significant difference will be taken when a "p" < 0.05 is obtained.

Results

A descriptive analysis was carried out at the CMN 20 de Noviembre in Mexico City. The study included patients of any age, who had their VEP in at least two replicas for each side, and who had a complete record in the service with all of the variables to be studied at the Neurophysiology Service Clinic from 2012 to 2018. The data collected were age (in months), sex, referral service, shipping diagnosis, pharmacological treatment, values obtained of amplitude (right and left), and latency (right and left).

A total sample of 36 patients was collected. The average age was 25.61 months (standard deviation 25.27 months, minimum 1 month, and maximum 96 months), of which 50% (n = 18) of the sample corresponds to the male gender and 50% (n = 18) to female gender. The most frequent comorbidity of the patients was prematurity, observed in 63.9% (n = 23). No statistically significant difference was observed in the distribution of findings found in the different amplitudes and latencies concerning the patient's age (Table 1). However, a statistically significant difference was found in the variable of right and left amplitude with respect to gender (Table 2).

To improve and standardize information management, the population was divided into six categories according to the age group to which they belonged (Table 3). Analysis of variance was performed according to the age groups previously described to find the mean and standard deviation of the variables of amplitude (right and left) and latency (right and left). In the group of children up to 6 months old, a mean value in the right amplitude of 16.44 uV (standard deviation of 5.25 uV, minimum 10uV, and maximum 22uV) was found. In patients from 7 to 12 months old, the average value found was of 21.23 uV (standard deviation 14.87, minimum 6uV, and maximum 56 uV). In the group of patients from 13 to 18 months old, an average of 26.70 uV was found (standard deviation of 8.43, minimum 20 uV, and maximum 38 uV). Patients from 19 to 24 months of age had a mean of 26.97 uV (standard deviation of 8.88 uV, minimum 20 uV, and maximum 37 uV). In patients with ages 25-48 months, mean right amplitude of 16.78 uV was found (standard deviation 9.21 uV, minimum 4 uV, and maximum 26 uV), and in the group over 49 months old, an average of 16.49 uV was found (standard deviation 11.50 uV, minimum 7, and maximum 23); taking into account all the data obtained, an average of 20.51 uV (standard deviation 11.5,

Table 3. Division by age groups of the studied population

Group	Age (months)	n	Percentage
1	Up to 6	4	11.1
2	7-12	15	41.7
3	13-18	4	11.1
4	19-24	3	8.3
5	25-48	6	16.7
6	Above to 49	4	11.1

Table 4. Analysis of amplitude and latency means by age group in patients undergoing visual evoked potentials from 2012 to 2018 at the Centro Médico Nacional 20 de Noviembre

	Up to 6 months	7-12 months	13-18 months	19-24 months	25-48 months	Above 49 months	p
Right amplitude (uV)	16.44	21.23	26.70	26.97	16.78	16.49	0.60
Left amplitude (uV)	21.91	22.85	16.23	24.37	23.25	20.05	0.84
Right latency (mseg)	136	155.33	143.5	133.67	134.67	142.36	0.46
Left latency (mseg)	139.25	149.20	137.25	139.67	137.17	140.08	0.51

minimum 4, and maximum 56), and a "p" = 0.609 of the right amplitude was obtained.

In the same way, statistical analysis was performed for the values obtained in left amplitude, finding an average measurement in patients up to 6 months of 21.91 uV (standard deviation 17.35 uV, minimum 7 uV, and maximum 46 uV). In the group from 7 to 12 months, an average of 22.85 uV was found (standard deviation 9.19 uV, minimum 7 uV, and maximum 42 uV). In 13-18 months patients, an average of 16.23 uV was obtained (standard deviation 12.29 uV, minimum 2uV, and maximum 31 uV). In patients aged 19-24 months, they had a mean of 24.37 uV (standard deviation 8.33 uV, minimum 17 uV, and maximum 33 uV). In patients from 25 to 48 months, a mean of 23.25 uV was found (standard deviation of 2.37 uV, minimum 20 uV, and maximum 27 uV), and in patients older than 49 months, an average of 20.05 uV was found (standard deviation 5.47 uV, minimum 13 uV, and maximum 27 uV); the average of the 36 values evaluated for the left amplitude was 21.89 uV (standard deviation of 9.32 uV, minimum 2 uV, and maximum 46 uV) and a "p" = 0.847. For the right latency, in the group of patients up to 6 months of age, an average of 136 ms was obtained (standard deviation 30 ms, min 120 ms, and maximum 181 ms). In the group of patients from 7 to 12 months, an average of 155 ms was reported (standard deviation of 41.8 ms, minimum 108 ms, and maximum 258 ms). In patients from 13 to 18 months, an average of 143.5 ms was obtained (standard deviation 28.9 ms, minimum 110 ms, and maximum 177 ms). The average found in patients aged 19-24 months was 133.67 ms (standard deviation of 25.0 ms, minimum 105 ms, and maximum 151 ms), in patients aged from 25 to 48 months, they had an average of 134.67 ms (standard deviation of 32.5 ms, minimum 107 ms, and maximum 194 ms), and in the group of patients older than 49 months there was an average of 117 ms (standard deviation of 11.74 ms, minimum 102 ms, maximum 129). For the right latency, a global average of 142.36 ms was obtained (standard deviation of 34,859 ms, min 102 ms, and max 258 ms) with a "p" = 0.460. Statistical analysis was also performed to assess left latency by groups and overall, in patients younger than 6 months. They obtained an average of 139.25 ms (standard deviation of 25.35 ms, minimum 119 ms, and maximum 176 ms). In the group of patients 7-12 months, an average of 149.2 ms was observed (standard deviation of 33.9 ms, minimum 106 ms, and max 200 ms). The average found in patients aged 13-18 months was 137.25 ms (standard deviation 25.6, minimum 115 ms, and maximum 174 ms). In the group of patients from 19 to 24 months, an average of 139.67 ms was found (standard deviation 27.46 ms, minimum 108 ms, and maximum 157 ms). In patients from 25 to 48 months, an average was determined of 137.17 ms (standard deviation 34.8 ms, minimum 102 ms, and maximum 198 ms), and in patients older than 49 months, an average of 114.25ms (standard deviation 7.1 ms, minimum 106 ms, and maximum 123 ms); the global left latency values had an average of 140.08 ms (standard deviation of 30.1 ms, range 102-200 ms), and a "p" = 0.51 was obtained. A compilation of the previous data can be seen in table 4.

Right amplitude data were matched with right latency and used Fisher's exact test getting a "p" = 0.62 and a correlation of 16.7%; in the same way, it was performed with data of left amplitude and left latency obtaining a "p" = 0.626 and a correlation of 17.1%. Dispersion data graph was made comparing the distribution of means by age groups of right amplitude and right latency, as well as left amplitude and left latency; observing in both graphs that at greater latency there is a less amplitude (Figures 1 and 2).

Discussion

Visual function is considered one of the most important perceptions for development. During motor development, vision provides crucial feedback to the vestibular and

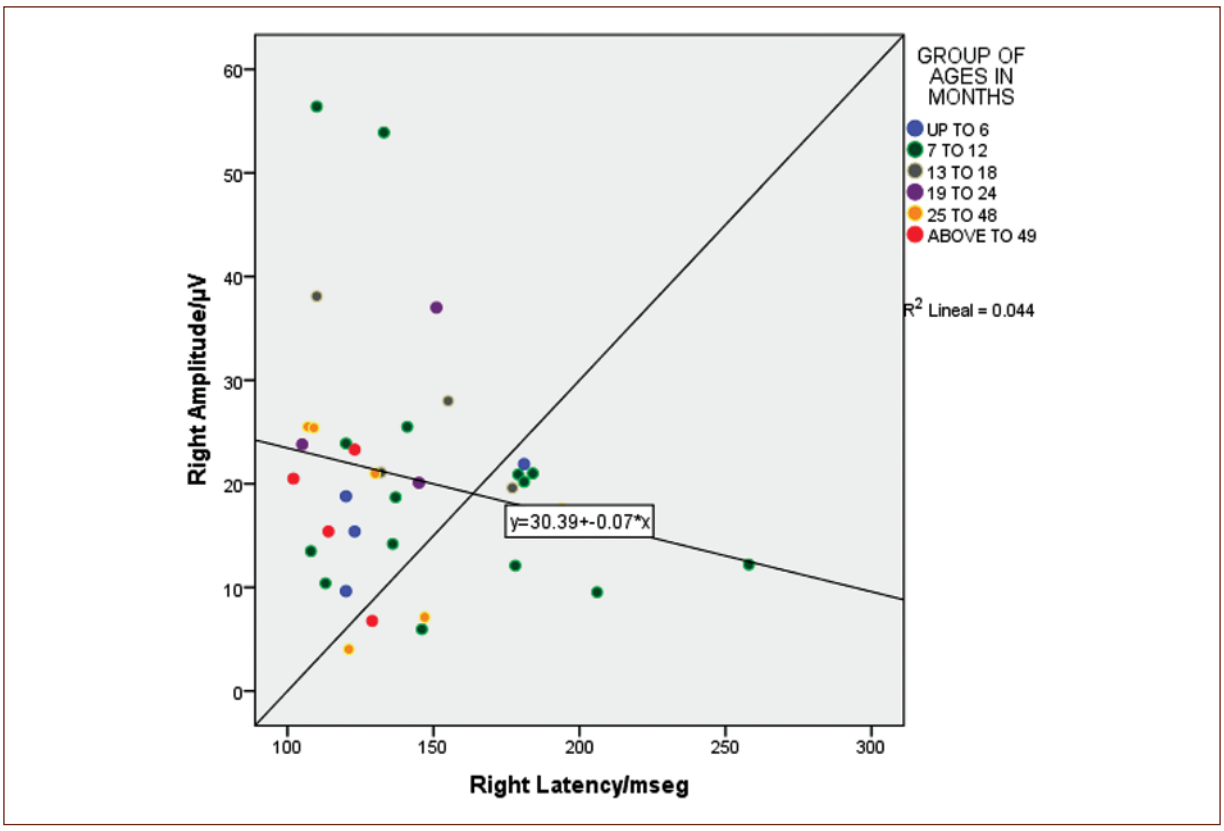

Figure 1. Dispersion by age groups of average right amplitude and right latency in patients undergoing visual evoked potentials at the Centro Médico Nacional 20 de Noviembre from 2012 to 2018.

proprioceptive systems. The vision allows the development of integrative functions such as hand-eye coordination, visual-manual-oral coordination, learning and object recognition, and learning and visual-spatial recognition.

VEPs are averaged cortical potentials that assess the integrity of the visual pathway. They are easily detectable in premature infants and show a different pattern of maturation. They have shown that they can predict adverse prognoses in infants with generalized CNS conditions, particularly hypoxic-ischemic encephalopathies.

The giant evoked potentials are evoked potentials that were first described by Dawson in 1947 in patients with myoclonus reflex to the sensory stimulus. They have also been described in other disorders, primarily related to cortical myoclonus associated with progressive myoclonic epilepsies (e.g., neuronal ceroid lipofuscinosis, Lafora disease, and mitochondrial cytopathies), generalized idiopathic epilepsies, post-anoxic, toxic, and infectious myoclonus[3].

In the present study, which was carried out at the CMN 20 de Noviembre of the Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, after analyzing the information collected in the period from 2012 to 2018 of the patients who met the inclusion criteria, a total sample of 36 patients was collected. The average age was 25.61 months, of which 50% of the sample corresponds to the male gender and 50% to the female gender. The most frequent comorbidity of the patients was prematurity, observed in 63.9% (n = 23)[3].

At the time of correlating the variables found, it was generally found that the greater the latency, the lower the amplitude, and a statistically significant difference was found in the variable of right and left amplitude with respect to gender. That is that the amplitude for the right side was significantly increased in female patients compared to male patients, while the amplitude for the left side was significantly increased in male patients compared to female patients. The above, together with the fact that the total sample corresponds to the same proportion of patients concerning gender, give greater validity to the finding, which could indicate a certain correlation of predominance of the side affected depending on gender. This could probably be related to the physiological and structural differences between

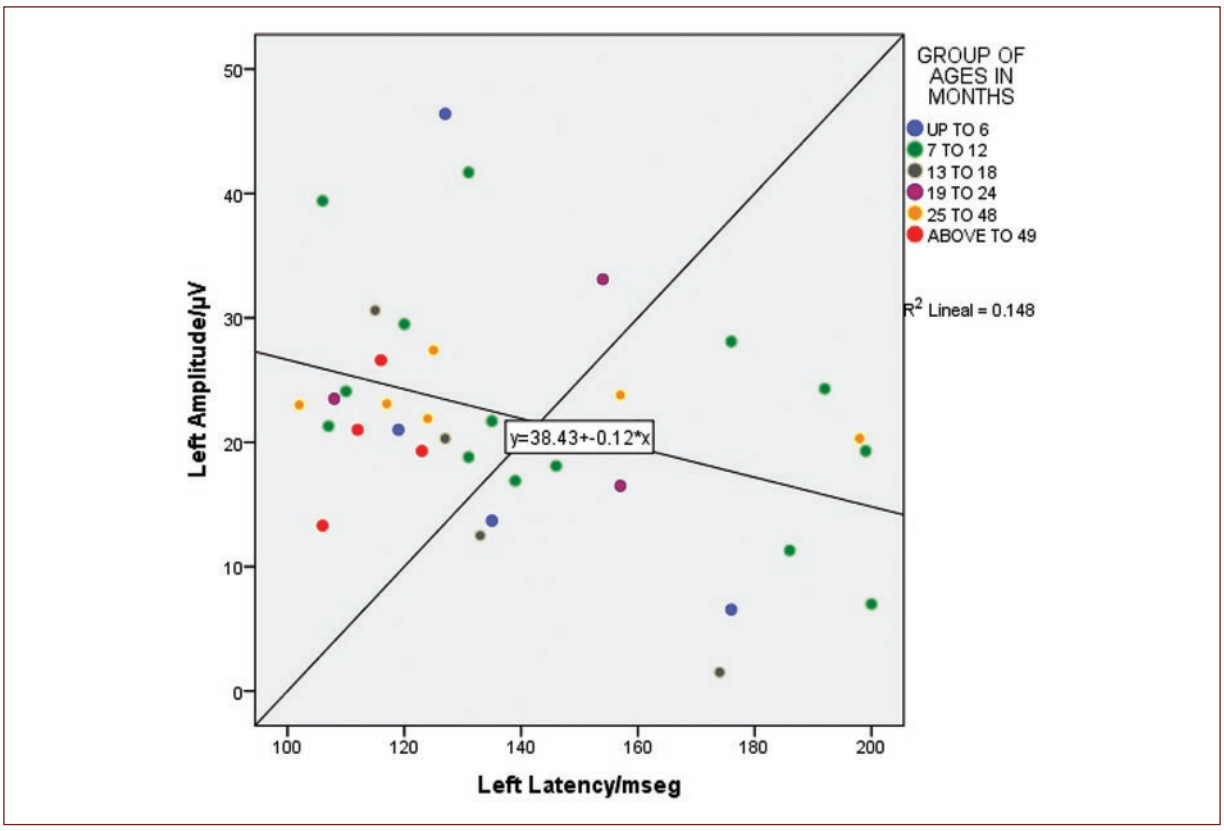

Figure 2. Dispersion by age groups of mean left amplitude and left latency in patients undergoing visual evoked potentials at the Centro Médico Nacional 20 de Noviembre from 2012 to 2018.

genders. This finding has not been documented in the published literature. On the other hand, only 1 patient (2.7%) of the total sample had the diagnosis of epilepsy (West Syndrome) in which an increase in the amplitudes of the VEP for both sides was found, which is related to the possible presence of cortical hyperexcitability described in the reference literature[3,10].

Another aspect that must be taken into consideration is the finding that most of the patients with giant VEPs were premature (63.9% of the total sample). This was a precedent and the reason for being sent. Such findings had not been previously reported in the literature and one of the hypotheses could be the fact that in the 1st year of life, there are lower impedances specific to the characteristics of the tissues at those ages such as the dimensions (thickness of skin and bone).

It must be admitted that the present study has multiple limitations due to its design: the number of the sample and the quantity of factors studied. However, it is important to add that this could be considered a pivotal study that can establish the basis for studies of greater statistical value such as prospective studies of control cases among others. Furthermore, due to the small sample, it was not possible to perform significant correlations between various factors. In such case, considering increasing the sample and including more factors such as metabolic, hemodynamic, and anthropometric measurements, results with greater statistical significance can be obtained.

Another possibility of study that can be considered based on the present and considering the theory of cortical hyperexcitability could be the performance of electroencephalograms in patients with giant VEPs and their correlation.

At present, no study in the published literature meets the characteristics of the present study, so in the present work, we tried to provide support for another possible utility for the evoked visual potentials. It was demonstrated by a statistical analysis that related factors exist with statistical significance, and this establishes the basis for further study on the subject.

Conclusion

It was generally verified that the greater the latency, there is less amplitude, and a statistically significant

difference was found in the variable of right and left amplitude with respect to gender. That is that the amplitude for the right side was significantly increased in female patients compared to male patients, while the amplitude for the left side was significantly increased in male patients compared to female patients. Furthermore, most of the patients with giant VEPs were premature; this has not been reported before. A possible explanation is because, in the 1st years of life, there are lower impedances specific to the characteristics of the tissues at those ages.

No significant correlation was found between the associations of the rest of the variables.

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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 declare that no patient data appear in this article.

References

1. Odom JV, Bach M, Brigell M, Holder GE, McCulloch DL, Mizota A, et al. ISCEV standard for clinical visual evoked potentials: (2016 update). Doc Ophthalmol. 2016;133:1-9.
2. Dawson GD. Cerebral responses to electrical stimulation of peripheral nerve in man. J Neurol Neurosurg Psychiatry. 1947;10:134-40.
3. Martín-Palomeque G, Castro-Ortiz A, Pamplona-Valenzuela P, Saiz-Sepúlveda MÁ, Cabañes-Martínez L, López JR. Large amplitude cortical evoked potentials in nonepileptic patients. Reviving an old neurophysiologic tool to help detect CNS pathology. J Clin Neurophysiol. 2017;34:84-91.
4. Liepert J, Haueisen J, Hegemann S, Weiller C. Disinhibition of somatosensory and motor cortex in mitochondriopathy without myoclonus. Clin Neurophysiol. 2001;112:917-22.
5. Ng K, Jones S. The “enhanced N35” somatosensory evoked potential: its associations and potential utility in the clinical evaluation of dystonia and myoclonus. J Neurol. 2007;254:46-52.
6. Baez Martín MM, Gómez Fernández L, Cabrera Abreu I, Alvarez González L, Araujo F. Giant evoked potentials. Rev Neurol. 2001;33:1120-5.
7. Acharya JN, Satischandra P, Asha T, Shankar SK. Lafora’s disease in South India: a clinical, electrophysiologic, and pathologic study. Epilepsia. 1993;34:476-87.
8. Calleja J, Carpizo R, Berciano J, Quintial C, Polo J. Serial waking-sleep EEGs and evolution of somatosensory potentials in Creutzfeldt-Jakob disease. Electroencephalogr Clin Neurophysiol. 1985;60:5048.
9. Drislane FW. Visual evoked potentials. In: Blum AS, Rutkove SB, editors. The Clinical Neurophysiology Primer. Totowa: Humana Press; 2007. p. 461-74.
10. Serrao M, Cardinali P, Rossi P, Perrotta A, Bartolo M, Parisi L, et al. Spinal myoclonus with giant somatosensory evoked potentials and enhanced long-loop reflex: a case report. Funct Neurol. 2004;19:203-6.

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REVIEW ARTICLE

Biomarkers of gliomas and their impact on diagnosis, prognosis, and treatment

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Abstract

Tumors of the central nervous system (CNS) are due to the abnormal growth of cells in the brain or spinal cord that can become malignant and spread by metastases. Gliomas are the most frequent malignant tumors of the CNS, characterized by their heterogeneity and invasiveness. The high lethality of gliomas is due, among other causes, to the low efficacy of current treatments. The few biomarkers effective for the classification, prognosis, and treatment of the various types of gliomas are a useful tool for their management. New markers are currently being sought to make a more accurate diagnosis and for their potential as therapeutic targets. In this review, we describe the traditional biomarkers and other biomarkers that could be used to improve the diagnosis, prognosis, and treatment of gliomas.

Key words: *Glioma. Biomarker. Diagnosis. Prognosis. Treatment.*

Biomarcadores de gliomas y su impacto en el diagnóstico, pronóstico y tratamiento

Resumen

Los tumores del sistema nervioso central (SNC) se deben al crecimiento anormal de las células de los tejidos del encéfalo o la médula espinal y pueden malignizarse y diseminarse por metástasis. Los gliomas son los tumores malignos más frecuentes del SNC y se caracterizan por su heterogeneidad e invasividad. La elevada letalidad de los gliomas se debe, entre otras causas, a la baja eficacia de los tratamientos actuales. Los escasos biomarcadores útiles para la clasificación, el pronóstico y el tratamiento de los diversos tipos de gliomas representan una herramienta útil para su manejo. Actualmente se buscan nuevos marcadores para hacer el diagnóstico más preciso y por su potencial como blancos terapéuticos. En esta revisión describimos los biomarcadores tradicionales y algunos otros que podrían mejorar el diagnóstico, pronóstico y tratamiento de los gliomas.

Palabras clave: *Glioma. Biomarcador. Diagnóstico. Pronóstico. Tratamiento.*

Primary tumors of the central nervous system (CNS) are a complex and heterogeneous group with wide diversity in diagnosis, prognosis, and treatment. Among more than 100 histological types of primary CNS tumors, the most frequent are the encephalic ones, which account for 85-90% of all diagnosed tumors[1].

Meningiomas and pituitary tumors are the most incident primary brain tumors (53.9%) followed by

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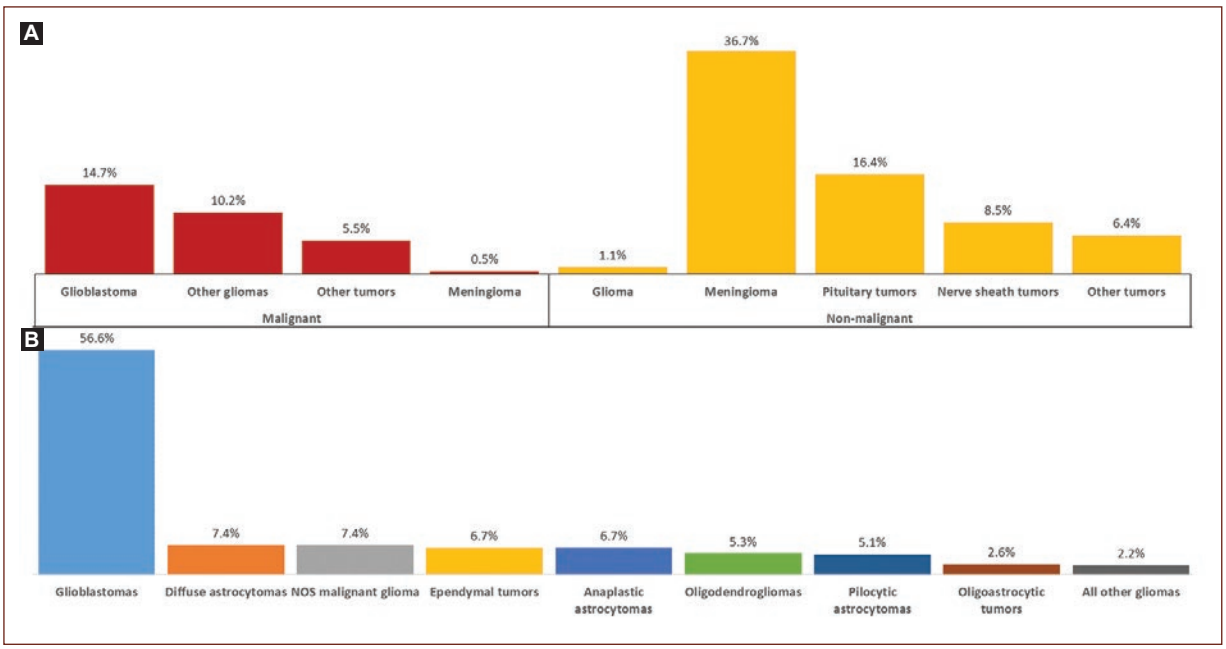

Figure 1. Incidence of malignant tumors of the central nervous system (CNS) and histological types of gliomas. **A:** incidence of CNS tumors; 69.1% non-malignant, 30.9% malignant. **B:** histological types of gliomas. *(Ostrom et al.[2]).*

glioblastomas. Glioblastomas are the most incident primary CNS malignant tumors (57.3%). The less frequent gliomas are oligoastrocitomas, and children are the most vulnerable group for brain tumor incidence[2].

The vast majority of gliomas do not spread to other parts of the body but only to other parts of the brain or the spinal cord[3].

Gliomas

Gliomas are a category of primary malignant tumors of the CNS with various subtypes of heterogeneous characteristics[4]. The molecular mechanism of glioma formation is not clear[4,5], it is considered that these tumors originate from progenitor glial cells or stem cells with glial properties. For these reason, different types of gliomas are named according to the cells from which they seem to have arisen[6].

Gliomas are the most frequent malignant tumors of the CNS (Fig. 1A), and their aggressiveness is mainly due to their invasiveness. The inefficacy of treatments for the wide variety of glioma subtypes implies an unfavorable prognosis[7], reflected in their high mortality rates[8].

Glioblastoma multiforme (GBM) is the most lethal and most common glioma subtype (Fig. 1B). Its high mortality rate derives from the inefficacy of the few available treatments[9]. Whilst low-grade gliomas have a low mortality rate, their highly epileptogenic characteristic seizures have a drastic impact on the patient's life quality[10].

Classi□cation of gliomas

Morphological

Gliomas are classified as diffuse or non-diffuse by the World Health Organization (WHO). Non-diffuse types have circumscribed growth patterns, and Grades II through IV are assigned to the diffuse ones according to their severity[11].

In the case of diffuse gliomas, the diagnosis based on the histological characteristics starts with the identification of the morphology and cell type from which they seem to have originated (Fig. 2)[12]. Some high-grade neoplasms have aggressive behaviors, reflected on the cell damage due to the tumor growth, making the diagnosis largely dependent on the experience of the analyst[11].

The WHO classification of gliomas based only on morphological and histological characteristics is subjective and inconsistent, since many histologically identical diffuse gliomas differ in progression, response to treatment, and outcome[13].

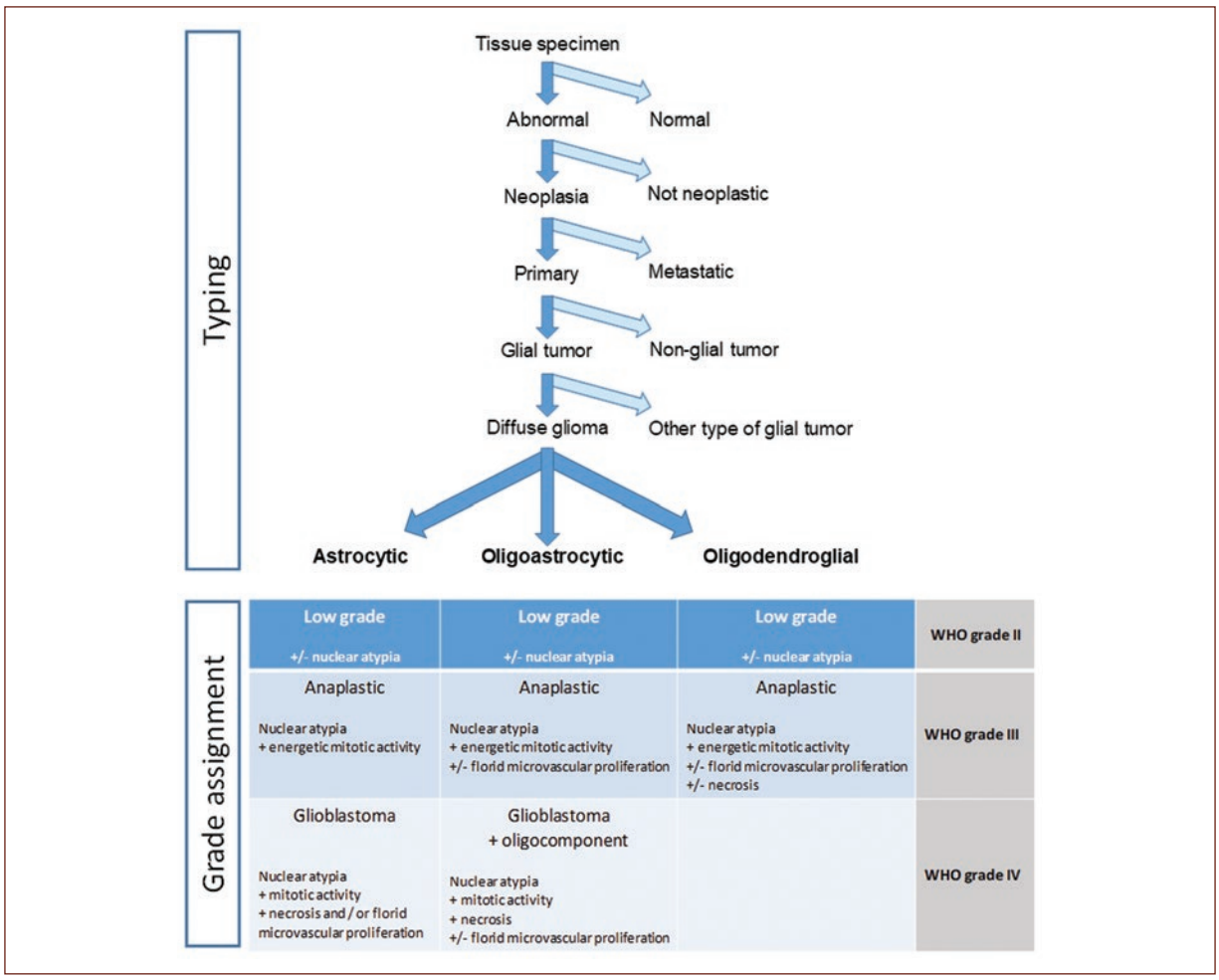

Figure 2. Algorithm for typing, grade assignment, and microscopic classification of diffuse gliomas. Decision tree for typing and grading of gliomas by histological methods, including microscopic criteria for the classification of diffuse gliomas *(adapted from Wesseling et al.[6]).*

Advances in molecular marker identification and image processing technologies have led to a more precise classification that has improved the accuracy of the diagnosis and prognosis of CNS tumors that complement the morphological and histological characteristics[14]. The fourth edition of the WHO CNS tumor classification included for the first time a criterion based on the presence/absence of two molecular markers in gliomas (Fig. 3): the isocitrate dehydrogenase (*IDH*) gene mutation and the 1p/19q codeletion[15].

IDH1 and *IDH2* mutations are found in astrocytomas, oligodendrogliomas, secondary glioblastomas, and in Grades II and III oligoastrocytomas, whereas Grades II and III diffuse gliomas with wild-type *IDH* genes have molecular characteristics and behavior of glioblastomas[11].

The presence of both an *IDH* mutation and the 1p/19q codeletion is characteristic of diffuse oligodendroglioma-type gliomas. In contrast, an *IDH* mutation without 1p/19q codeletion identifies astrocytoma-type gliomas[11].

These new criteria have helped to integrate the diagnosis, characterization, surgical interventions, prognosis, and multiple options of new glioma treatments[10,14,16].

Magnetic resonance and basic biomarkers

A biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogens, or pharmacological responses to a therapeutic intervention"[17]. Many biomarkers correspond to molecular characteristics that provide information for the diagnosis and prognosis of diseases. In the field of CNS tumors, biomarkers represent a means to understand the molecular pathways and deregulation mechanisms related to these tumors

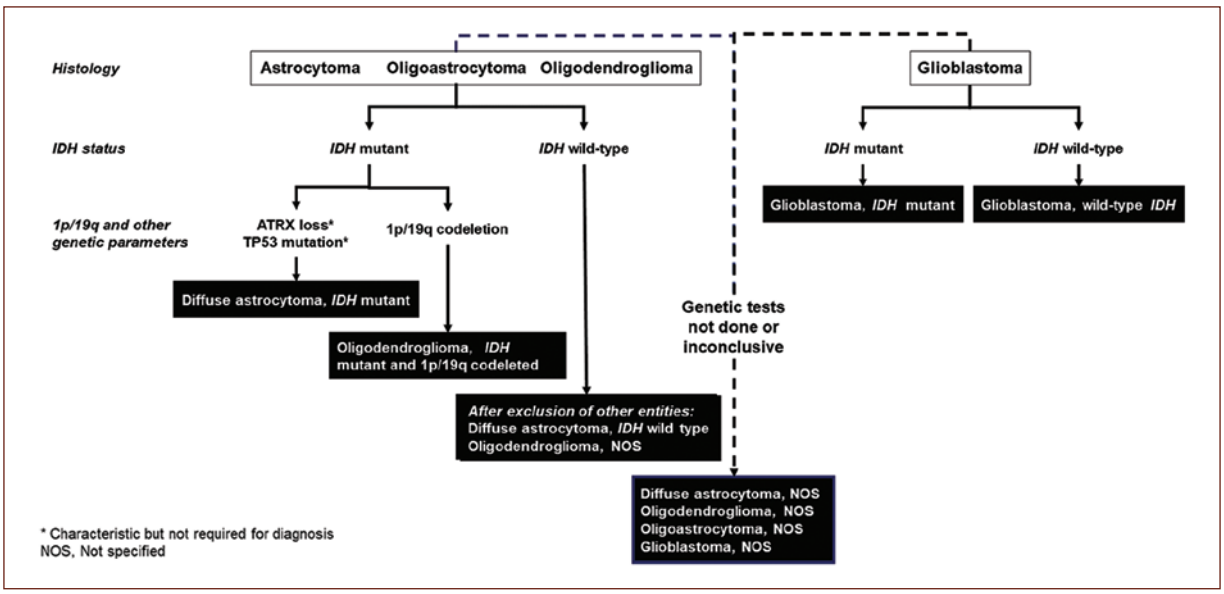

Figure 3. Simplified algorithm for glioma classification based on molecular biomarkers. The World Health Organization classification of gliomas uses this algorithm based on molecular biomarkers *(adapted from Louis et al.[30]).*

that even have the potential to be extended to other cancer types[12,16].

The incorporation of a criterion based on the molecular characteristics of gliomas greatly served to redefine tumor subtypes in the WHO classification[11,13]. This is why molecular tools are currently used for the diagnosis of gliomas besides traditional histology and imaging methods[4].

In the field of neuro-oncology, machine learning methods based on magnetic resonance imaging (MRI) in conjunction with biomarkers outperform traditional statistical methods[18].

The list of current biomarkers for human gliomas is limited and the search for new markers is relevant not only to improve diagnosis but also for the potential to find new therapeutic targets for various glioma types[19].

MRI, basic and additional biomarkers for the diagnosis, prognosis, and treatment of gliomas (Table 1) are described in this and the following sections.

MRI

MRI is a routine procedure for the diagnosis of gliomas that gives a structural overview of the location, detailed anatomy, and pathological information of the tumor and allows the acquisition of additional physiological details in conjunction with other advanced techniques. Many studies to determine the molecular profiles, histological grade, and prognosis of gliomas are based on magnetic resonance images acquired when the tumor is first detected[18].

Biomarkers in conjunction with MRI help to improve the classification, prognosis, and choice of glioma treatment[9]. An example is a radiomics-based method with three-dimensional MRIs obtained with specialized equipment allowing non-invasive estimation of the IDH1 gene mutation status[16].

IDH mutations

IDH genes are traditional glioma biomarkers. Mutations in the loci encoding the human isoforms 1 (*IDH1*) and 2 (*IDH2*) are associated with better prognosis and therapeutic response of patients with gliomas[16,20]. In low-grade gliomas and few secondary glioblastomas have been identified, the single nucleotide polymorphism in codon 132 (R132H), which determines the amino acid changes from arginine to histidine in the IDH1 isoform, as well as in the 172 codon analog of the IDH2 isoform[20].

Besides the fact that IDH1 and IDH2 gene mutations are relevant diagnosis and prognosis biomarkers, they are also associated with the incidence of pre-operative seizures in patients with low-grade gliomas[10]. In conjunction with the analysis of IDH1/2 mutations, two more markers are used for a more accurate diagnosis of gliomas: the chromosome codeletion 1p/19q[21] and the methylation of the O^6-methylguanine-DNA-methyltransferase (MGMT) gene promoter[13].

Table 1. Basic and additional glioma biomarkers

Biomarkers		Types of gliomas	Use	References
Basic	Magnetic resonance imaging	Diffuse astrocytoma WHO (II-IV)	Identify *IDH* mutant status	16
	IDH1/2 mutation	WHO (II-III)	Favorable prognosis	10
	MGMT promoter methylation	Glioblastoma multiforme WHO Grade IV	Favorable prognosis Chemotherapy sensitivity	13
	1p/19q codeletion	Oligodendrogliomas	Favorable prognosis	13
Additional	*ATRX* mutation	Anaplastic astrocytoma	Favorable prognosis	21
	GFAP expression	Astrocytomas	Not a marker of lesser malignancy	4
	SND1 overexpression	WHO Grades III-IV	Unfavorable prognosis Promotes RhoA expression Potential target	24
	RhoA overexpression	WHO Grades III-IV	Unfavorable prognosis Promotes cell proliferation	24,25
	TIP30 expression	WHO Grades III-IV	Favorable prognosis Suppress *EGFR*	19,27
	EGFR mutation	WHO Grades IV	Unfavorable prognosis	13
	LncRNAs H19, MALAT1, POU3F3	WHO Grades II-IV	Unfavorable prognosis	29

Reviewing the IDH1/2 mutation status is a routine study for glioma classification[13], complemented with non-invasive methods that detect the IDH status to quantify the patterns in various types of gliomas, mainly of low grade. An example is a non-invasive method that correlates MRI with the estimation of the IDH1 status in Grade II gliomas through segmentation, extraction of high-performance characteristics, selection, and classification of three-dimensional images through the use of radiomics.[16]

MGMT gene promoter methylation

The MGMT gene encodes a DNA repair protein whose expression is affected by epigenetic changes such as methylation, which induces silencing[22].

MGMT gene promoter methylation is a favorable prognostic marker for patients with high-grade astrocytic gliomas and also predicts a favorable response to the chemotherapy of anaplastic gliomas and glioblastomas with wild-type *IDH*1/2 profiles, as well as glioblastomas in older adults[13].

1p/19q codeletion

A marker widely used in the classification of gliomas is the codeletion or loss of the heterozygous 1p/19q region, due to a centromeric translocation[23]. Glial tumors with this codeletion are defined as oligodendroglial tumors and have a favorable prognosis[13].

Additional biomarkers

Staphylococcal nuclease domain 1 (SND1)

Overexpression of the SND1 protein is a common phenomenon in various malignant human tissues. SND1 promotes the malignant glioma phenotype through an epigenetic route that generates the topologic interaction of chromatin by promoting histone acetylation besides stimulating downstream transcription activation of the *RhoA* (Ras homolog family member A) gene that encodes the GTPase1 and promotes cell proliferation and invasiveness. SND1 and RhoA are, therefore, independent indicators of unfavorable prognosis of gliomas[24].

Silencing the SND1 gene suppresses the proliferation and invasion of glioma cells, a finding indicating that the gene is not only a biomarker but a potential therapeutic target[24].

RhoA

Overexpression of the RhoA protein has been associated with tumor cell proliferation and metastasis[25]. The inclusion of RhoA as a non-favorable

prognostic biomarker of high-grade gliomas derives from the fact that SND1 activates transcription of the RhoA gene in cultured glioma cells and that the RhoA protein regulates the expression of *CCND1*, *CCNE1, CDK4,* and *CDKN1B* genes and accelerates the G1/S transition of the cell cycle that promotes proliferation[16].

Glial fibrillary acidic protein (GFAP)

The GFAP, a classic astrocytoma marker, is used to determine glial differentiation associated with lesser malignancy and is currently in the clinical and experimental phase for other glioma subtypes. However, GFAP does not seem to be a good marker of lower malignancy and differentiation among astrocytoma subtypes, because it is not only expressed in mature astrocytes but also during the development of stem cells in the adult brain[4].

GFAP has a large number of splicing variants and different expression ratios of the α and δ GFAP isoforms (GFAPδ/α) may be found. A GFAPδ/α low expression ratio is associated with low-grade astrocytomas, whereas a high ratio is associated with high-grade astrocytomas[26]. Quantification of the GFAP α and δ isoforms differentiates high- and low-grade astrocytomas and avoids confusing overall GFAP expression with less malignancy[4,26].

TIP30

The TIP30 gene encodes the Tat30 interaction protein, a tumor suppressor protein involved in tumor cell growth, metastasis, and angiogenesis in various cancers[27]. TIP30 regulates tumor formation and provides a clear prognosis to glioma patients[19].

TIP30 expression correlates inversely with histological classification, pathological grade, tumor size, and epidermal growth factor receptor (EGFR) expression[19]. *TIP30* expression levels decrease significantly in glioma tissue, and patients with positive *TIP30* expression have greater survival and longevity than those with silenced *TIP30*[19].

In glioma cell cultures *TIP30* decreases the expression of the *EGFR* and downstream associated kinase genes such as *ERK* and *AKT*. These findings indicate that *TIP30* could suppress oncogenesis and glioma progression and serve not only as a prognostic biomarker but also as a potential therapeutic target[19].

ATRX

The *ATRX* gene encodes a protein essential for development, which regulates gene expression at the level of transcription by chromatin remodeling[28].

ATRX gene mutation is a widely used biomarker for the classification of astrocytomas, and its loss is a favorable prognostic marker. *ATRX* loss and 1p/19q codeletion status have been used to reclassify anaplastic oligoastrocytomas. Tumors with *ATRX* loss have a course similar to that of anaplastic astrocytomas, whereas those with both *ATRX* loss and 1p/19q codeletion have a course similar to that of anaplastic oligodendrogliomas[21].

EGFR

The *EGFR* gene mutation is a glioma biomarker because it cancels EGFR expression[13] and correlates inversely with TIP30 overexpression[19].

Long non-coding RNAs (LncRNAs)

LncRNAs are a class of non-protein-translated RNAs[29]. There is a high expression of LncRNAs participating in brain development under normal conditions and in various pathogenic processes that include glioma formation.

The association of LncRNAs with the initiation, differentiation, progression, recurrence, and characteristics of glioma progenitor stem cells makes them potential biomarkers for glioma subclassification, diagnosis, and prognosis. Knowledge of the key routes of LncRNAs for brain development can help to understand glioma formation and to find potential therapeutic targets[29].

Impact of biomarkers

When a glioma is suspected, immediate actions are directed to obtain the MRI of the tumor and to confirm the diagnosis by biopsy. *IDH* status, *MGMT* promoter methylation, and 1p/19q codeletion are the major biomarkers for tumor classification. The presence of wild-type *IDH* is associated with poor prognosis, while 1p/19q codeletion and *MGMT* promoter methylation are associated with favorable prognosis.

Since the aggressiveness of the various glioma types is variable, developing additional prognostic markers could improve patient management. The addition of SND1 could provide key elements for the

classification of high-grade (III-IV) gliomas[24]. The distinction between the GFAPα and GFAPδ isoforms favors the classification of astrocytomas, and the identification of LncRNAs such as H19, MALAT1, and POU3F3, related to high-grade malignant gliomas, can improve the classification and the evaluation of malignancy[29].

SND1 and RhoA are associated with poor prognosis, in contrast to *TIP30* expression and *ATRX* loss, considered as better prognosis biomarkers.

The current treatment of the various glioma types mostly includes radiotherapy, surgical intervention, and chemotherapy. The use of each method depends on the severity of the tumor, and more advanced cases require a combined approach.

The choice of treatment is relevant to the patient's life quality. A current problem is the lack of specific therapies that should be developed for each glioma subtype.

Advances in the field of glioma biomarkers open a landscape of opportunities to find additional targets such as SND1 and TIP30, which can inhibit the growth of tumor cells. The study of LncRNAs is also a promising nascent route to improve glioma treatment.

Conclusion

Biomarkers have substantially contributed to improve the diagnosis, prognosis, and treatment of gliomas. The combination of traditional imaging methods with molecular markers such as *IDH1* and *IDH2* gene mutations, *MGMT* gene promoter methylation, and 1p/19q codeletion considerably improves the effectiveness of statistical and histological methods that in most of the cases depend of the analyst's experience. SND1, GFAPα, and GFAPδ are three recently found promising biomarkers to improve diagnosis. TIP30 protein expression and *ATRX* gene deletion denote a favorable prognosis, and both are potential therapeutic targets. LncRNAs should be examined to assess their use as glioma biomarkers.

Conflicts of interest

The authors declare no 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.

References

1. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2011-2015. Neuro Oncol. 2018;20:1-86.
2. Ostrom QT, Cioffi G, Gittleman H, Patil N, Waite K, Kruchko C, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2012-2016. Neuro Oncol. 2019;21:1-100.
3. Reifenberger G, Blümcke I, Wesseling P, Pietsch T, Paulus W. Pathology and classification of tumors of the central nervous system. In: Oncology of CNS Tumors. Cham: Springer International Publishing; 2019. p. 3-89.
4. Van Bodegraven EJ, Van Asperen JV, Robe PA, Hol EM. Importance of GFAP isoform-specific analyses in astrocytoma. Glia. 2019;67:1417-33.
5. Li Y, Cai B, Chen S, Fu X, Pang X, Zhu X, et al. Overexpression of tat-interacting protein 30 inhibits the proliferation, migration, invasion and promotes apoptosis in bladder cancer cells. J Cancer Res Ther. 2018; 14:S713-8.
6. Wesseling P, Kros JM, Jeuken JW. The pathological diagnosis of diffuse gliomas: towards a smart synthesis of microscopic and molecular information in a multidisciplinary context. Diagn Histopathol. 2011;17:486-94.
7. Buckner JC. Factors influencing survival in high-grade gliomas. Semin Oncol. 2003;30:10-4.
8. Ghotme KA, Barreto GE, Echeverria V, Gonzalez J, Bustos RV, Sanchez M, et al. Gliomas: new perspectives in diagnosis, treatment and prognosis. Curr Top Med Chem. 2017;17:1438-47.
9. Farias-Eisner G, Bank AM, Hwang BY, Appelboom G, Piazza MA, Bruce SS, et al. Glioblastoma biomarkers from bench to bedside: advances and challenges. Br J Neurosurg. 2012;26:189-94.
10. Li Y, Shan X, Wu Z, Wang Y, Ling M, Fan X. IDH1 mutation is associated with a higher preoperative seizure incidence in low-grade glioma: a systematic review and meta-analysis. Seizure. 2018;55:76-82.
11. Wesseling P, Capper D. WHO 2016 classification of gliomas. Neuropathol Appl Neurobiol. 2018;44:139-50.
12. Wu S, Li J, Cao M, Yang J, Li YX, Li YY. A novel integrated gene coexpression analysis approach reveals a prognostic three-transcription-factor signature for glioma molecular subtypes. BMC Syst Biol. 2016;10:71.
13. Siegal T. Clinical relevance of prognostic and predictive molecular markers in gliomas. Adv Tech Stand Neurosurg. 2016;43:91-108.
14. Thon N, Tonn JC, Kreth FW. The surgical perspective in precision treatment of diffuse gliomas. Onco Targets Ther. 2019;12:1497-508.
15. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol. 2016;131:803-20.
16. Yu J, Shi Z, Lian Y, Li Z, Liu T, Gao Y, et al. Noninvasive IDH1 mutation estimation based on a quantitative radiomics approach for grade II glioma. Eur Radiol. 2017;27:3509-22.
17. Strimbu K, Tavel JA. What are biomarkers? Curr Opin HIV AIDS. 2010;5:463-6.
18. Booth TC, Williams M, Luis A, Cardosa J, Keyoumars A, Shuaib H, et al. Machine learning and glioma imaging biomarkers. Clin Radiol. 2020; 75:20-32.

19. Hu Y, Chen F, Liu F, Liu X, Huang N, Cai X, et al. Overexpression of TIP30 inhibits the growth and invasion of glioma cells. Mol Med Rep. 2016;13:605-12.
20. Fraser AR, Bacci B, le Chevoir MA, Long SN. Isocitrate dehydrogenase 1 expression in canine gliomas. J Comp Pathol. 2018;165:33-9.
21. Wiestler B, Capper D, Holland-Letz T, Korshunov A, von Deimling A, Pfister SM, et al. ATRX loss refines the classification of anaplastic gliomas and identifies a subgroup of IDH mutant astrocytic tumors with better prognosis. Acta Neuropathol. 2013;126:443-51.
22. Hegi ME, Diserens AC, Gorlia T, Hamou MF, De Tribolet N, Weller M, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med. 2005;352:997-1003.
23. Reifenberger J, Reifenberger G, Liu L, James CD, Wechsler W, Collins VP. Molecular genetic analysis of oligodendroglial tumors shows preferential allelic deletions on 19q and 1p. Am J Pathol. 1994;145:1175-90.
24. Yu L, Xu J, Liu J, Zhang H, Sun C, Wang Q, et al. The novel chromatin architectural regulator SND1 promotes glioma proliferation and invasion and predicts the prognosis of patients. Neuro Oncol. 2019;21:742-54.
25. Porter AP, Papaioannou A, Malliri A. Deregulation of Rho GTPases in cancer. Small GTPases. 2016;7:123-38.
26. Stassen OM, van Bodegraven EJ, Giuliani F, Moeton M, Kanski R, Sluijs JA, et al. GFAPδ/GFAPα ratio directs astrocytoma gene expression towards a more malignant profile. Oncotarget. 2017;8:88104-21.
27. Yu X, Li Z, Wu WK. TIP30: a novel tumor-suppressor gene. Oncol Res. 2015;22:339-48.
28. Gibbons RJ, Wada T, Fisher CA, Malik N, Mitson MJ, Steensma DP, et al. Mutations in the chromatin-associated protein ATRX. Hum Mutat. 2008;29:796-802.
29. Kiang KM, Zhang XQ, Leung GK. Long non-coding RNAs: the key players in glioma pathogenesis. Cancers (Basel). 2015;7:1406-24.
30. Louis D, Ohgaki H, Wiestler O, Cavenee W. WHO Classification of Tumors of the Central Nervous System. 4th ed. Lyon, France: IARC Press; 2016. Available from: https://www.publications.iarc.fr/Book-And-Report-Series/Who-Iarc-Classification-Of-Tumours/Who-Classification-Of-Tumours-Of-The-Central-Nervous-System-2016.

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REVIEW ARTICLE

Role of disease-modifying oral drugs in multiple sclerosis: A systematic review with meta-analysis

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Abstract

The purpose of the study was to evaluate the efficacy and safety of cladribine tablets compared with all oral therapies used in patients with relapsing-remitting multiple sclerosis (RRMS). A systematic review of the literature was conducted to identify published clinical trials about RRMS and a network meta-analysis was performed to determine the efficacy and safety of available treatments. We identified seven relevant studies, which were selected based on three criteria that allowed us to construct comparisons of efficacy and safety. Regarding the annualized relapse rate (ARR), there were no significant differences with respect to the decrease of this between cladribine tablets, dimethyl fumarate and fingolimod; although teriflunomide and cladribine tablets showed a significant difference. In relation to the mean number of gadolinium-enhanced T1 lesions, dimethyl fumarate showed a lower number of lesions (–0.85 [–1.21; –0.48]), as did cladribine tablets versus placebo. No statistically significant differences were identified between cladribine tablets and fingolimod (–0.08 [–0.35; 0.19]) and cladribine versus teriflunomide (–0.28 [–0.64; 0.08]). While comparing adverse events that caused discontinuation, cladribine tablets showed an adequate safety profile, which was quantitatively similar to the compared drugs. Cladribine tablets demonstrated efficacy in terms of decrease of ARR and gadolinium-enhanced T1 lesions; although there is no significant difference between cladribine tablets, fingolimod and teriflunomide, the ARR is a stronger measure of efficacy compared to the number of T1 lesions made in contrast with long-term RRMS. Cladribine also demonstrated an adequate safety and tolerability profile promoting therapeutic adherence.

Key words: *Relapsing-remitting multiple sclerosis. Cladribine tablets. Disease-modifying treatments.*

Papel de los fármacos orales modificadores de la enfermedad en la esclerosis múltiple: una revisión sistemática con metanálisis

Resumen

El propósito del estudio fue evaluar la eficacia y seguridad de las tabletas de cladribina en comparación con todas las terapias orales utilizadas en pacientes con EMRR. Se realizó una revisión sistemática de la literatura para identificar ensayos clínicos publicados sobre EMRR y un metanálisis de red para determinar la eficacia y seguridad de los tratamientos disponibles. Identificamos 7 estudios relevantes, que se seleccionaron en base a 3 criterios que nos permitieron construir

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comparaciones de eficacia y seguridad. En cuanto a la tasa de recaída anualizada, no hubo diferencias significativas con respecto a la disminución de ésta entre las tabletas de cladribina, dimetilfumarato y fingolimod; aunque las tabletas de teriflunomida y cladribina mostraron una diferencia significativa. En relación con el número medio de lesiones T1 potenciadas con gadolinio, dimetilfumarato mostró un menor número de lesiones (–0.85 [–1.21; –0.48]), al igual que las tabletas de cladribina frente a placebo. No se identificaron diferencias estadísticamente significativas entre las tabletas de cladribina y fingolimod (–0.08 [–0.35; 0.19]) y cladribina vs teriflunomida (–0.28 [–0.64; 0.08]). Al comparar los eventos adversos que causaron la suspensión, las tabletas de cladribina mostraron un perfil de seguridad adecuado, que fue cuantitativamente similar a los medicamentos comparados. Las tabletas de cladribina demostraron eficacia en términos de disminución de la tasa de recaída anualizada y lesiones T1 potenciadas con gadolinio; Aunque no existe una diferencia significativa entre las tabletas de cladribina, fingolimod y teriflunomida, la tasa de recaída anualizada es una medida más fuerte de eficacia en comparación con el número de lesiones T1 realizadas en contraste con la EMRR a largo plazo. Cladribina también demostró un perfil adecuado de seguridad y tolerabilidad que promueve la adherencia terapéutica.

Palabras claves: *Esclerosis múltiple recurrente-remitente. Tabletas de cladribina. Tratamientos modificadores de la enfermedad.*

Introduction

Multiple sclerosis (MS) is a chronic degenerative autoimmune disease of the central nervous system characterized by inflammatory demyelination resulting in axonal and neuronal damage. Relapsing-remitting MS (RRMS) being the most common type (85-90%)[1,2]. Patients with RRMS suffer episodes that can cause fainting, this clinical condition can be disabling[3]. In Mexico, the prevalence reports ranges from 12 to 30 cases per 100,000 people[4].

Various therapies for MS require regular long-term self-injection that can result in patient dissatisfaction, which can severely affect therapeutic adherence and cause a secondary efficacy reduction[5]. Considering that the worldwide rate of non-adherence for MS is at 44%, which is similar to that of chronic diseases[6], oral medications have been introduced to improve adherence and, therefore, have an impact on therapeutic efficiency[7]. Oral cladribine (2-chloro-2'-deoxyadenosine) is an analog of adenosine deaminase resistant to deoxyadenosine[8,9]. It is a prodrug that requires intracellular phosphorylation, with a chlorine substitution in the purine ring. This protects it from degradation and increases its intracellular time[10].

In treatment with cladribine tablets, patients in the 3.5 and 5.25 mg group had fewer magnetic resonance imaging (MRI) lesions[11] than those patients in the placebo group, for gadolinium-enhanced T1 lesions (mean 0.11 and 0.12, respectively, vs. 0.91 in placebo) and T2 lesions (mean 0.38 and 0.33, respectively, vs. 1.43 in placebo)[12]. There is not enough information to directly compare the oral therapeutic strategies available for RRMS in Mexico. The aim of this study was to evaluate the efficacy and safety of cladribine tablets compared to oral therapies currently used in patients with RRMS by means of a systematic review and a network meta-analysis, considering the annualized relapse rate (ARR), T1 lesions, and adverse events that cause discontinuation of treatment.

Methods

Search method

In accordance with the Cochrane methodology, the authors searched for data from 1980 to March 1, 2019, under the criteria of the population, intervention, control, and outcomes question "Evaluate the efficacy and safety of cladribine tablets in patients diagnosed with RRMS compared with dimethyl fumarate, fingolimod, and teriflunomide," on PubMed, Cochrane, ScienceDirect, Web of Science, the Health Economic Evaluations Database, EMBASE databases, and regional databases such as LILACs, Scielo Citation Index, Medigraphic, REDALYC, Imbiomed, and Artemisa. The MeSH terms used were "MS," "RRMS," "cladribine," "dimethyl fumarate," "fingolimod hydrochloride," and "teriflunomide," both in English, Spanish, and Portuguese, limited to controlled clinical that included oral disease-modifying therapies.

Inclusion and exclusion criteria

Primary data sources were articles from randomized controlled clinical trials (RCTs). To avoid bias, study selection and data extraction were performed by two independent reviewers. RCTs assessing the effect of cladribine tablets and dimethyl fumarate, fingolimod, or teriflunomide in direct comparison with placebo for the

treatment of MS or RRMS were included, and a third reviewer provided consensus when there was disagreement on the inclusion of an article.

Data extraction information

Information was recorded on study design, selection criteria, population, patient characteristics, ARR, T1 lesions, and adverse events.

Quality assessment

The process of rating the quality of the best available evidence in the clinical studies was assessed following the approach proposed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group and in accordance with the GRADE Handbook.

Outcomes

Efficacy evaluation was performed based on the decrease of ARR and the change in the mean number of gadolinium-enhanced T1 lesions in the MRI. The safety profile was assessed by the number of patients who discontinued treatment due to adverse events.

Statistical analysis

Indirect comparisons were calculated using a network meta-analysis, since this is the most appropriate way of summarizing data to provide a series of unbiased effects obtained from direct and indirect comparisons. A random effects model was used as this is more appropriate than fixed effect models when there is heterogeneity between patient populations and between trials. To ensure a closed network, a placebo was used as a common point. Three interventions were used as comparators: dimethyl fumarate, fingolimod, and teriflunomide versus cladribine tablets; each study had both an intervention and a placebo. Direct evidence of the defined outcomes of each study was incorporated. Statistical significance was determined as $p > 0.05$. All calculations were performed with the software R version 3.5.2.

Main results

Search results

A total of 1034 articles were identified in the systematic review of the included databases. After duplicated removal, 761 papers were considered. Twenty-six of the potentially relevant articles were assessed for eligibility, and finally, seven clinical trials that met the efficacy and safety criteria were included (Chart 1). The characteristics of included studies are summarized in table 1.

Table 2 shows population data by intervention and cladribine dosage groups included in the analysis: cladribine tablets 3.5 mg, dimethyl fumarate 240 mg twice daily, teriflunomide 14 mg, and fingolimod 0.5 mg. The posology of interventions was validated through the Basic Table and Catalogue of Health Sector Inputs (CBCISS) of the General Health Council (CSG) for the Mexican population.

From the seven selected studies, data from the annual relapse rate, the average of gadolinium-enhanced T1 lesions, were extracted when available (gadolinium-enhanced T1 lesions data were not available for the TOWER study); for safety data, adverse events that led to the interruption of the study drug were evaluated; this was presented as a rate (Table 3).

Patient characteristics

Studies were conducted from 2010 to 2014 with similar demographic characteristics, all studies included patients diagnosed with RRMS; as for study design, treatment arms of all studied had the common point a placebo group. All studies included a high percentage (65.9-81%) of female patients (Table 2).

Outcomes report

Comparisons of cladribine tablets with dimethyl fumarate, fingolimod, and teriflunomide were made with efficacy, on the decrease of ARR and the change in the mean number of gadolinium reinforced T1 lesions in the MRI, and safety criteria data extracted through the systematic review.

ARR

Cladribine tablets showed no statistically significant differences with regard to the decrease of ARR compared to dimethyl fumarate and fingolimod, however, a lower relapse rate is shown with cladribine tablets when compared to placebo and teriflunomide (Chart 2).

Gadolinium-enhanced T1 lesions

In relation to the mean number of gadolinium-enhanced T1 lesions, treatment with cladribine reported a

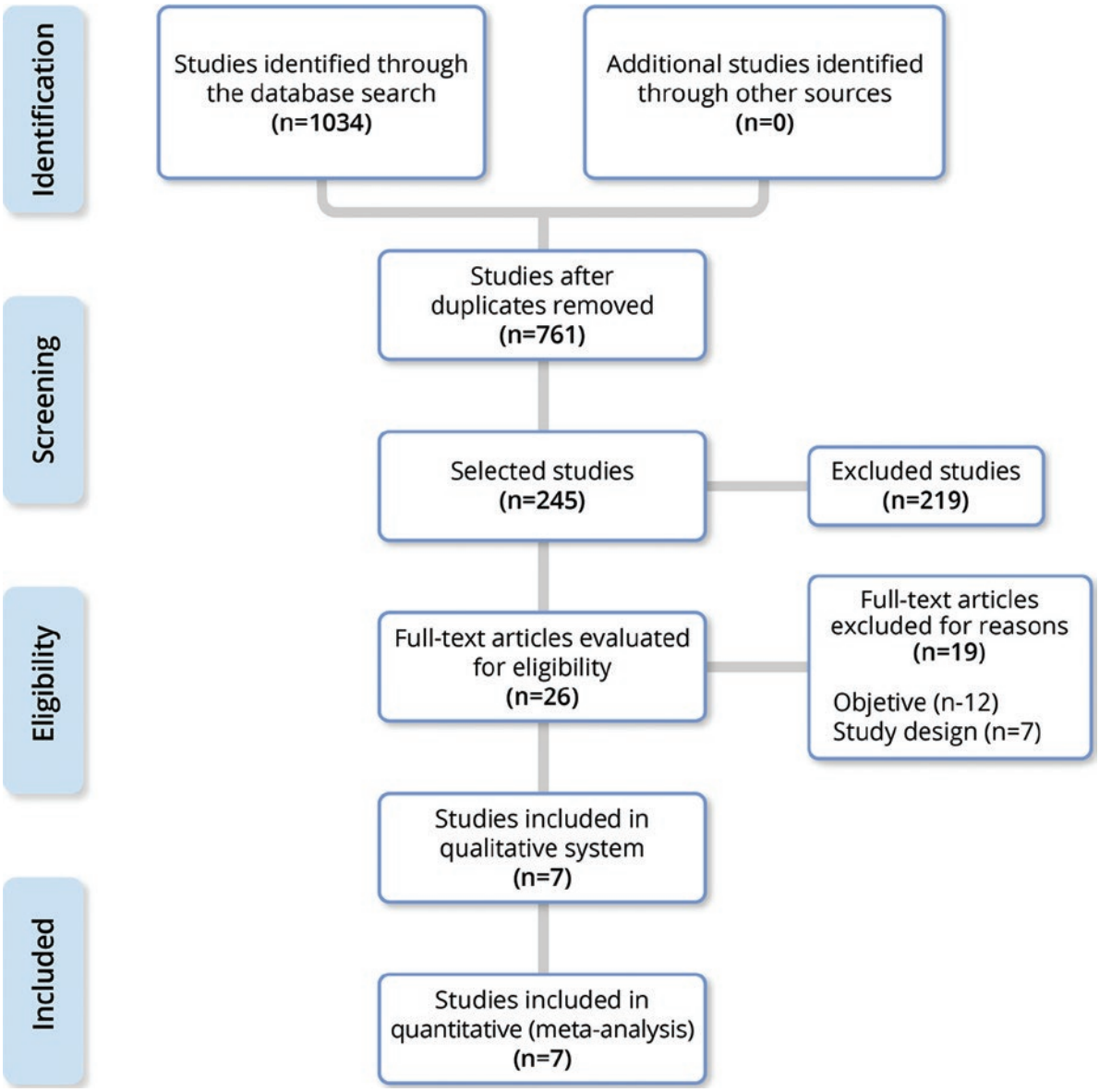

Chart 1. Flowchart summarizing the systematic review adapted to the PRISMA statement.

lower number of lesions when compared against dimethyl fumarate or placebo (Chart 3). This difference was statistically significant. On the other hand, no statistically significant differences were identified when comparing treatment with cladribine with fingolimod (–0.08 [–0.35; 0.19]) and teriflunomide (–0.28 [–0.64; 0.08]).

Adverse events that lead to a discontinuation of study drugs

No significant differences were found between cladribine tablets and the other evaluated treatments (Chart 4). In this case, the null effect is represented by the number one.

Discussion

In the absence of randomized clinical studies comparing all interventions for RRMS, a network meta-analysis is a plausible alternative for obtaining relative efficacy estimators. In Mexico, there are very few studies evaluating the efficacy and safety of treatments for MS.

A network meta-analysis by Siddiqui et al. (2018) in patients with RRMS showed that oral cladribine is among

Table 1. Included articles characteristics

Study	Study design	Participants	Intervention and dosing	n	Duration (Months)	Reported outcomes
CLARITY[16] NCT00213135	Multicentric RCT Phase III	Adults. RRMS McDonald criteria, EDSS (0-5.5). At least one relapse in the past 12 months.	Placebo Cladribine 3.5 mg Cladribine 5.25 mg	437 433 456	22	ARR, FRR. Time to first relapse. Mean number of gadolinium-enhanced T1 lesions, weighted active lesions on T2 and combined single lesions. Incidence of treatment emergent adverse events.
FREEDOMS[15] NCT00289978	Double-blind randomized, placebo-CT, Phase 3	Adults. RRMS McDonald criteria, EDSS (0-5.5).	Placebo Fingolimod 0.5 mg Fingolimod 1.25 mg	418 425 429	24	ARR. Time of disability progression. Number of gadolinium-enhanced lesions.
FREEDOMS II[17] NCT00355134	Double-blind randomized, placebo-CT, parallel groups, multicentric Phase 3.	Adults. RRMS McDonald criteria, EDSS (0-5.5).	Placebo Fingolimod 0.5 mg Fingolimod 1.25 mg	355 358 370	22	ARR. Change percentage in brain volume. Time of disability progression. Number and volume of gadolinium-enhanced T1 lesions. Adverse events.
TEMSO[18] NCT00134563	Double-blind randomized, placebo-CT, parallel group, Phase 3	Adults. RRMS McDonald criteria, EDSS (0-5.5). At least two relapses in the previous 2 years or one relapse in the previous year, but not within 60 days before randomization.	Placebo Teriflunomide 7 mg Teriflunomide 14 mg	363 365 358	25	ARR. Disability progression. Total volume of the lesion. Number of unique active lesions. Adverse events.
TOWER[19] NCT00751881	Double-blind randomized, placebo-CT, Phase 3	Adults. RRMS McDonald criteria, EDSS (0-5.5). At least one relapse in the last year or two relapses in the last 2 years and none in the 30 days prior to randomization.	Placebo Teriflunomide 7 mg Teriflunomide 14 mg	389 407 372	11	ARR. Time up to 12 weeks of sustained accumulation of disability. Adverse events.
DEFINE[20] NCT00420212	Double-blind randomized, placebo-CT, Phase 3	Adults. RRMS McDonald criteria, EDSS (0-5.5). At least one relapse the year before randomization.	Placebo Twice daily BG-12 240 mg Three times a day BG-12 240 mg	408 410 416	24	Relapses. Number of gadolinium-enhanced lesions. Time of disability progression. Adverse events.
CONFIRM[21] NCT00451451	Double-blind randomized, placebo-CT, Phase 3	Adults. RRMS McDonald criteria, EDSS (0-5). At least one relapse in the past 12 months or at least one gadolinium-enhanced lesion 0-6 weeks before randomization.	Placebo Twice daily BG-12 240 mg Three times a day BG-12 240 mg Glatiramer acetate 20 mg	363 359 345 350	22	ARR. Number of new T2 hypertensive lesions or increasing number of T2 lesions, T1-enhanced images. Adverse events.

RCT: randomized controlled clinical trial; EDSS: expanded disability status scale; ARR: annualized relapse rate; FRR: free relapse rate.

the most effective disease-modifying treatments and has an adequate safety profile comparable to other treatments, it also presents a significant reduction in relapse rate compared to teriflunomide and even parenteral drugs[13]. In addition to this, Papadopoulos et al. conducted a safety analysis on the likelihood to help or harm, defined as the ratio of number needed to harm to the number needed to treat with respect to adverse events causing discontinuation of treatment (NNTH AE-D), which showed favorable evidence for cladribine (72 [95% CI 27.9 to

Table 2. Population characteristics

Reference	Clinical form of the disease	Study arms	Sample size	Age	% women
Giovannoni et al., 2010[16]	RRMS	Placebo	437	38.7 ± 9.9	288 (65.9)
		Cladribine 3.5 mg	433	37.9 ± 10.3	298 (68.8)
		Cladribine 5.25 mg	456	39.1 ± 9.9	312 (68.4)
Kappos et al., 2010[15]	RRMS	Placebo	418	37.2 ± 8.6	298 (71.3)
		Fingolimod 0.5 mg	425	36.6 ± 8.8	296 (69.6)
		Fingolimod 1.25 mg	429	37.4 ± 8.9	295 (68.8)
Calabresi et al., 2014[17]	RRMS	Placebo.	355	40.1 ±8.4	288 (81)
		Fingolimod 0.5 mg	358	40.6 ± 8.4	275 (77)
		Fingolimod 1.25 mg	370	40.9 ± 8.9	281 (76)
O´Connor et al., 2011[18]	RRMS	Placebo.	363	38.4 ± 9.0	275 (75.8)
		Teriflunomide 7 mg	365	37.4 ± 9.0	255 (69.7)
		Teriflunomide 14 mg	358	37.8 ± 8.2	255 (71.0)
Confavreux et al., 2014[19]	RRMS	Placebo	389	38.1 ± 9.1	273 (70)
		Teriflunomide 7 mg	407	37.4 ± 9.4	300 (74)
		Teriflunomide 14 mg	372	38.2 ± 9.4	258 (69)
Gold et al., 2012[20]	RRMS	Placebo	408	38.5 ± 9.1	306 (75)
		Twice a day BG-12 240 mg	410	38.1± 9.1	296 (72)
		Three times a day BG-12 240 mg	416	38.8 ± 8.8	306 (74)
Fox et al., 2012[21]	RRMS	Placebo	363	36.9 ± 9.2	251 (69)
		Twice a day BG-12 240 mg	359	37.8 ± 9.4	245 (68)
		Three times a day BG-12 240 mg	345	37.8 ± 9.4	250 (72)
		Glatiramer acetate 20 mg	350	36.7 ± 9.1	247 (71)

RRMS: relapsing-remitting multiple sclerosis.

–129.5])[14]. In this context, our findings are consistent with published reports of cladribine and its safety profile.

In relation to the ARR, cladribine tablets had no significant difference in its effect on relapses compared with the other interventions, however, it had a statistically significant when compared to teriflunomide. The CLARITY study reports an effect size with a greater than 50% decrease in annual relapses, a decrease in disability of up to 30%, and the effect was consistent in sub-population analysis.

The analysis for the gadolinium-enhanced T1 lesions outcome found that the effect of cladribine was comparable to those presented with fingolimod[15]. Although there is no significant difference between cladribine, fingolimod, and teriflunomide, it must be taken into to consideration that the reported ARR is a stronger measure of efficacy compared to the number of T1 lesions.

The evidence provided by the therapeutic options individually, allows us to put the agents that are used on a daily basis into context, seen in a broader way. This review of oral administered drugs makes it possible to assess important clinical outcomes, while at the same time taking into account that the difference between the characteristics of each drug may affect the clinical outcome. At present, a range of disease-modifying drugs with different mechanisms of action is available, with simplified dosages and periodicity schedules. Cladribine tablets are a therapeutic option that offers the expected therapeutic effect, with an annualized administration scheme that confers comfort to the

Table 3. Data included in the meta-analysis

	Annualized relapse rate				Gadolinium-enhanced T1 Lesions				Adverse events leading to discontinuation of the study drug			
	Placebo		Intervention		Placebo		Intervention		Placebo		Intervention	
Study	n	Rate	n	Rate	$\bar{\mu}$	SD	$\bar{\mu}$	SD	n	Rate	n	Rate
CLARITY[16]	437	33%	433	14%	0.91	2.10	0.12	2.7	435	2.07%	430	3.49%
FREEDOMS[15]	418	40%	425	18%	1.1	2.40	0.2	0.80	418	7.66%	425	7.53%
FREEDOMS II[17]	355	40%	358	21%	1.2	2.97	0.4	1.84	355	10.42%	358	18.44%
TEMSO[18]	363	54%	358	37%	1.33	2.96	0.26	1.16	360	8.06%	358	10.89%
TOWER[19]	388	50%	370	32%	-	-	-	-	385	6.23%	371	15.63%
DEFINE[20]	408	36%	410	17%	1.8	4.20	0.1	0.60	408	13.48%	410	15.85%
CONFIRM[21]	363	40%	359	22%	2	5.60	0.5	1.70	363	10.47%	359	12.26%

$\bar{\mu}$ average; SD: standard deviation.

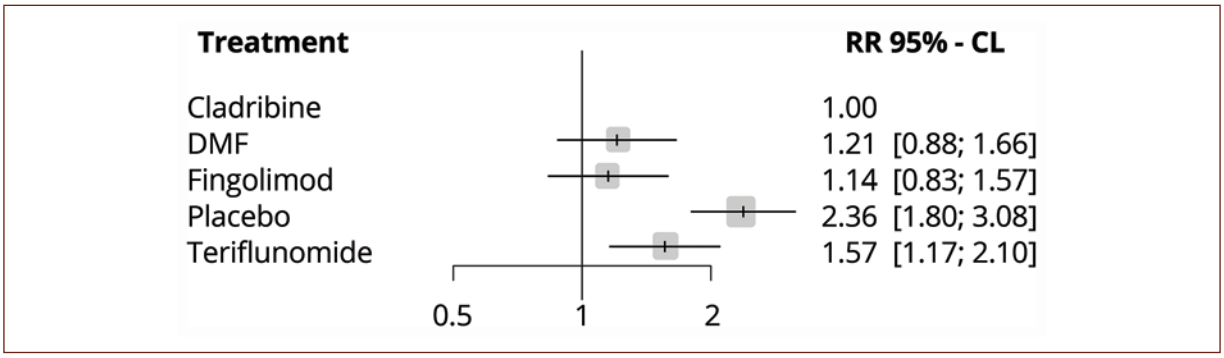

Chart 2. Forest plot in patients with relapsing-remitting multiple sclerosis randomized to receive cladribine tablets, dimethyl fumarate (DMF), fingolimod, teriflunomide, or placebo treatment with 95% confidence level and relative risk for annualized relapse rates (ARRs).

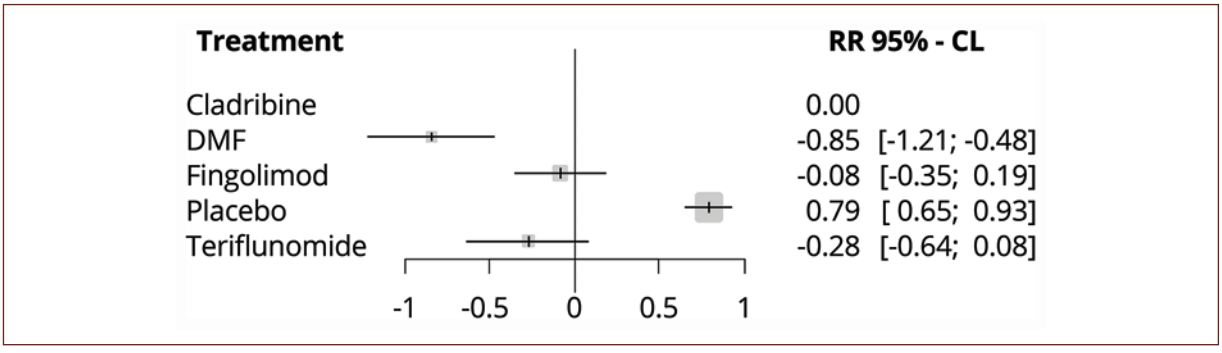

Chart 3. Forest plot in patients with relapsing-remitting multiple sclerosis randomized to receive cladribine tablets, dimethyl fumarate (DMF), fingolimod, teriflunomide, or placebo treatment with 95% confidence level. Difference in gadolinium-enhanced T1 lesions means per patient.

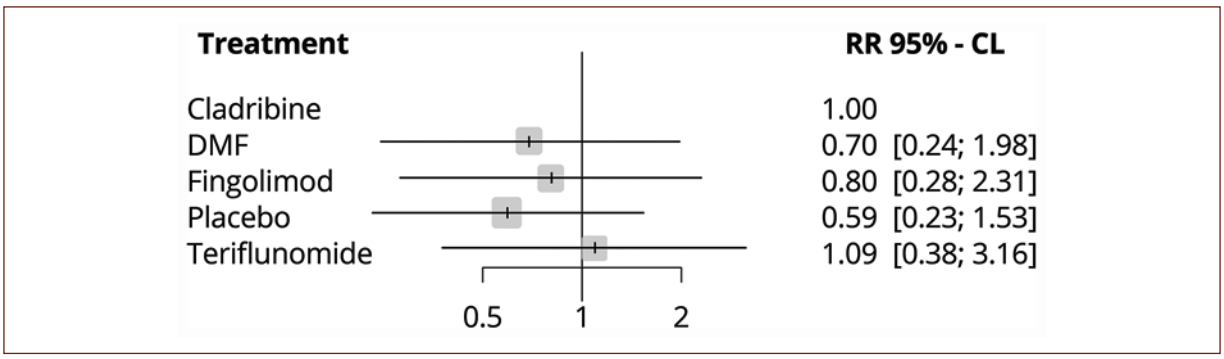

Chart 4. Forest plot in patients with randomized relapsing-remitting multiple sclerosis to receive cladribine tablets, dimethyl fumarate (DMF), fingolimod, teriflunomide, or placebo treatment with 95% confidence level. Relative risk for adverse events causing treatment interruption.

Table 4. Safety profile of oral drugs

Drug	Short-term side effects	Long-term efficacy	Long-term side effects	Important safety aspects
Fingolimod	Bradycardia, average of 8 bpm during the first infusion (2.3%). Macular edema. Elevation of liver function enzymes. Mild infections. Herpes zoster infection.	Data to 7 years: 84-96% free of gadolinium lesions, 70% free of T2-weighted lesions. Average PBVC: –2.8 for more than 84 months.	No new aspects to known side effects of crucial tests.	Herpes zoster infection in a small number of patients. PML risk 1/18.000.
Dimethyl fumarate	Flushing or redness. Gastrointestinal irritation. Lymphopenia.	ARR from years 1-5: 0.202, 0.163, 0.139, 0.143, and 0.138.	PML, so far 5 patients > 230,000 who have been treated with DMF, some cases reported with FUMADERM.	PML risk of 1/50,000. In people > 50 years, early lymphocyte reduction is associated with an increased risk of PML.
Teriflunomide	Asymptomatic increase of alanine aminotransferase. Headache. Diarrhea. Hair thinning. Nausea.	9 years of TEMSO follow-up. 55% relapse free. Stable EDSS scale average > 50% without progression.	No pattern of malignancies, especially hematologic cancers such as leukemia or lymphoproliferative tumors.	
Cladribine	Lymphopenia. Herpes zoster infection (< 10%). There is no increased risk of malignant tumors.	Data not available	Data not available	No reported cases of PML in multiple sclerosis.

*PML: progressive multifocal leukoencephalopathy (adapted from Faissner and Gold, 2018)[22].

patient and his caregiver, which undoubtedly favors therapeutic adherence. Cladribine tablets reach quickly and steadily its effect on lymphocytes after an administration, resulting in a good efficacy, safety, and proven tolerability profile.

The specific evidence establishes that all interventions require careful patient selection. According to the safety profile and tolerability of cladribine tablets, in the CLARITY study[16] due to its dose-dependent mechanism action, the most common adverse effect was lymphopenia, increasing the risk of an opportunistic infection; however, there are no reports of progressive multifocal leukoencephalopathy (PML), bradycardia, or macular edema attributable to cladribine tablets on patients with MS (Table 4). In relation to the safety profile, this meta-analysis shows no statistically significant

differences in adverse effects, but simply a different pattern.

Limitations and strengths of the study

The main limitation of the study remains that on Mexican population, regarding this disease, information is poor or scarce; so the results of the analysis must be interpreted with caution. Nevertheless, international literature did not provide randomized clinical trials that would allow direct comparisons, making an indirect comparison an alternative to explore the existent and limited alternatives.

The main strength of the study is the use of a network meta-analysis with a random effects model that allows homogenizing the main biases within the analysis to make indirect comparisons. The selection of the articles was carried out by specialists on the subject and in the event of any lack of concession, a third reviewer intervened.

Conclusion

Cladribine tablets demonstrated efficacy in terms of decrease of ARR and gadolinium-enhanced T1 lesions made in contrast with patients with long-term RRMS, as well as a good safety profile and tolerability that promote therapeutic adherence, becoming an appropriate therapeutic option for patients with RRMS. It is important to evaluate the different therapeutic interventions from a standardized perspective for an appropriate treatment selection that positively delays or modifies the natural course of this disease and can contribute to the quality of life of patients with RRMS.

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Con icts of interest

The authors LRM, GVS, DAO, BLYO, and SMH are responsible for the article content and declare have received honoraria from Merck. GVS, DAO, BLYO, and SMH are employees of HS Estudios Farmacoeconómicos S.A. de C.V., are ISPOR members and declare have received honoraria also from Roche, Novartis, Sanofi, Pfizer, and Biogen as well as have served in a consulting or advisory role for Roche, Celgene, and AstraZeneca. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Ethical disclosures

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

Con dentiality 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

1. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med. 2000;343:938-952.
2. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology. 2014;83:278-86.
3. Ziemssen T. Symptom management in patients with multiple sclerosis. J Neurol Sci. 2011;311:S48-52.
4. Rivera VM, Medina MT, Duron RM, Macias MA. Multiple sclerosis care in Latin America. Neurology. 2014;82:1660-1.
5. Giovannoni G, Southam E, Waubant E. Systematic review of disease-modifying therapies to assess unmet needs in multiple sclerosis: tolerability and adherence. Mult Sclerosis. 2012;18:932-46.
6. World Health Organization. Adherence to Long-term Therapies. Evidence for Action (WHO/MN/0.30.1). Washington, DC: World Health Organization; 2003. p. 211.
7. Bruce JM, Hancock LM, Lynch SG. Objective adherence monitoring in multiple sclerosis: initial validation and association with self-report. Mult Sclerosis 2010;16:112-20.
8. Beutler E. Cladribine (2-chlorodeoxyadenosine). Lancet. 1992;340:952-6.
9. Brousil JA, Roberts RJ, Schlein AL. Cladribine: an investigational immunomodulatory agent for multiple sclerosis. Ann Pharmacother. 2006;40:1814-21.
10. Science Medicines Health. Summary of Product Characteristics: mavenclad (cladribine). Netherlands: European Medicines Agency, Science Medicines Health; 2017. p. 1-41.
11. Alva CIE. El Significado Psicológico de la Experiencia del Parto Con el Apoyo Continuo de Doula: un Estudio Comparativo Con Redes Semánticas Naturales. Colima: Tesis de Maestría, Universidad de Colima; 2006.
12. Giovannoni G. Cladribine to treat relapsing forms of multiple sclerosis. Neurotherapeutics. 2017;14:874-87.
13. Siddiqui MK, Khurana IS, Budhia S, Hettle R, Harty G, Wong SL. Systematic literature review and network meta-analysis of cladribine tablets versus alternative disease-modifying treatments for relapsing-remitting multiple sclerosis. Curr Med Res Opin. 2018;34:1361-71.

14. Papadopoulos D, Mitsikostas DD. Oral disease-modifying treatments for relapsing multiple sclerosis: a likelihood to achieve no evidence of disease activity or harm analysis. CNS Drugs. 2018;32:1069-78.
15. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010;362:387-401.
16. Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Soelberg Sørensen P, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med. 2010;362:416-26.
17. Calabresi PA, Radue EW, Goodin D, Jeffery D, Rammohan KW, Reder AT, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13:545-56.
18. O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med. 2011;365:1293-303.
19. Confavreux C, O'Connor P, Comi G, Freedman MS, Miller AE, Olsson TP, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13:247-56.
20. Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012;367;1098-107.
21. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012;367:1087-97.
22. Faissner S, Gold R. Efficacy and safety of the newer multiple sclerosis drugs approved since 2010. CNS Drugs. 2018;32:269-87.