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A brief background of Neurology in Mexico

Breve historia de la neurología en México

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There are several events that can make a difference in the evolution of a society, some important facts are presented in this chronological account of world events and the history of Mexican neurology:

1500 B.C.
Mayan evidence of trepanation for god sacrifices, for relieving migraine or traumatic head bleeding intervention.

1500 B.C.
Edwin-Smith and Ebber’s Papyrus: First treatise on herbal medicine and migraine treatments.

200 B.C.
The Corpus Hippocraticum states that Epilepsy is not a “sacred disease” but rather a cerebral alteration of its equilibrium.

1300 DC.
“Tlazoltéotl”, goddess of Medicine. Polytheism and magical beliefs mixed with observations and herbal medicine.

1500 DC.
The oldest American culture trepanation was performed, for severe migraine, “to release demons” causing epilepsy, to drain epidural or subdural hematomas. Mescaline as psychotropic and anesthetic.

1400 DC.
Epilepsy as a ‘divine disease’, distinction between GTC (“Huapahualiztti”) and myoclonic crisis (“Hixcayotl”).

1300 DC.
“The Great Tenochtitan” (by Diego Rivera: 1945); “Tlazoltéotl,” goddess of Medicine. Polytheism and magical beliefs mixed with observations and herbal medicine.

1551 DC.
The Royal and Pontifical University of Mexico (now Universidad Nacional Autónoma de México [UNAM]) is founded. A few years later, on 1578, the first chair of medicine in Latin America was established.

1579-1592 DC.
“A Brief Treaty of Anatomy and Surgery”, written by Agustín Farfán describing trepanation procedure, its indications and technique.

Rising of Psychiatry in Mexico and America: Friar Bernardino de Alvarez became pioneer with the foundation on of San Hipolito’s, Holy Cross, the first psychiatric facilities in the continent and Pontificial University of Mexico, Manuel Carpio started the general and nervous physiology chair while Casimiro Liceaga became in charge of the first chair in mental illnesses in the continent.
A. Ramírez-González and I. Rodríguez-Leyva: Editorial

1837-1873-1906
Purkinje, Golgi, and Cajal achieved with a novel silver stain to describe the “Neuronal Doctrine” and the synapse, with the latter 2 being awarded with the Nobel Prize in Medicine or Physiology.

Charcot instituted the first chair of Neurology at La Pitié Salpêtrière. Mexican neurologists started to then follow the French school through the Brevie Neurologie journal and to train in Paris.

1882
Miguel Alvarado, first Neurology Chairman at the Royal and Pontifical University of Mexico, which included professors of pathology, surgery and morphological description of the nervous system.

1891
Rafael Lavista describes a case of apparent Brais-Jacksonian epilepsy and its notorious improvement posterior to the surgery, as well as the successful cerebral tumor resection and recovery of a young boy.

1899-1910
The first public and private mental institutions started attending patients with the novel advances in psychiatry. The most important mental infirmaries were the Rafael Lavista’s and La Castañeda, this last one founded upon the direct instruction of Porfirio Diaz.

1925
Boom in nervous physiology thanks to Harvard researchers Walter Cannon and his Mexican collaborators Arturo Roseblueth and José Joaquin Izquierdo, who described the function of the autonomic nervous system.

1924-1936
EEG invention by Hans Berger and alpha-waves description; posteriorly, Teodoro Flores Covarrubias built his own and started electrophysiological cabinets in the main hospitals in the country.

1935-1940
Established in 1937, the Mexican Society of Neurology and Psychiatry allowed the national integration of an important spectrum of specialists in the field of neurosciences.

The National Institute of Neurology and Neurosurgery opens its doors with the first stereotactic-guided surgery in our country performed by its founder, Manuel Velasco Suarez.

1971-1975
The certified Board for the Mexican Council of Neurology was established and the Mexican Academy of Neurology, and the National Chapter of the International League Against Epilepsy “CAMELICE” were founded.

2020
New neurological societies in critical areas have appeared: AMEVASC (for cerebrovascular disease), Mexc-trims (multiple sclerosis and immunological problems), AMCEMIG (for the study of headache and migraine), and SOMA (abnormal movements), among others.

Ten neurology programs for the formation of new specialists are open in the whole country, looking for international recognition (WFN, ANA) upon the direct instruction of and the Board of the Mexican Neurology Council.

There are so many things to do in our beloved Mexico in order to improve the education in the neurological area but our societies and institutions are working hard for making it possible. The quest is to have the best quality and best educated neurologists in Mexico, following the standards of the best in the world.
Myasthenia gravis in a reference Western Mexican Hospital: Comparison of a new cohort versus a historical one

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Abstract

Background: Myasthenia gravis (MG) is a post-synaptic autoimmune disease of the neuromuscular junction, whose cardinal manifestations are weakness and fatigue. Objective: The objective of the study was to report a cohort of patients with a diagnosis of MG in a West Mexican hospital and compare the clinical profile, diagnostic, and therapeutic approach and prognosis against a previously published cohort of the same hospital. Materials and methods: Consecutive patients included in two cohorts: the first one already published from 1999 to 2007 and the second one reported here from 2008 to 2018. Results: The most recent cohort included 39 patients, 23 women (59%), with an average age of 50 years, and superior to the previous cohort (43 years). Hypertension (39%) and diabetes (18%) were observed with a marked increase in the current cohort. The distribution in the Osserman staging was very similar. The positivity of acetylcholine receptor antibodies (ACRA) increased from 37% to 88%. In both cohorts, most patients received pyridostigmine and in two-thirds steroids. The previous cohort recorded 4% of patients treated with a steroid-sparing immunosuppressant, contrasting with 90% (azathioprine 85%, and mycophenolate 5%) of the current cohort. Thymectomy was a less frequent practice in 12%. Mortality showed a significant decrease from 16% to 0%. Conclusion: Differences were observed among the cohorts, highlighting in the most recent one a higher age, the appearance of chronic-degenerative diseases, greater positivity to ACRA, optimization of pharmacological management, less thymectomy, and no mortality. Replicas of this work in other hospital settings are pertinent.

Key words: Acetylcholine receptor antibodies. Mexico. Myasthenia gravis. Thymectomy.

Miastenia gravis en un hospital de referencia del occidente de México: Comparación de una cohorte nueva versus una histórica

Resumen

Antecedentes: La miastenia gravis (MG) es una enfermedad autoinmune postsináptica de la unión neuromuscular, cuyas manifestaciones cardinales son debilidad y fatiga. Objetivo: Reportar una cohorte de pacientes con diagnóstico de MG en un hospital del occidente de México y comparar el perfil clínico, el enfoque diagnóstico y terapéutico, y el pronóstico frente
a una cohorte publicada previamente del mismo hospital. Material y métodos: Pacientes consecutivos incluidos en dos cohortes: la primera ya publicada (de 1999 al 2007) y la reportada aquí (del 2008 al 2018). Resultados: En la cohorte más reciente se incluyeron 39 pacientes, 23 mujeres (59%), con edad promedio de 50 años, superior a la cohorte previa (43 años). Hipertensión arterial (39%) y diabetes (18%) se observan con marcado incremento en la cohorte actual. La distribución en la estadificación de Osserman fue similar. La positividad de los anticuerpos contra el receptor de acetilcolina (ACRA) aumentó del 37 al 88%. En ambas cohortes la mayoría de los pacientes recibieron piridostigmina y dos terceras partes esteroides. La cohorte previa registró un 4% de pacientes tratados con inmunosupresores ahoradores de esteroides, contrastando con el 90% (azatioprina 85%, micofenolato 5%) de la cohorte actual. La timectomía fue una práctica menos frecuente, en el 12%. La mortalidad presentó un importante decremento, del 16% al 0%. Conclusión: Se observan diferencias entre las cohortes, destacando en la más reciente una mayor edad de presentación, aparición de enfermedades cronicodegenerativas, mayor positividad a ACRA, optimización del manejo farmacológico, menos timectomía y nula mortalidad. Son pertinentes réplicas de este trabajo.


Introduction

Myasthenia gravis (MG) is a post-synaptic autoimmune disease of the neuromuscular junction with a classic bimodal presentation related to sex, most often affecting young women under 40 and men over 50 years of age. Epidemiological data support an increase in its prevalence, which are explained by the presence of better diagnostic tools, greater sensitivity to diagnosis, and increased survival of patients. Thus, the prevalence from studies carried out in the 60’s accounted for 0.77 cases per 100,000 inhabitants, while the most recent report a greater affection in ranges between 13 and 25/100,000.

The objective of this study is to describe the clinical presentation, diagnostic, and therapeutic approaches, as well as the prognosis of patients with MG enrolled from years 2008 to 2018 in a reference hospital of West Mexico and compare the results against a historical cohort from years 1999 to 2007 in the same hospital, the latter already published in this journal.

Materials and methods

All consecutive adult patients diagnosed with MG treated at the outpatient clinic of the Guadalajara Civil Hospital “Fray Antonio Alcalde” (HCG) in a 10-year period between January 2008 and August 2018 were captured. Hospitalized patients were also included in the analysis, as well as those referred by other services such as Internal Medicine, Rehabilitation, Geriatrics, and Intensive Therapy.

To establish the diagnosis of MG, patients had to comply at least one positive test of the following: (a) Tensilon test; (b) supramaximal repetitive nerve stimulation test (Jolly test); (c) ice pack test; (d) acetylcholine receptor antibodies (ACRA); and (e) muscle-specific kinase antibodies (anti-MuSK). In addition, sociodemographic factors, comorbid, clinical presentation, abnormalities to neurological examination, findings in complementary labs, medical treatment, surgical approach, histopathological results, complications, and death were taken into account.

The disease was staged using the Osserman scale: I (only ocular compromise, ptosis, and diplopia); Ila (moderate diffuse skeletal muscle involvement, generalized weakness, ptosis, and diplopia without respiratory deficit); Iib (severe muscular involvement associated with ocular and bulbar involvement, marked weakness, dysphagia, dysarthria, and impaired mastication); III (rapidly progressive muscular involvement associated with ocular and bulbar muscle involvement, and with respiratory deficit); IV (chronic myasthenia with severe diffuse, ocular and bulbar muscle involvement, and resulting from types I, II, and III gradual progression).

Due to the bimodal presentation of the MG, the population was divided into four groups for analysis: ≤ 30 versus > 30 years of age and ≤ 50 versus > 50 years of age. The ethics committee in our hospital approved the study; as this is an observational study, not informed consent of the participants was required.

The resulting data were captured and analyzed using the SPSS v25.0 system. Pearson’s Chi-squared test was used for nominal variables in the univariate analysis. The Mann–Whitney U-test was used to compare abnormally distributed continuous variables (determined by the Shapiro–Wilk test). The results with p < 0.05 were considered significant.

In a retrospective and introspective analysis, the results were compared to a cohort of patients with MG published in this journal by Echeverría et al. in 2008, with data collected from the year 1999 to 2007.
conducted in the same hospital (Guadalajara Civil Hospital “Fray Antonio Alcalde”) and by the same chief investigator; the same inclusion criteria were applied to our cohort, except for that they did not include ice pack test and anti-MuSK in the diagnostic approach. For further information on this work, kindly consider look at the original article. No patients of that previous article were included in this cohort. The observations of this comparison are the basis of the discussion.

Results

During the established period from 2008 to 2018, 50 patients with diagnosis of MG were initially considered, 11 were excluded because they had insufficient data for analysis or correspond to another diagnosis, resulting in a final 39 enrolled patients, 23 women (59%) and 16 men (41%), with a sex ratio of 1.4:1. The age range was between 17 and 80 years, with an average of 49.8 years, 48.5 for women, and 51.7 for men (p = 0.78). A total of 21 (54%) patients were > 50 years old and 8 (20.5%) were ≤ 30 (Table 1).

The staging of the disease was predominantly distributed in Grades I, IIa, and IIb of Osserman, without significant differences with respect to sex; in the group of ≤ 30 years, there was no Grade I. Important aspects in signs and symptoms were the presence of ptosis in 92% of cases, most frequently in women (100% vs. 81%) (p = 0.03); bilateral ptosis had a predominance in men (69% vs. 30%) (p = 0.02). Extraocular muscle paralysis at exploration was much more frequent in the group > 30 years (p = 0.003) and in the group > 50 years (p = 0.003) (Table 1).

Regarding MG diagnosis, the Tensilon test was positive in the only patient who was performed, while the supramaximal repetitive nerve stimulation test (Jolly test) was positive in 20 of the 24 patients evaluated (83%). One case was diagnosed by the ice pack test. The ACRA analysis was performed on 34 patients, and the result was positive in 30 of them (88%), while anti-MuSK were requested in two patients, both negative. Chest-computed tomography (CT) was performed in 30 patients, finding thymic alteration in 15 cases (50%) (Table 1).

In total, 37 patients were treated with pyridostigmine (95%) in a dose range of 90-540 mg and an average of 184 mg. Corticosteroids were prescribed in varying doses to 27 patients (69%), azathioprine (AZA) was indicated to 33 patients (85%) in doses of 50-150 mg, with an average of 80 mg and mycophenolate mofetil was only indicated to two patients (5%). Two patients were treated with plasmapheresis and one with intravenous immunoglobulin for exacerbation of symptoms or diagnosis of myasthenic crisis (Table 1).

Surgical treatment (transsternal thymectomy) was performed in 16 (41%) patients, being a little more frequent among men (56% vs. 30%). This procedure was significantly more frequent in the group ≤ 30 years compared to > 30 years (75% vs. 32%, p = 0.02). Fourteen patients (87.5%) presented benign histopathological findings: twelve (75%) corresponded to thymic hyperplasia (7 women vs. 5 men, p = 0.04) and 2 (12.5%) to being thymoma; in the remaining two patients (12.5%), malignant thymoma was reported (Table 1).

Information related to the follow-up of the cases was obtained in 31/39 patients, with an average of 32 months of follow-up (minimum of two and a maximum of 108 months). No deaths were reported at any time, even during exacerbations or myasthenic crises. Table 2 shows the comparison of patient’s characteristics in the two cohorts, their diagnostic approach, medical and surgical treatment, histopathological findings, and mortality. The differences or similarities between are discussed below.

Discussion

MG had a mild predominance in women with a frequency almost equal to the previous cohort of 58%; however, in both cohorts this figure is less than 60-88% of what was reported by other authors. Regarding age, different publications in the past two decades in Mexico stand out for a growing average age of patients; the average age reported in 2002 was 32 years; in our previous cohort from 1999 to 2007 it was 43 years; another study of our group reported 47 years in 2008 and the current one, 50 years. This aging of the population diagnosed with MG has also been observed in the United States, Europe, Japan, and China. The typical bimodal distribution associated with sex was not observed by our group; however, this may be associated with insufficient samples, since in a Mexican study of 2010 in which more than 500 cases were analyzed, the bimodal presentation was evident. Chronic-degenerative comorbidities (arterial hypertension and diabetes) significantly increased their frequency;
Table 1. General description of the current cohort (2008-2018), according to sex and age group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n = 39)</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Male (n = 16)</td>
<td>N/A</td>
<td>Female (n = 23)</td>
<td>N/A</td>
<td>N/A</td>
<td>Male (n = 16)</td>
<td>N/A</td>
<td>Female (n = 23)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>23 (59)</td>
<td>N/A</td>
<td>23 (100)</td>
<td>N/A</td>
<td>4 (50)</td>
<td>19 (61)</td>
<td>–</td>
<td>12 (67)</td>
<td>11 (52)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>16 (41)</td>
<td>16 (100)</td>
<td>N/A</td>
<td>N/A</td>
<td>4 (50)</td>
<td>12 (39)</td>
<td>–</td>
<td>6 (33)</td>
<td>10 (48)</td>
<td>–</td>
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<tr>
<td>Autoimmune disease, n (%)</td>
<td>5 (13)</td>
<td>1 (6)</td>
<td>4 (17)</td>
<td>–</td>
<td>0 (0)</td>
<td>5 (16)</td>
<td>–</td>
<td>4 (22)</td>
<td>1 (5)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Ptosis, n (%)</td>
<td>36 (92)</td>
<td>13 (81)</td>
<td>23 (100)</td>
<td>0.03</td>
<td>7 (87)</td>
<td>28 (90)</td>
<td>–</td>
<td>16 (89)</td>
<td>20 (95)</td>
<td>–</td>
<td></td>
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<tr>
<td>Bilateral ptosis, n (%)</td>
<td>16/36 (44)</td>
<td>9/13 (69)</td>
<td>7/23 (30)</td>
<td>0.02</td>
<td>4/7 (57)</td>
<td>12/29 (41)</td>
<td>–</td>
<td>8/16 (50)</td>
<td>8/20 (40)</td>
<td>–</td>
<td></td>
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<tr>
<td>Unilateral ptosis, n (%)</td>
<td>20/36 (56)</td>
<td>4/13 (31)</td>
<td>16/23 (70)</td>
<td>0.02</td>
<td>3/7 (43)</td>
<td>17/19 (59)</td>
<td>–</td>
<td>8/16 (50)</td>
<td>12/20 (60)</td>
<td>–</td>
<td></td>
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<tr>
<td>Extraocular muscle paralysis, n (%)</td>
<td>23 (59)</td>
<td>10 (62)</td>
<td>13 (57)</td>
<td>–</td>
<td>1 (12.5)</td>
<td>22 (71)</td>
<td>0.003</td>
<td>6 (33)</td>
<td>17 (81)</td>
<td>0.003</td>
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<tr>
<td>Ossoerman at arrival</td>
<td></td>
<td>11 (28)</td>
<td>14 (36)</td>
<td>13 (33)</td>
<td>15/30 (50)</td>
<td>2 (12)</td>
<td>8 (50)</td>
<td>6 (26)</td>
<td>9 (39)</td>
<td>–</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Jolly (+), n (%)</td>
<td></td>
<td>20/24 (83)</td>
<td>15/15 (100)</td>
<td>9/16 (64)</td>
<td>0.04</td>
<td>4/6 (66)</td>
<td>16/18 (89)</td>
<td>–</td>
<td>10/12 (83)</td>
<td>13/14 (93)</td>
<td>9/16 (56)</td>
</tr>
<tr>
<td>ACRA (+), n (%)</td>
<td></td>
<td>30/34 (88)</td>
<td>15/15 (100)</td>
<td>0 (0)</td>
<td>6 (7)</td>
<td>24/27 (89)</td>
<td>0.02</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>CT scan (+), n (%)</td>
<td></td>
<td>15/30 (50)</td>
<td>10 (62)</td>
<td>13 (57)</td>
<td>0.03</td>
<td>5/6 (62)</td>
<td>11/22 (45)</td>
<td>0.04</td>
<td>3 (17)</td>
<td>8 (38)</td>
<td>6 (29)</td>
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<tr>
<td>Medical treatment</td>
<td></td>
<td>37 (95)</td>
<td>11 (69)</td>
<td>14 (87)</td>
<td>–</td>
<td>8 (100)</td>
<td>29 (84)</td>
<td>–</td>
<td>18 (100)</td>
<td>19 (90)</td>
<td>–</td>
</tr>
<tr>
<td>Pyridostigmine, n (%)</td>
<td></td>
<td>27 (69)</td>
<td>11 (69)</td>
<td>14 (87)</td>
<td>–</td>
<td>5 (62)</td>
<td>22 (71)</td>
<td>–</td>
<td>12 (67)</td>
<td>15 (71)</td>
<td>18 (86)</td>
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<tr>
<td>Corticoids, n (%)</td>
<td></td>
<td>33 (85)</td>
<td>15 (94)</td>
<td>22 (96)</td>
<td>–</td>
<td>7 (87)</td>
<td>26 (84)</td>
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<td>15 (83)</td>
<td>18 (86)</td>
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<tr>
<td>Azathioprine, n (%)</td>
<td></td>
<td>37 (95)</td>
<td>11 (69)</td>
<td>14 (87)</td>
<td>–</td>
<td>8 (100)</td>
<td>29 (84)</td>
<td>–</td>
<td>18 (100)</td>
<td>19 (90)</td>
<td>–</td>
</tr>
<tr>
<td>Thymectomy/ histopathology</td>
<td></td>
<td>16 (41)</td>
<td>9 (56)</td>
<td>7/23 (30)</td>
<td>–</td>
<td>6/8 (75)</td>
<td>10/13 (22)</td>
<td>0.02</td>
<td>10/18 (56)</td>
<td>6/21 (29)</td>
<td>–</td>
</tr>
<tr>
<td>Thymectomy, n (%)</td>
<td></td>
<td>14/16 (87)</td>
<td>7/9 (78)</td>
<td>7/7 (100)</td>
<td>0.04</td>
<td>6/6 (100)</td>
<td>8/10 (80)</td>
<td>–</td>
<td>9/10 (90)</td>
<td>5/6 (83)</td>
<td>–</td>
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<tr>
<td>Benign, n (%)</td>
<td></td>
<td>12/16 (75)</td>
<td>5/9 (55.5)</td>
<td>7/7 (100)</td>
<td>–</td>
<td>6/6 (100)</td>
<td>6/10 (60)</td>
<td>–</td>
<td>9/10 (90)</td>
<td>3/6 (50)</td>
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<td>Hyperplasia, n (%)</td>
<td></td>
<td>2/16 (12.5)</td>
<td>0/7 (0)</td>
<td>0/7 (0)</td>
<td>–</td>
<td>0/6 (0)</td>
<td>2/10 (20)</td>
<td>–</td>
<td>0/10 (0)</td>
<td>2/6 (33.3)</td>
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<td>Benign thymoma, n (%)</td>
<td></td>
<td>2/16 (12.5)</td>
<td>0/7 (0)</td>
<td>0/7 (0)</td>
<td>–</td>
<td>0/6 (0)</td>
<td>2/10 (20)</td>
<td>–</td>
<td>1/10 (0)</td>
<td>1/6 (17)</td>
<td>–</td>
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<tr>
<td>Malignant thymoma, n (%)</td>
<td></td>
<td>5 (13)</td>
<td>3 (19)</td>
<td>2 (9)</td>
<td>1/8 (12)</td>
<td>4/31 (13)</td>
<td>–</td>
<td>2 (11)</td>
<td>3 (14)</td>
<td>–</td>
<td></td>
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<tr>
<td>Exacerbation, n (%)</td>
<td></td>
<td>5 (13)</td>
<td>4 (25)</td>
<td>1 (4)</td>
<td>1/8 (12)</td>
<td>4/31 (13)</td>
<td>–</td>
<td>1 (6)</td>
<td>4 (19)</td>
<td>–</td>
<td></td>
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<tr>
<td>Myasthenic crisis, n (%)</td>
<td></td>
<td>5 (13)</td>
<td>4 (25)</td>
<td>1 (4)</td>
<td>1/8 (12)</td>
<td>4/31 (13)</td>
<td>–</td>
<td>1 (6)</td>
<td>4 (19)</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

ACRA: acetylcholine receptor antibodies; CT: computed tomography; N/A: not apply; –: not significant.

moreover, diabetes is a new comorbid that was not observed in the previous cohort. This is likely to reflect the usefulness of timely detection programs and/or be the result of the epidemiological and pandemic transition of chronic-degenerative diseases in our country, a proposal supported by the Mexico National Survey of Health and Nutrition Mid-way 2016 (ENSANUT MC 2016). The associated diagnosis of autoimmune diseases had a slight increase of only 4% compared to the previous cohort (9%); however, it continues to be...
The Tensilon test showed a clear decrease in its performance, since it has been displaced by other more practical and less risky diagnostic methods. The repetitive nerve stimulation test continued to be a useful and frequently requested diagnostic method, especially in ACRA seronegative patients. Single fiber electromyography is the most sensitive tool for the diagnosis of MG, it is positive in 95% of patients with generalized MG and in 90–95% with ocular MG; however, it is not yet available in West Mexico, a significant delay compared to other countries where it is available in the majority of reference centers. In a particular patient with high clinical suspicion, the diagnosis was made using the ice pack test (with high positive predictive value), after being negative for both ACRA and supra-maximal repetitive nerve stimulation test.

A very prominent point in our center is the increase in the percentage of positive ACRA patients (30 of 34 patients tested [88%]) compared to the previous cohort (14 of 38 patients tested [37%]). It is likely that at that time the detection of the antibodies by the local laboratory was deficient with respect to the methods and processing of the samples and therefore the results were unintentionally affected. Although the percentage obtained here is very consistent with the reported worldwide, with 12% of cases being seronegative, anti-MuSK are not usually requested even though they represent 1–10% of cases; Ryanodine antibodies present in 70% of patients with thymoma and MG are not available, neither do antibodies against lipoprotein receptor-related protein 4 found in 1–3% of cases. The percentage of thymic alteration in the CT scan was similar to the 57% of the previous cohort.

Almost all of our patients were treated with pyridostigmine. Corticosteroids continued to be used in two-thirds of the cases. An important advance was the increase in the use of steroid-sparing agents, administered to 90% of patients. The medical management of MG in our hospital is consistent with the worldwide consensus of experts and data from controlled trials that support the use of prednisone in combination with AZA as a first-line treatment. Good results have been obtained with the use of rituximab and should be considered, especially for refractory cases.

Compared to the previous cohort (53%), thymectomy was performed in a smaller number of patients, predominantly in men, younger subjects, and generalized stages. Our patients were selected for surgery based on the CT findings, however, in patients with autoimmune MG without thymoma, thymectomy is performed.

### Table 2. Comparison of the two evaluated cohorts

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>43</td>
<td>39</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>25 (58)</td>
<td>23 (59)</td>
</tr>
<tr>
<td>Average age, years</td>
<td>43</td>
<td>50</td>
</tr>
<tr>
<td>Systemic arterial hypertension, n (%)</td>
<td>2 (4)</td>
<td>15 (38.5)</td>
</tr>
<tr>
<td>Type II diabetes, n (%)</td>
<td>0 (0)</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Autoimmune disease, n (%)</td>
<td>4 (9)</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Osserman at arrival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I, n (%)</td>
<td>9 (21)</td>
<td>11 (28)</td>
</tr>
<tr>
<td>IIa, n (%)</td>
<td>14 (33)</td>
<td>14 (36)</td>
</tr>
<tr>
<td>IIb, n (%)</td>
<td>19 (44)</td>
<td>13 (33)</td>
</tr>
<tr>
<td>III, n (%)</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>IV, n (%)</td>
<td>0 (0)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Tensilon (+), n (%)</td>
<td>13/13 (100)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Jolly (+), n (%)</td>
<td>31/32 (97)</td>
<td>20/24 (83)</td>
</tr>
<tr>
<td>ACRA (+), n (%)</td>
<td>14/38 (37)</td>
<td>30/34 (88)</td>
</tr>
<tr>
<td>CT scan (+), n (%)</td>
<td>20/35 (57)</td>
<td>15/30 (50)</td>
</tr>
<tr>
<td>Pyridostigmine, n (%)</td>
<td>43 (100)</td>
<td>37 (95)</td>
</tr>
<tr>
<td>Corticoids, n (%)</td>
<td>27 (63)</td>
<td>27 (69)</td>
</tr>
<tr>
<td>Azathioprine, n (%)</td>
<td>2 (4)</td>
<td>2 (8.5)</td>
</tr>
<tr>
<td>Mycophenolate, n (%)</td>
<td>0 (0)</td>
<td>2 (5.1)</td>
</tr>
<tr>
<td>Thymectomy, n (%)</td>
<td>23 (53)</td>
<td>16 (41)</td>
</tr>
<tr>
<td>Histopathologic result</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal, n (%)</td>
<td>8/23 (35)</td>
<td>0/16 (0)</td>
</tr>
<tr>
<td>Hyperplasia, n (%)</td>
<td>11/23 (48)</td>
<td>12/16 (75)</td>
</tr>
<tr>
<td>Benign thymoma, n (%)</td>
<td>4/23 (17)</td>
<td>2/16 (12.5)</td>
</tr>
<tr>
<td>Malignant thymoma, n (%)</td>
<td>0/23 (0)</td>
<td>2/16 (12.5)</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>7 (16)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

ACRA: acetylcholine receptor antibodies; CT: computed tomography.
as an option to avoid or minimize the dose and duration of immunosuppressants, if patients do not respond to an initial immunosuppressive trial or have intolerable side effects\textsuperscript{12,22,25}. A recent study showed special benefit in patients with generalized disease, disease duration of < 3-5 years, age of < 60-65 years, and symptoms not completely relieved with anticholinesterase drugs\textsuperscript{1,10}.

In addition, a report from the National Medical Center “20 de Noviembre” in Mexico found that there is a statistically significant improvement (\(p = 0.000\)) on the quantitative myasthenia gravis score scale when comparing the clinical condition of patients 1 year before versus 4 years after thymectomy\textsuperscript{26}.

In this analysis, the frequency of thymic hyperplasia is consistent with that reported in other articles. Our thymoma percentage (25%) is high, and we do not identify cases of thymic atrophy\textsuperscript{1,2,9,10,12}. In contrast to the previous study (48%), thymic hyperplasia represents a higher percentage, with a decrease in normal results, probably due to an improvement in sample processing; also, no cases of malignant thymoma were identified in the previous cohort\textsuperscript{7}.

Regarding prognosis, there is a clear decrease in mortality compared to the previous cohort, where it was recorded in 16\%\textsuperscript{7}. While it is true that there was a loss of follow-up in eight cases, there is certainty in the neurological staff and group that publish this report that no death was recorded in our hospital. A comparative analysis related to the prognosis with other hospitals in our country is not feasible due to the particular objectives of the studies or the small number of samples\textsuperscript{27,28}. As a weakness, the response to treatment was not followed with validated functional scales; however, these will be included in prospective.

### Conclusion

There are differences between the cohorts of our hospital, highlighting in the last one an older age of presentation, the appearance of chronic-degenerative diseases, greater positivity to ACRA, optimization of pharmacological management, less thymectomy, and no mortality. Much progress has been made in the diagnosis and treatment of MG in our hospital in the past decade; however, there still are areas of opportunity such as single-fiber electrodiagnosis, the realization of other non-ACRA antibodies and optimization of a flowchart for surgical treatment. We encourage the replicas of this work in other hospital centers.

### Acknowledgments

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### Funding

None.

### Conflicts of interest

The authors declare they have no conflicts of interest in this study.

### Ethical responsibilities

Protection of people and animals. The authors declare that no experiments were performed on humans or animals for this research.

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

Stroke terminology in Mexico: Consensus using the Delphi method

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Abstract

Background: In the Spanish language, there exists a considerable heterogeneity regarding the translation and use of the term “stroke,” which has multiple implications for epidemiology and science as well as the general population. Objective: The objective of the present study was to complete a Delphi exercise on the terminology for the Spanish equivalent for the term “stroke” in a group of Mexican experts in vascular neurology. Methods: A 3-phase consensus process was carried out using the Delphi method. The convened experts who agreed to participate completed an initial questionnaire. Subsequent questionnaires were designed based on the initial results. The final consensus was validated in a different group of researchers. Results: 69 stroke specialists participated in the first round, 78% also participated in the second round, and 72% in all three rounds. From an initial list of 33 terms derived from an initial search of the medical literature in Spanish, a consensus of more than 70% was obtained to designate stroke as: “Enfermedad Vascular Cerebral (EVC)” and ischemic and hemorrhagic stroke as “infarto cerebral” and “hemorragia cerebral,” respectively. Likewise, the so-called “stroke units” were designated as “unidades neurovasculares”. Conclusions: This is the first work that seeks to solve, through a consensus methodology, the great diversity that exists in the Spanish language regarding the terminology of stroke.


Terminología para enfermedad vascular cerebral en México: consenso utilizando el método Delphi

Resumen

Antecedentes: Existe gran heterogeneidad en cuanto a la traducción y el uso del término stroke en el idioma español, lo cual tiene múltiples implicaciones epidemiológicas, científicas y demográficas. Objetivo: El objetivo de este estudio fue llevar a cabo un ejercicio Delphi acerca de la nomenclatura para el término stroke en un grupo de expertos en neurología vascular en México. Métodos: Se realizó un proceso de consenso en tres fases mediante el método Delphi. Los expertos...
Introduction

Unlike other Spanish-speaking countries such as Spain, where the term “ictus” is widely used\(^1\), in Mexico, there is no unified terminology to refer to stroke. This has resulted in the indiscriminate use of multiple words, both among health professionals and the general population. Such a diversity of terms can sometimes convey misconceptions about the nature of vascular pathology in the central nervous system. The lack of clarity in terminology is one of the potential causes of the low level of knowledge about vascular risk factors and warning symptoms in the general population\(^2\), which, in turn, decreases the possibility of early detection and treatment.

Due to the health implications of the variability in the terminology used to refer to the pathology that affects the brain vessels, we designed the present study with the primary objective of obtaining a standardized terminology for application in the medical, academic, and general population settings.

Methods

We carried out a 3-phase consensus process using the Delphi method.

Phase 1

a) Search of the scientific literature in Spanish.

Search strategy and selection criteria.

References for this work were identified by searching the IBECS, Lilacs and Scielo electronic databases. No date limits were used, and we included articles published until July 2018. Types of articles included reviews, original studies, and treatment guidelines. The search was conducted exclusively in Spanish using the terms: first term: “México,” “mexicano,” and “mexicana;” second term: “epidemiología,” “mortalidad,” “carga,” “incidencia,” “prevalencia,” “pronóstico,” “registro,” “vigilancia,” “factores de riesgo,” “prevención,” and “diagnóstico;” and third term: “accidente cerebrovascular,” “enfermedad vascular cerebral,” “EVC,” “ACV,” “AVC,” “evento vascular cerebral,” “isquémico,” “hemorrágico,” “infarto cerebral,” “hemorragia cerebral,” “trombosis cerebral,” “hemorragia intracerebral,” “ictus,” “vascular,” “neuroógica,” “terapia intensiva,” “unidad de cuidados,” “unidad de ictus,” and “especializado.” Based on the title and summary, articles for full-text review were selected.

b) Creation of an initial list of terms.

The terms found in the text of the articles identified in the literature search were used to create a list. The first list was for the translation of stroke as an umbrella term for cerebrovascular disease and another three lists were created to designate the subtypes of ischemic and hemorrhagic stroke and for the designation for stroke units.

Phase 2

A 3-round Delphi process\(^3\) was carried out. Neurology experts specialized in stroke who agreed to participate in the three rounds of questionnaires were involved. Questionnaires were designed to achieve a consensus of opinions about which words should be used to designate stroke and its subtypes. Participants were recruited from among those attending the Annual Meeting of the Mexican Association of Stroke. The questionnaires were applied electronically through an online platform. The surveys could be quickly answered, with an average completion time of fewer than 10 min. All participants remained anonymous during the process; their responses were tracked through initials and the date of birth. After each round, their answers were used as feedback to update the following questionnaire, eliminating the less popular terms.

Phase 3

Once consensus was reached with the findings of the first two phases, a small group of experts was asked for their views on the resulting terms, thus concluding the consensus process. The final list of selected words was sent to all participants by e-mail.
**Results**

Table 1 shows the initial list derived from the literature search. This list includes 33 items that were used in the first questionnaire. Seventy-one specialists participated in the first round of the Delphi process. However, the responses of two specialists had to be eliminated because the country where they practiced neurology was not Mexico (1 in Costa Rica and 1 in El Salvador). Of the remaining 69 specialists, 77.5% (55 specialists) answered the second questionnaire and 51 participated in the third (72%). Consensus was achieved when at least 70% of the respondents considered the term as the most appropriate.

For the final phase of the consensus, three prominent specialists with extensive experience in epidemiology and research methodology were invited to test the pilot process of the final term list. They all agreed to participate. The consensus reached in this phase was 100%; the final list formed by the terms is shown in table 2.

The four terms obtained are recommended as translation standards and for use in scientific manuscripts, scientific dissemination texts, advertising campaigns,
Discussion

This is the first project that seeks to solve the great diversity that exists in Mexico regarding the terminology referring to stroke through a consensus methodology. The literature search carried out in the first phase of the study demonstrated the wide variety of terms currently in use. This variety of terms can have severe and multiple implications, both medical and otherwise. Below we discuss some of the most important.

In epidemiology, it may cause underreporting in morbidity/mortality statistics reported in the country due to inadequate coding. For example, in a study of 26 death certificates completed in a general hospital in Mexico, it was found that only 26.9% of them had good quality data, and in 30.7% of them, the quality was rated as poor to terrible. The most common error was the presence of blank spaces followed by the use of abbreviations. Although the above data do not refer exclusively to stroke, data obtained from death certificates show that in Mexico’s general hospitals stroke constitutes between 20 and 50% of the causes of hospitalization, so a substantial amount of those certificates does contain data from patients with stroke.

Another example related to this problem is the inclusion of the diagnosis of “embolia” in both the “Guide for the filling of death certificates and fetal death,” from the General Directorate of Health Information of Mexico, and the “Self-learning guide for the correct filling of the death certificate,” from the Mexican Center for the Classification of Diseases. The term “embolia” although widely used among the general population of Mexico, it is also sometimes encountered in the medical literature. For example, in a study of patients with cardioembolic ischemic stroke (IS), the only term used throughout the text to refer to (IS) is “embolia.” Given the fact that “embolia” means obstruction caused by an embolus; the use of this term excludes both hemorrhagic stroke and IS due to other mechanisms such as atherosclerosis and hypoperfusion. Therefore, its use is highly discouraged.

Another example at the international level is the World Health Organization’s web site, where the corresponding page in Spanish of the page dedicated to providing general information about stroke defines it as cerebrovascular accident.

We believe that the use of the term accident implies inevitability or randomness in its origin. Since most of the risk of stroke derives from chronic or potentially preventable factors, the use of the term: cerebrovascular accident has been discouraged and broadly eliminated in English. Nonetheless, to this day, the Code 8820, of the international classification of diseases in its current revision in Spanish, corresponds to cerebrovascular accident.

Another aspect where the standardized use of words has implications beyond the clarity of language is that of clinical research since the use of different terms makes it difficult to search for medical literature. Lack of standardization may introduce biases when conducting systematic reviews, meta-analyses, or even in simple searches derived from daily clinical practice. For example, in a single study of morbidity and mortality in cardiac and cerebral vascular diseases, five different terms and abbreviations are used interchangeably throughout the manuscript: “enfermedad cerebrovascular, ECV, AVC, enfermedad isquémica cerebrovascular y evento cerebrovascular” (cerebrovascular disease, ECV, AVC, ischemic cerebrovascular disease, and cerebrovascular event), ultimately making unclear whether the epidemiological data reported corresponded to stroke or to IS.

The health needs of Mexico and Latin America require high-quality data. Therefore, we believe that a systematic approach is essential to be able to adequately estimate the burden of disease associated with stroke, to increase comparability among populations, and to design campaigns of awareness for the general population, among other essential objectives. These goals are hampered by the lack of homogeneity in the terminology of stroke. We acknowledge that the issue of heterogeneity was earlier addressed by the Iberoamerican Society of Cerebrovascular Disease (SIECV) that resulted in the recommendation for the use of the term “ictus.” Unfortunately, as previous research shows, the knowledge and use of the term “ictus” are very scarce among the general population in Mexico.

Table 2. Final terms

<table>
<thead>
<tr>
<th>In English</th>
<th>In Spanish</th>
<th>Acronym in Spanish</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>Enfermedad Vascular Cerebral</td>
<td>EVC</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>Infarto Cerebral</td>
<td>IC</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>Hemorragia Cerebral</td>
<td>HC</td>
</tr>
<tr>
<td>Stroke unit</td>
<td>Unidad Neurovascular</td>
<td>UNV</td>
</tr>
</tbody>
</table>
Consistently, our results also show that a highly selected sample of neurologists did not consider the use of the term “ictus” to be the most adequate, in fact, “ictus” did not even reach the last round of the Delphi exercise, which illustrates the difficulty of homologizing the terminology according to the recommendations of the SIECV. Further complicating the problem, it is worth noting that despite its recommendation, the SIECV does not use in its name the term “ictus” but instead cerebrovascular disease.

Hence, we consider that the development of standardized terms to designate stroke is a first step toward improving the quality of epidemiological data and informative materials. Even though we agree that the use of ictus as the standard translation of stroke is preferable, our results show that among Mexican professionals in vascular neurology, “ictus” has yet to be widely accepted, thus severely difficulty its widespread use among the general population.

As with any result derived from a consensus approach, the present study has the limitation that its results could only reflect the opinions of its participants. However, the Delphi method has been widely used in medicine to solve problems analogous to the one presented in this paper. In addition, we consider that we have reached a large percentage of consensus in a highly qualified population of Mexican vascular neurology practitioners. Likewise, the experts who participated in the final validation also showed a broad consensus on the usefulness and relevance of the results. It follows that this work may be useful for health professionals, educators, and the general population.

Conclusions
Projects aimed at measuring the potential impact of the use of these results and their applicability in other Spanish-speaking countries should be further researched.

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The authors would like to thank the Delphi process respondents for their voluntary participation in this project.
To Brigitte van Gils for the editorial review of the manuscript.

Conflicts of interest
None.

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

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

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

References

J.M. Marquez-Romero, et al.: Stroke terminology in Mexico
Neuropsychological differences between types of multiple sclerosis: relapsing remitting versus primary progressive

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Abstract

Background: Multiple sclerosis (MS) is a neurodegenerative disease whose clinical deterioration is observed at a physical, cognitive, and socio-emotional level, affecting the quality of life of the patient. Several scientific studies show early cognitive alterations in MS and profiles of different cognitive affection according to the clinical form of the disease. Objective: The objective of the study was to analyze the existence of significant differences between relapsing remitting MS (RRMS) and primary progressive MS (PPMS) in neuropsychological processes such as attention, memory, language, visuoperception, executive function, and processing speed. Methods: The sample consisted of 20 patients with MS with chronological ages between 20 and 50 years of both sexes belonging to the Psique de Medellín Foundation, who were administered the paced auditory serial addition test and the digit-symbol test to assess attention, the complex figure of Rey to evaluate memory, the Boston test, and verbal fluency to assess language, complex figure of Rey copy for visuoperception, Wisconsin to assess executive function, and trail making test to measure processing speed. A descriptive, inferential, and transversal design was used. Results: There are no significant differences between the scores of patients with RRMS and PPMS in any assessed neuropsychological process. Conclusion: Knowing the neuropsychological profile of MS in early stages can be useful as an indicator of prognosis and to suggest therapeutic and follow-up strategies in patients with RRMS and PPMS.

Key words: Multiple sclerosis. Attention. Memory. Language. Executive function.
integrated with 20 patients with multiple sclerosis and chronological ages of 20 to 50 years of both sexes belonging to the Foundation Psique de Medellín, subject to the administration of the PASAT and the Digi-símbolo test to measure the attention, the Rey Complex Figure Test to measure the memory, the Boston and Fluidez Verbal tests to measure the language, the Rey Complex Figure Test to measure the processing speed. Se utilizó un diseño descriptivo, inferencial y transversal. Resultados: No existen diferencias significativas entre las puntuaciones de pacientes con esclerosis múltiple remitente recurrente y esclerosis múltiple progresiva primaria en ningún proceso neuropsicológico valorado. Conclusiones: Puede ser de utilidad conocer el perfil neuropsicológico de la EM en fases tempranas como indicador de pronóstico y para sugerir formas terapéuticas y de seguimiento en pacientes con esclerosis múltiple remitente recurrente y esclerosis múltiple progresiva primaria.


Introduction

Multiple sclerosis (MS) is a neurodegenerative pathology that affects the central nervous system, characterized by presenting heterogeneity of symptoms and progressive disability that impairs the quality of life of patients. Nowadays, various research studies show that MS is a demyelinating disease in which immune processes are altered, unknown etiology but involving an interplay between genetic and environmental factors.

MS is clinically characterized by relapses and/or progression, being relapses or not associated with progression. Relapses refer to acute or subacute episodes of neurological dysfunction that may or may not be followed by a remission, spontaneously or after treatment, resulting in a partial or complete recovery. These relapses are the result of acute, multifocal or monofocal, inflammation, that is recurrent with the appearance of new injuries. Symptoms associated with a relapse include diplopia, dizziness and vertigo, paresthesia, optic neuritis, paraparesis, and pyramidal syndrome. Progression is defined as a steadily increasing objectively documented neurological dysfunction/disability without unequivocal recovery (fluctuations and phases of stability may occur).

At present, several disease courses or phenotypes of MS have been identified. The clinical manifestations of MS, in both progression and relapses, include motor and sensory dysfunctions, accompanied by cognitive deficits and emotional, and/or psychiatric disorders. Cognitive impairment has a high prevalence and has been reported in 43-70% of MS patients, and can occur at any stage of the disease. This cognitive dysfunction is a manifestation of axonal injury that is widely distributed throughout the brain and manifests as neuropsychological deficits, in attention, memory, learning, executive function, and processing speed. Using magnetic resonance imaging (MRI) measures, Filippi et al. noted that cognitive impairment in MS is related to atrophy in the gray matter damage and Cruz-Gómez et al. suggest that low performance in episodic and declarative memory tasks is associated with reduced functional connectivity of the left hippocampus. Several studies show that cognitive deficits are present in the early stages of the MS, and the impairment include alterations in processes such as attention, memory, executive function, and processing speed. In the study carried out by Duque et al., they find the performance was worse for MS patients than for control participants in verbal memory tasks, working memory, and processing speed. Achiron et al. and Desousa et al. reported on cognitive disturbances in memory, verbal fluency, attention, and processing speed in patients with MS. More specifically, after studying cognitive impairment among phenotypes of MS, Huijbregts et al. suggest that patients with different forms of MS are associated with different cognitive impairment profiles. Along the same lines, Wachowiak et al. find that patients with progressive form of MS show greater cognitive impairment than patients with recurrent form of MS, and exhibit lower performance in tasks of visual memory, processing speed, and attention. Macías-Islas et al. assert that patients with relapsing-remitting MS (RRMS) perform significantly better in working memory, processing speed, and attention tasks than patients with primary progressive MS (PPMS). In short, it is necessary to know the involvement of the neuropsychological processes of each type of MS, to provide an adequate, early, and optimal neuropsychological intervention with the aim of delaying neurological disability and improving the quality of life of patients. For this reason, the objective of this research is to verify the existence of statistically significant differences in some neuropsychological processes such as attention, memory, language, visuoperceptual processing, executive function,
and processing speed between patients with RRMS and PPMS.

Methods

A non-experimental descriptive and inferential design were used with the aim of describing the values of the study variables and comparing differences between groups (RRMS and PPMS). It was adopted an ex post facto and cross-sectional design, using a quantitative information-gathering methodology. The participants in this study were 20 MS patients from patients from the Psyque Foundation in the City of Medellin, Colombia, between the ages of 22 and 52 (M = 37.40; DE = 8.56), both sexes, 12 women and eight men. The RRMS group consisted of 11 patients, seven women, and four were men, aged between 22 and 46 (M: 37.55; DE: 6.54). The PPMS group consisted of nine patients, five women and four were men, aged between 22 and 52 (M: 37.27; DE: 10.24). All participants were of legal age and signed informed written consent expressing their agreement with participation in the study. The sample was non-random and the criteria for inclusion were as follows: to have MS diagnoses according to the McDonald criteria of 2005 (collected in Polman et al.24), to have a diagnosis time of the disease < 1 year, to have at least one level of high school studies, and to belong to the Psyche Foundation of Medellin.

The exclusion criteria were illiteracy, perceptual alterations that prevented evaluation and psychiatric disorders or another neurological disease in the anamnesis; to verify the latter, the diagnosis report was requested from participants, with no additional tests being performed for the assessment of depression and anxiety that are common in MS patients. To verify that the intellectual level of participants was > 70, they were administrated K-BIT, which is an intelligence quotient (IQ) screening that verified that all patients had an IQ above 70, both the RRMS group (M: 76.22; SD: 16.81) and the PPMS group (M: 74.27; SD: 12.60).

The variables under study were attention, Wisconsin Cards Sorting test, Heaton et al.31, executive function and processing speed, and the evaluation instruments for measuring them were, respectively: paced auditory serial addition test (PASAT) to evaluate auditory attention, symbol digit modalities test (SDMT) for auditory and visual attention, Rey Complex Figure Test (copy) for visual memory and visuoperceptual processing, Boston test to assess the naming abilities at a linguistic level and a verbal fluency test, the Wisconsin cards sorting test (WCST) to evaluate cognitive flexibility (one component of executive function), and Trail Making Test to assess processing speed.

The Paced Auditory Serial Addition Test (PASAT), Gronwall25 is a neuropsychological test used to assess divided attention; in this study the PASAT 3 version has been used.

The Symbol Digit Modalities Test (SDMT), Smith26 evaluates sustained attention and in the present research both versions (auditory and visual) have been used.

The Trail Making Test, Jarvis and Bart27 is used to assess attention and processing speed. In this study, only part B has been used and it has been registered the time spent performing the task.

Rey Complex Figure, Rey28 is a test that allows to assess the organization and visuospatial memory. In this study, the copy task is used to measure visuoperceptual ability and short-term visuospatial memory task.

The Boston test, Goodglass and Kaplan29 is used to assess naming abilities.

Verbal Fluency task, Ardila and Rosselli30 is a task of semantic verbal fluency.

Wisconsin Cards Sorting test (WCST), Heaton et al.31: this test evaluates cognitive flexibility.

Before the assessment, informed consents were requested from participants of the Psyque Foundation of the City of Medellin, both RRMS and PPMS patients. Subsequently, the tests were clinically administered, i.e., a single researcher and patient in a ward.

The neuropsychological assessment was organized into three sessions of approximately 40 min each and the order of the tests remained constant for all patients. Lighting and loudness conditions were controlled in each room to make them the most optimal possible. The study was conducted in accordance with established ethical standards. The research was approved by the Bioethics Committee of the Pampuri Foundation – International NGO, in compliance with the ethical standards of the Helsinki Declaration of 2000.

The data were analyzed using the SPSS statistical program, version 20.0 for Windows. Descriptive statistics of the variables were calculated to represent the central tendency: mean, and standard deviation; and Student’s parametric t-test, and Mann–Whitney’s non-parametric U-test (after analysis of the Shapiro normality test) were used to check for significative differences between groups in the variables under study with a significance level α = 0.05.
Results

The results of descriptive analyses of the attention, memory, language, visuoperceptual processing, executive function, and processing speed variables in the two EMRR and EMPP study groups are shown in Table 1. The data in this table reveal a higher means for the variables sustained auditory attention, sustained visual attention, divided auditory attention, visual memory, denomination, and visuoperceptual processing in the patients RRMS. However, the mean of the variable cognitive flexibility is higher in PPMS. In processing speed RRMS patients used less time to finish the task. In the verbal fluency task, the performance of patients with RRMS and PPMS seems similar.

The results of the inferential analysis were obtained by Student’s parametric t-test and Mann–Whitney’s non-parametric U-test with a significance level of 0.05, and show that there are no significant differences between EMRR and EMPP in any of the neuropsychological variables studied. Table 1 shows the results of the inferential analysis between RRMS and PPMS in all the neuropsychological measures.

To confirm the difference between MS patients and expected normal means, inferential statistics were in each of the neuropsychological tests with a significance level of 0.05. The results using the Mann-Whitney U test showed significant differences in sustained auditory attention (p = 0.000), divided auditory attention (p = 0.000), processing speed (p = 0.000) and naming (p = 0.000). The comparative analysis using the Student t-test found significant differences in verbal fluency (t = 8.212; p = 0.000) and sustained visual attention (t = 11.665; p = 0.000). No significant differences were found in visual memory (p = 0.108), visuoperceptual processing (p = 0.602) and cognitive flexibility (p = 0.602).

The differences between RRMS and PPMS were also analyzed based on age (t = 0.072; p = 0.944) intellectual level (IQ) (p = 0.421) and the schooling years (t = 1.201; p = 0.245), and no significant differences were found.

The estimated sample size to find a significant difference has been calculated for the two variables closest to statistical significance: sustained visual attention and divided auditory attention. The number of participants estimated to find significant differences between groups with a 95% CI is 52 for sustained visual attention and 40 for divided auditory attention, half of each subtype.

Discussion

The results of the present study show that there are no significant differences between RRMS and PPMS in the neuropsychological processes evaluated in this research such as: attention, processing speed, memory, language, visuoperceptual processing, and cognitive flexibility. These findings are in line with previous studies that found no significant differences in verbal

Table 1. Neuropsychological variables: inferential and descriptive results

<table>
<thead>
<tr>
<th>Neuropsychological variables</th>
<th>EMRR</th>
<th>EMPP</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained visual attention</td>
<td>21.18*</td>
<td>15.66*</td>
<td>1.700</td>
<td>0.10</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>10.27*</td>
<td>10.11*</td>
<td>0.104</td>
<td>0.91</td>
</tr>
<tr>
<td>Sustained auditory attention</td>
<td>9.90*</td>
<td>7.77*</td>
<td>0.456</td>
<td></td>
</tr>
<tr>
<td>Divided auditory attention</td>
<td>10.81*</td>
<td>5.33*</td>
<td>0.120</td>
<td></td>
</tr>
<tr>
<td>Processing speed</td>
<td>239.27*</td>
<td>318.33*</td>
<td>0.456</td>
<td></td>
</tr>
<tr>
<td>Visual memory</td>
<td>15.18*</td>
<td>8.33*</td>
<td>0.710</td>
<td></td>
</tr>
<tr>
<td>Denomination</td>
<td>51.18*</td>
<td>44.88*</td>
<td>0.331</td>
<td></td>
</tr>
<tr>
<td>Visuoperceptual processing</td>
<td>23.09*</td>
<td>16.66*</td>
<td>0.456</td>
<td></td>
</tr>
<tr>
<td>Executive function: cognitive flexibility</td>
<td>4.27*</td>
<td>6.22*</td>
<td>0.710</td>
<td></td>
</tr>
</tbody>
</table>

*Normal mean expected for the different tests: sustained auditory attention (48,38); sustained visual attention (42,97); divided auditory attention (48,3); processing speed (90,4); visual memory (14,1); denomination (44,2); verbal fluency (17,04); visuoperceptual processing (32); cognitive flexibility (5,7).
fluency and executive function between RRMS and PPMS. However, these authors do find in their study that RRMS patients have better performance than PPMS patients in attention and processing speed tasks. In this same vein, Olivares et al.\textsuperscript{32} found significant differences between RRMS and PPMS in visual memory, attention, and processing speed tests. Johnen et al.\textsuperscript{33}, in a meta-analysis of forty-seven empirical studies conducted with neuropsychological, found significant differences between PPMS and RRMS in favor of RRMS in IQ, speed processing, verbal learning, verbal memory, visual memory, working memory, cognitive fluency, visuo-perception and executive function. These authors found that cognitive differences between MS subtypes persist regardless of clinical and demographic characteristics of the two subtypes, so they may be due to pathogenic differences or aspects related to the sample itself. In a systematic review of eighteen studies Vollmer et al.\textsuperscript{34} they highlight the relation between decreased brain volume with low scores on neuropsychological tests, suggesting that in PPSS there is a greater atrophy of the grey substance possibly generating decreased performance in neuropsychological tasks. Brochet y Ruet\textsuperscript{35} point out that the PPMS subtype presents more cognitive deficits than the RRMS subtype, specifically in tasks in memory, attention, processing speed, verbal fluency, executive functions, and working memory.

The lack of significant differences between RRMS and PPMS encountered in this research is not consistent with the expression of the two clinical profiles of MS. Several studies\textsuperscript{4} indicate that the progressive form of MS is more affected cognitively from the early stages of the disease than the recurrent form of MS, and therefore should be expected worse performance in neuropsychological tasks in those patients with PPMS since the onset of the disease.

However, the results of this research, conducted with a sample diagnosed less than a year ago, indicate that there are no differences in the first stage of the disease between patients with RRMS and PPMS in cognitive impairment in neuropsychological processes such as attention, processing speed, visual memory, language, visuo-perceptual processing, and executive function. The results suggest that in early moments, despite anatomical differences due to cortical loss and pathogenic factors typical of each subtype of MS, the performance of patients in neuropsychological tests is not affected, specifically, no significant differences were found among the patient group versus normal values in cognitive flexibility, visual memory and visuo-perception tasks. This finding goes in the opposite direction than the results of the study conducted by Ruet et al.\textsuperscript{36}, who found worse performance in patients with MS, both PPMS and RRMS subtypes, compared to control group, with more severe cognitive deficits in PPMS than in RRMS, due to pathogenic factors inherent in PPMS. In relation to language (naming), attention, processing speed, verbal fluency and IQ, the performance of patients diagnosed with MS is significantly lower than the mean of the normal population. These results are in line with those found by other studies\textsuperscript{33,37}, suggesting that some cognitive domains are more impaired than others in the first months of the disease. It is true that the data obtained in the present study are conditioned by the sample size, due to the difficulty in finding participants who met the inclusion criteria, especially among patients who were diagnosed at most in 1 year, since the objective of the study was to check for differences between groups in neuropsychological impairment the onset of the disease. In addition, in this study, an attempt has been made to control the effect of the educational level, selecting patients with the same educational level (high school), since several studies\textsuperscript{38-40} have shown the effect of this factor on the performance of neuropsychological tests in patients with MS. Regarding the intellectual level (IQ), there are no significant differences between the MS subtypes, in the opposite direction to the results found in other studies\textsuperscript{33,34,36}. The present study raises the possibility that there are no different profiles of cognitive dysfunction in the execution of neuropsychological tests between RRMS and PPMS in patients with less than one year of symptoms. It is possible that the specific moment of the disease in the participants and the heterogeneity of measures of assessment of cognitive functioning used in the different studies may be influencing the results obtained.

This work has certain limitations: the size of the sample and lack of assessment of other variables that may affect the association of the clinical profile of MS and the cognitive impairment, such as cortical volume loss or white matter observed with MRI and the assessment of functional status or disability, preventing conclusion with a neuropsychiatric deterioration factor.

The results of this study may help the clinician in taking preventive decisions regarding the design and development of the neuropsychological rehabilitation plan of MS patients. The location of neuropsychological deficits in MS is essential to design intervention strategies for each MS subtype. In this study, despite having found no significant differences, the PPMS profile has a worse performance in neuropsychological tasks except for cognitive flexibility, which suggests the early
need for more specialized treatment than the RRMS profile. It could be considered whether an early cognitive intervention in the first months could decrease the difference in terms of cognitive impairment in patients with PPMS versus the RRMS subtype.

Conclusion

In short, this study provides information on the neuropsychological differences between RRMS and PPMS in the initial phase of the disease and about the early neuropsychological profile of both types of MS.

Overall, RRMS patients have better scores on all neuropsychological measures (except cognitive flexibility), although the differences do not become significant in the sample under study. These results may indicate that RRMS/PPMS patients do not differ significantly from each other in the execution of neuropsychological processes in the 1st year after diagnosis. It is important to highlight that the participants of the two groups of MS subtypes in this study are both in the initial stage of the disease (diagnosed for less one year), and they have similar educational level, age, years of schooling and IQ. This data can help by providing information on the status of early-stage cognitive processes of both phenotypes and clinical forms of MS, as an indicator of prognosis and to suggest therapeutic and follow-up strategies in patients with RRMS/PPMS.

As a proposal for future research, it is important to increase the size of the sample and select patients with RRMS and PPMS with more years of disease evolution so that it can be compared the differences between the two types of MS patients in neuropsychological decline, with the passage of time and the effect of medication.

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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 declare that no patient data appear in this article.

References

Symptomatic palatal tremor: A descriptive cohort study of 27 cases in a tertiary hospital

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Abstract

Background: Symptomatic palatal tremor (SPT) is an uncommon hyperkinetic movement disorder caused by the interruption of the dentato-rubro-olivary pathway due to a lesion in the brainstem or cerebellum. Methods: We describe a cohort of consecutive patients with SPT who were assessed by a single neurologist in a tertiary reference center. Results: A total of 27 patients were included in this cohort from 1998 to 2016; 16 males and 11 females, with a mean age of 47 years (range 19-89). The average time from initial insult to a diagnosis of SPT was 14.5 months (range 2-48 months). The most common etiology of SPT was cerebrovascular disease (CVD) in 21 (78%) patients. Other etiologies included infectious and demyelinating diseases of the central nervous system. The remaining unclassified case was accompanied by progressive ataxia pointing toward a neurodegenerative etiology. Twenty-six patients had a history of posterior fossa injury, and all patients had rhomboencephalic signs with severe dysarthria. None of them responded significantly to pharmacological treatment. Conclusion: SPT is a more common finding than expected, especially in patients with posterior fossa injury secondary to CVD. The main clinical syndrome was the rhomboencephalic phenotype, with a predominance of dysarthria. There was no effective treatment in any of the patients.


Temblor palatal sintomático: un estudio de cohorte descriptivo de 27 casos en un hospital terciario

Resumen

Antecedentes: El temblor palatino sintomático (TPS) es un trastorno hiperkinético del movimiento poco frecuente secundario a la interrupción de la vía dentato-rubro-olivar por una lesión en el tronco encefálico o el cerebelo. Métodos: Describimos una cohorte de pacientes consecutivos con TPS que fueron evaluados por un mismo neurólogo en un centro de tercer nivel. Resultados: Se incluyeron un total de 27 pacientes entre 1998 y 2016; 16 hombres y 11 mujeres, con una edad media de...
Introduction

Symptomatic palatal tremor (SPT) is an uncommon hyperkinetic movement disorder1. The pathophysiological basis of SPT is hypertrophic olivary degeneration (HOD), causing interruption of the dentato-rubro-olivary pathway due to lesions in the olivary body at the medulla oblongata. These lesions usually affect the Guillain–Mollaret triangle (GMT) formed by the red nucleus, the inferior olivary nucleus (ION), and the dentate nucleus2. The interruption of the cerebellar inhibitory output to the ION gradually causes hypertrophy, leading to abnormal neuronal discharges and subsequent tremor 3. In SPT, the levator veli palatini is the main affected muscle, causing a 1-2 Hz palatal tremor that usually persists during sleep; other signs such as ocular, pharyngeal or rubral tremor, ataxia, and pendular nystagmus can also be present4,5.

Although sometimes considered myoclonus, its rhythmic nature and bilateral, symmetrical affection of the soft palate and pharynx is consistent with a tremor. Rhythmic myoclonus is often slower than tremor, is present at rest, is not modified significantly by voluntary movements, and often persists during sleep6,7.

The average reported time between an initial GMT lesion and SPT development is 10-11 months8. SPT reports in the past have described it as a medical curiosity, but this could be due to a low level of diagnostic suspicion and late-onset appearance8,9.

Methods

We describe a large cohort of consecutive patients with SPT who were assessed by the same neurologist in a tertiary referral center, including clinical findings, diagnostic workup, and treatment. Subsequent patients > 18 years with an oscillatory palatal tremor of 1-2 Hz and history of posterior fossa disease were included. All patients included were evaluated for treatment response with a mean follow-up of 11 months.

Results

A total of 27 patients were included in this cohort from 1998 to 2016; 16 males and 11 females, with a mean age of 47 (range 19-89 years). The average time from presentation to the diagnosis of SPT was 14.5 months (range 2-48 months). The main etiology of SPT was cerebrovascular disease (CVD) with 21 (78%) patients, of which 14 (66%) were classified as ischemic. There were 3 (11%) cases related to infectious diseases: one case due to neurocysticercosis of the fourth ventricle and two others secondary to cerebral toxoplasmosis (in the context of HIV infection) of the posterior fossa. Two females (7%) had brainstem lesions due to neuromyelitis optica spectrum disorder (NMOSD). The remaining case was a young man with progressive ataxia with a probable neurodegenerative disease. Inferior olivary degeneration (T2 sequence hyperintensity on magnetic resonance imaging [MRI]) with or without hypertrophy was observed in 13 of 14 (93%) patients who had available MRI performed at follow-up (Figs 1-3).

The study was approved by the local ethical committee and classified as a non-risk study with no intervention. Clinical, images, or video film records were obtained from corresponding patient authorization by written consent in all cases.

Discussion

Since its first report by Oppenheim in 1887, HOD continues to be an uncommon condition with a variety
of etiologies and clinical manifestations, with palatal tremor as a unifying criterion\textsuperscript{10}.

In this study spanning almost two decades, our neurology staff was able to identify approximately 1.5 new cases of SPT per year using the following approach: a history of posterior fossa disease, a careful physical examination, and ordering appropriate neuroimaging studies; making SPT a more common condition than previously reported\textsuperscript{6,7}. Patients with a history of posterior fossa surgery were not included in our registry, making this condition probably more frequent in neurosurgery departments. Clinically, the HOD can also cause dentato-rubral tremor (Holmes tremor) and ocular myoclonus as late-onset manifestations; however,
Table 1. Symptomatic palatal tremor etiologies, time to diagnosis, treatment, outcome, and MRI findings

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex/age</th>
<th>Etiology (initial neurological insult)</th>
<th>Time to diagnosis (months)</th>
<th>Treatment</th>
<th>Follow-up (months)</th>
<th>Palatal tremor outcome</th>
<th>MRI inferior olivary hyperintensity/ hypertrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/48</td>
<td>Cerebellar infarct</td>
<td>24</td>
<td>Propranolol</td>
<td>4</td>
<td>Unsuccessful</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>M/34</td>
<td>Progressive ataxia</td>
<td>11</td>
<td>Clonazepam / botulinum toxin</td>
<td>6</td>
<td>Decrease in frequency</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>M/25</td>
<td>Multiple infarcts in vertebrobasilar territory</td>
<td>9</td>
<td>None</td>
<td>8</td>
<td>Unsuccessful</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>F/25</td>
<td>Multiple infarcts in vertebrobasilar territory</td>
<td>12</td>
<td>Clonazepam</td>
<td>10</td>
<td>Unsuccessful</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>F/47</td>
<td>Right cerebellar hypertensive hemorrhage</td>
<td>36</td>
<td>None</td>
<td>36</td>
<td>Unsuccessful</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>M/41</td>
<td>Cerebellar peduncular hemorrhage</td>
<td>13</td>
<td>Propranolol</td>
<td>4</td>
<td>Unsuccessful</td>
<td>Unknown</td>
</tr>
<tr>
<td>7</td>
<td>F/75</td>
<td>Mesencephalic infarct</td>
<td>8</td>
<td>Propranolol / levetiracetam</td>
<td>14</td>
<td>Unsuccessful</td>
<td>Unknown</td>
</tr>
<tr>
<td>8</td>
<td>M/69</td>
<td>Cerebellar infarct</td>
<td>9</td>
<td>Propranolol / levetiracetam</td>
<td>2</td>
<td>Unsuccessful</td>
<td>Unknown</td>
</tr>
<tr>
<td>9</td>
<td>M/24</td>
<td>Multiple infarcts in vertebrobasilar territory</td>
<td>10</td>
<td>None</td>
<td>3</td>
<td>Unsuccessful</td>
<td>Unknown</td>
</tr>
<tr>
<td>10</td>
<td>M/64</td>
<td>Cerebellar hypertensive hemorrhage</td>
<td>24</td>
<td>Propranolol / levetiracetam</td>
<td>13</td>
<td>Unsuccessful</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>M/28</td>
<td>Multiple infarcts in vertebrobasilar territory</td>
<td>12</td>
<td>Acetazolamide / levetiracetam</td>
<td>25</td>
<td>Decrease in frequency</td>
<td>Yes</td>
</tr>
<tr>
<td>12</td>
<td>F/20</td>
<td>Cerebellar hemorrhage</td>
<td>11</td>
<td>Propranolol</td>
<td>8</td>
<td>Unsuccessful</td>
<td>Unknown</td>
</tr>
<tr>
<td>13</td>
<td>F/34</td>
<td>Fourth ventricle neurocysticercosis</td>
<td>48</td>
<td>Propranolol</td>
<td>1</td>
<td>Unsuccessful</td>
<td>Unknown</td>
</tr>
<tr>
<td>14</td>
<td>M/46</td>
<td>Multiple infarcts in vertebrobasilar territory</td>
<td>17</td>
<td>None</td>
<td>4</td>
<td>Unsuccessful</td>
<td>Unknown</td>
</tr>
<tr>
<td>15</td>
<td>F/19</td>
<td>Thalamomesecephalic hemorrhage</td>
<td>29</td>
<td>Propranolol</td>
<td>8</td>
<td>Speech improvement</td>
<td>No</td>
</tr>
<tr>
<td>16</td>
<td>M/78</td>
<td>Cerebellar infarct</td>
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<td>Propranolol</td>
<td>9</td>
<td>Unsuccessful</td>
<td>Unknown</td>
</tr>
<tr>
<td>17</td>
<td>M/70</td>
<td>Pontine hypertensive hemorrhage</td>
<td>5</td>
<td>Propranolol</td>
<td>5</td>
<td>Unsuccessful</td>
<td>Unknown</td>
</tr>
<tr>
<td>18</td>
<td>M/43</td>
<td>Multiple infarcts in vertebrobasilar territory</td>
<td>12</td>
<td>Propranolol</td>
<td>19</td>
<td>Unsuccessful</td>
<td>Yes</td>
</tr>
<tr>
<td>19</td>
<td>F/61</td>
<td>Multiple infarcts in vertebrobasilar territory</td>
<td>2</td>
<td>Propranolol</td>
<td>9</td>
<td>Unsuccessful</td>
<td>Unknown</td>
</tr>
<tr>
<td>20</td>
<td>M/35</td>
<td>Toxoplasmosis of cerebellum and roof of fourth ventricle</td>
<td>11</td>
<td>Propranolol</td>
<td>7</td>
<td>Unsuccessful</td>
<td>Yes</td>
</tr>
<tr>
<td>21</td>
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<td>Multiple infarcts in vertebrobasilar territory</td>
<td>6</td>
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<td>5</td>
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<td>Unknown</td>
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<tr>
<td>22</td>
<td>F/68</td>
<td>Multiple infarcts in vertebrobasilar territory</td>
<td>10</td>
<td>Propranolol / levodopa / biperidine</td>
<td>8</td>
<td>Unsuccessful</td>
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<tr>
<td>23</td>
<td>M/56</td>
<td>Multiple infarcts in vertebrobasilar territory</td>
<td>18</td>
<td>Nifedipine</td>
<td>3</td>
<td>Unsuccessful</td>
<td>Unknown</td>
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<tr>
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<td>F/56</td>
<td>Brainstem and diencephalic hemorrhage</td>
<td>16</td>
<td>Propranolol / Levetiracetam</td>
<td>16</td>
<td>Unsuccessful</td>
<td>Yes</td>
</tr>
</tbody>
</table>

(Continues...)
these symptoms did not occur in any of our patients during follow-up\textsuperscript{2,11}.

In our study, the most common cause of SPT was brainstem or cerebellar CVD, representing almost 80\% of reported cases. These data are consistent with results from other studies, in which the main causes of SPT were CVD, trauma, metastatic, and astrocytic tumors, multiple sclerosis, surgical interventions, syringobulbia, Behçet’s disease, and encephalitis\textsuperscript{12-14}.

Although most of the patients with HOD and SPT have no symptomatic discomfort, several drugs, including beta-blockers, antiepileptic, benzodiazepines, and neuroleptics, are commonly used\textsuperscript{12}. They usually offer partial and non-sustained symptom control in most cases, as reported in this study. Some recent models have demonstrated the influence of cerebellar Purkinje-cell modulation to the hypertrophic ION in SPT, suggesting drug combination therapy for a “double” inhibition with more satisfactory results. These therapies include the use of drugs with GABA-enhancing inhibitory and glutamatergic-coupling effects\textsuperscript{15}.

Other non-pharmacological options include the administration of botulinum toxin, a safe and effective therapy in selected patients with SPT, and marginal benefits using special dental devices that have been used by some authors in patients with lingual-palatal tremor\textsuperscript{15-18}.

Deep brain stimulation has not been studied in SPT but is a secure and beneficial procedure in other movement disorders such as essential tremor and Parkinson’s disease. It could provide some benefit for SPT in the future\textsuperscript{9,20}.

Patients with a history of brainstem or cerebellar injury with no palatal tremor at diagnosis should be kept under vigilance since SPT can appear during follow-up, up to 30 months after initial presentation. Patients with an incidental finding of palatal tremor should be evaluated to rule out lesions in the posterior fossa since over 75\% of cases reveal an underlying symptomatic cause\textsuperscript{21}. This could be a typical scenario of patients with undiagnosed multiple sclerosis or NMOSDs who initially present with posterior fossa symptoms and visit another specialist (such as an otorhinolaryngologist) for medical advice.

During the study, we have been able to identify three clinical characteristics that may facilitate and increase a diagnosis of SPT: (1) history of posterior fossa disease; (2) persistence of severe rhombencephalic signs during the 1st year of symptom onset; and (3) predominance of severe spastic or ataxic dysarthria. More prospective studies with consecutive clinical evaluations should be done to determine the predictive factors involved in these reported findings.

**Conclusion**

In conclusion, SPT is not as rare as previously reported, and physicians should be aware of associated signs and symptoms for adequate diagnosis, especially in patients with a history of posterior fossa disease.

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**Conflicts of interest**

None to report.
Ethical disclosures

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

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

Right to privacy and informed consent. The authors 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

COVID-19 and Guillain-Barré Syndrome: A fortuitous relationship?

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Abstract

Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mainly affects the respiratory system, multiple neurological manifestations have been described. Guillain-Barré syndrome (GBS) is one of those. Despite the limited existence of cases reporting the association between GBS and coronavirus disease 2019 (COVID-19), the number of publications on this subject is increasing, thus making it relevant to compile and synthesize analytically all the nascent information. The objective of this article is to describe the association between COVID-19 and GBS. SARS-CoV-2 is neuroinvasive, neurotropic, and neurovirulent, which allows it to cause neurological damage, including GBS. There have been case reports of a possible association between COVID-19 and GBS in China, the United States of America, Iran, Italy, Spain, France, Germany, and other countries. GBS is emerging as a possible neurological complication in patients with COVID-19. The current evidence does not prove the veracity of a relationship between COVID-19 and GBS, but it justifies its verisimilitude. Further studies on the topic will provide biomedical personnel with a more complete understanding of the performance of GBS in patients with COVID-19, as well as information regarding how to successfully treat it.

Key words: COVID-19. SARS-CoV-2. Guillain-Barré syndrome.

COVID-19 y síndrome de Guillain-Barré: ¿una relación fortuita?

Resumen

Aunque el coronavirus tipo 2 del síndrome respiratorio agudo grave (SARS-CoV-2) afecta principalmente al sistema respiratorio, múltiples manifestaciones neurológicas han sido descritas. El síndrome de Guillain-Barré (SGB) constituye una de estas; y pese a existir pocos reportes de su asociación con la enfermedad por coronavirus de 2019 (COVID-19), el número de publicaciones relativas al tema incrementa por día, lo cual hace que la recopilación y síntesis analítica de toda la información emergente cobren vital relevancia. El objetivo de este artículo es describir la asociación existente entre la COVID-19 y el SGB. El SARS-CoV-2 es neuroinvasivo, neurotrópico y neurovirulento, lo cual justifica su capacidad para ocasionar trastornos neurológicos, incluido el SGB. Existen reportes de casos con posible asociación entre la COVID-19 y el SGB en China, Estados Unidos de América, Irán, Italia, España, Francia, Alemania, entre otros países. El SGB está emergiendo como una potencial complicación neurológica en pacientes con COVID-19. La evidencia existente hasta el momento, si bien no demuestra una relación entre la COVID-19 y el SGB, sí justifica la verosimilitud de esta asociación. Estudios que en el futuro se realicen habrán de proporcionar un conocimiento más completo sobre el comportamiento del SGB en pacientes con COVID-19 y cómo tratarlo.


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Introduction

In December 2019, several patients with respiratory symptoms and pneumonia were notified in Wuhan (China). The causative agent was a novel coronavirus (2019-nCoV) which taxonomic designation changed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on February 11, 2020. A few hours later, the disease was named coronavirus disease 2019 (COVID-19). With its ulterior increase in the number of cases and its spread throughout the globe, it was declared a pandemic by the World Health Organization on March 11, 20201.

Even though SARS-CoV-2 has been observed to mainly affect the respiratory system, some neurological disorders have been reported, such as febrile seizures, headache, dizziness, myalgia, ataxia, smell and taste disorders, encephalopathy, encephalitis, strokes, disorders of consciousness, and peripheral neuropathies. In this last category, there have been some reports of patients with Guillain-Barré syndrome (GBS)2-4.

COVID-19 is a disease for which practitioners and researchers are still learning signs/symptoms, risk factors, comorbidities, and outcomes. Although COVID-19 research is vertiginously evolving, novel findings require in-depth scrutiny before they allow us to formulate new hypotheses and draw solid conclusions. This is the circumstance of the association between COVID-19 and GBS, for which are few case reports5.

While it is true that there are not many publications on the said relationship, the unceasing increase of such numbers is a fact. This justifies the extraordinary importance of compiling, analyzing, and synthesizing all the nascent information on the topic, geared toward boosting the current diagnostic, therapeutic, and prophylactic capacities of the biomedical personnel that fights against the challenges of COVID-19 around the world. In the spirit of contributing to the achievement of such a laudable purpose, the objective of this article is to describe the association between COVID-19 and GBS.

A literature review was conducted using Google Scholar as a search engine (no time limit), with the following descriptors (and their equivalents in Spanish): COVID-19, SARS-CoV-2, GBS, and neurological complications/manifestations. The last information search was carried out on June 19, 2020. Articles from journals indexed in PubMed, ScienceDirect, Wiley & Sons, ISI Web of Science, and Scopus were consulted. Articles that had not been peer-reviewed, duplicated articles, or those that could be biased due to the methodology followed in their elaboration were excluded from the study. Twenty-three publications with the required scientific quality were finally selected, including literature reviews, case reports, systematic reviews, letters to the editors, editorials, and clinical series. Their content was carefully analyzed and synthesized.

SARS-CoV-2: neuroinvasive, neurotropic and neurovirulent

Respiratory viruses can penetrate the central nervous system (CNS) (neuroinvasiveness), affect neurons and glial cells (neurotropism), and induce a wide range of neurological disorders (neurovirulence)6.

SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor and invades the cells that express it. This receptor is present in the pneumocytes of the lower respiratory tract (main target), pulmonary parenchyma, vascular endotheliocytes, kidneys, smooth muscle, heart, testicular tissue, bowels, bone marrow, spleen, skin, adipocytes, and the CNS. Some cells, like hepatocytes, can be infected even if such receptor is absent. In the CNS, it is predominantly expressed in the cerebellum, thalamic nuclei, inferior olivary nuclei, nuclei of the solitary tract, and the ventrolateral medulla oblongata1,6-8.

Residue 394 (glutamine) in the SARS-CoV-2 receptor-binding domain is recognized by residue 31 (lysine) on the ACE2 receptor. This produces a conformational change in the spike protein of the virus that facilitates the fusion between the SARS-CoV-2 envelope and the membrane of infected cells, with the subsequent entrance of the genomic RNA of the virus to the intracellular compartment6.

The neurophysiopathogenic mechanisms of SARS-CoV-2 (Fig. 1) that have been cited in the literature are:

- Direct damage after neuroinvasion. SARS-CoV-2 can enter the CNS through a blood pathway (with the production of some cytokines that increase the permeability of the blood–brain barrier [BBB]), or a neuronal pathway; most evidence revolves around the second one. SARS-CoV-2 can infect nerve endings and achieve retrograde or anterograde neuronal transport mediated by motor proteins (dynein and kinesins). Through the olfactory bulb (it is suggested that this particular pathway is related to the hyposmia/anosmia described in certain patients with COVID-19), the virus can reach the brain within 7 days, where it causes an inflammatory reaction (with reactive astrogliosis and microglial activation) and
demyelination. The invasion may occur through peripheral nerves as well.\(^2,^3\)

- Hypoxic damage. When the virus proliferates in lung tissue cells, it causes diffuse alveolar and interstitial inflammatory exudation, as well as edema. These, in turn, lead to alveolar gas exchange disorders causing hypoxia in the CNS, which increases anaerobic metabolism in the mitochondria of brain cells. Accumulation of metabolic acids can cause cerebral vasodilatation, swelling of brain cells, interstitial edema, obstruction of cerebral blood flow, and even headache due to ischemia and congestion. If the hypoxia continues unabated, cerebral edema and the cerebral circulation disorder may worsen sharply. With intracranial hypertension, brain function gradually deteriorates; and drowsiness, bulbar conjunctival edema, and even coma can be observed. In addition, for patients at particular risk of developing cerebrovascular diseases, hypoxia may also induce the occurrence of acute cerebrovascular diseases such as acute ischemic stroke.\(^2,^3,^12\)

- Damage from a combination of neuroinflammation and hypoxia. The systemic inflammation associated with SARS-CoV-2 infection endangers the BBB integrity, which severely disturbs brain homeostasis and causes the death of neuronal cells. Subsequently, infection of the brain stem may affect chemo sensory neural cells associated with cardiorespiratory regulation, as well as neurons of the respiratory center. This damages the ventilatory lung function and exacerbates respiratory failure leading to profound hypoxia. A combination of hypoxia with existing neuroinflammation causes damage to the hippocampal and cortical areas resulting in the neuropsychiatric effects of the virus.\(^10\)

- Immunological damage. The pathology of severe viral infections is closely linked to the development of systemic inflammatory response syndrome (SIRS). This syndrome could be abnormally initiated in severe pneumonia caused by SARS-CoV-2 infection. Therefore, COVID-19 has resulted in a large number of fatalities, most of which have been due to multiple organ dysfunction syndrome caused by virus-induced SIRS or SIRS-like immune disorders. The ability of this virus to infect macrophages, microglia, and astrocytes in the CNS has great importance since it allows SARS-CoV-2 to activate neuroglia and induce a pro-inflammatory state. SARS-CoV-2 infection of the CNS activates TCD4+ cells of the immune system. These, in turn, induce macrophages to secrete interleukin (IL) 6 by

![Figure 1. Pathogenesis of nervous system injury caused by coronaviruses. ACE2: angiotensin-converting enzyme 2; BBB: blood–brain barrier; IL: interleukin; MHC: major histocompatibility complex; SIRS: systemic inflammatory response syndrome.](adapted from Wu et al. 2020).
producing granulocyte-macrophage colony-stimulating factor. IL-6, a predominant component of cytokine storm syndrome in patients with COVID-19, has been positively correlated with increased severity of the disease. Furthermore, in vitro studies have shown that glial cells produce pro-inflammatory cytokines (IL-6, IL-12, IL-15, and tumor necrosis factor α) after being infected by a coronavirus, which suggests a similar in vivo behavior. Activation of immune cells of the brain causes chronic inflammation and cerebral damage\(^2,9,11,13\).

- ACE2 inhibition damage. ACE2 is a cardio-cerebral vascular protection factor that exists in a variety of organs, including the nervous system and skeletal muscles, playing a major role in regulating blood pressure and mechanisms of antiatherosclerosis. Since SARS-CoV-2 has high binding affinity to the ACE2 receptors, after binding to them it inhibits the enzyme and increases angiotensin II levels, which causes abnormally elevated blood pressure and increases the risk of a cerebral hemorrhage. In addition, given that the SARS-CoV-2 spike protein can interact with ACE2 expressed in the capillary endothelium, the virus may also damage the BBB and enter the CNS by attacking the vascular system. It has also been proposed that nicotine stimulation of the nicotinic acetylcholine receptors can increase ACE2 expression in neural cells, placing smokers at a higher risk for neurological complications by SARS-CoV-2 infection\(^2,9,11,13\).

- Other mechanisms. Biological properties of the CNS may facilitate exacerbation of the neurological damage caused by SARS-CoV-2 infection. The CNS has a dense parenchymal structure, and the usual lack of permeability of its blood vessels is a barrier to viral invasion. However, if a virus gains access to the CNS, it is difficult to remove. Due to the lack of major histocompatibility complex antigens in nerve cells, the elimination of viruses in those cells depends solely on the role of cytotoxic T cells; however, apoptosis of mature neurons after being infected also has a relatively protective effect. Furthermore, homeostatic features of cells in the CNS contribute to the continued existence of the virus\(^6\).

Hypotheses of neuroinvasiveness and neuroviro- lence of SARS-CoV-2, supported by the principles of causality enunciated by Bradford Hill in 1965\(^14\), are based on the following evidence: biological plausibility extrapolated from affection of the CNS by other respiratory viruses, evidence of neurological damage produced by coronaviruses in other species, animal models of the CNS infection by human coronaviruses, the existence of neurological manifestations originated by other coronaviruses, and patients with COVID-19 that have experienced neurological complications\(^6\).

**COVID-19 and GBS**

GBS is caused by an abnormal autoimmune response against antigens (due to a preceding infection) that damage the gangliosides of peripheral nerves. It can deteriorate hastily, thus requiring high clinical suspicion, early identification, and appropriate management. In the past, also in the context of a viral disease outbreak, it has been pinpointed that Zika virus may be a risk factor for GBS. It is highly unknown if COVID-19 patients are also at high risk of GBS. However, the extensive evidence between Zika virus and GBS makes it relevant to study and decipher if COVID-19 is also associated with this peripheral neuropathy. SARS-CoV and Middle East respiratory syndrome coronavirus have both been associated with GBS as well\(^3,5\).

Zhao et al. reported GBS associated with COVID-19 in a 61-year-old woman, who presented acute weakness in both legs, and severe fatigue, progressing within a day. Neurological examination disclosed symmetric weakness Grade 4/5 (Medical Research Council [MRC] scale), and areflexia in both legs and feet. Three days after admission, muscle strength was Grade 4/5 in both arms and hands, and 3/5 in both legs and feet. Sensation to light touch and pinprick was decreased distally. Nerve conduction studies (day 5) showed delayed distal latencies and absent F waves in early course, supporting demyelinating neuropathy. On day 8, the patient developed a dry cough and a fever. Considering the temporal association, Zhao and collaborators speculate that SARS-CoV-2 infection might have been responsible for the development of GBS in this patient. Since the onset of GBS symptoms overlapped with the period of SARS-CoV-2 infection, they suggest that this peripheral neuropathy might have followed the pattern of a parainfectious profile, instead of the classic postinfectious one. This case is limited by the absence of microbiological testing on admission; therefore, it is prudent to consider the alternative explanation that the patient coincidentally developed GBS of unknown cause and acquired SARS-CoV-2 infection in a nosocomial manner (Table 1)\(^15\).

Virani et al. reported a 54-year-old male patient, with complaints of numbness and lower-limb weakness of 2-day duration. The patient reported having a fever and a non-productive cough of 10-day duration that did not improve with a short course of oral amoxicillin
Table 1. Relevant data extracted from the case reports

<table>
<thead>
<tr>
<th>First author/Country</th>
<th>COVID-19 diagnosis</th>
<th>COVID-19 symptoms onset</th>
<th>Sex and age</th>
<th>GBS</th>
<th>Treatment</th>
<th>Outcome</th>
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<td>GBS</td>
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<td>F, 61</td>
<td>GBS</td>
<td>IVIg</td>
<td>All symptoms resolved over a 30-day course</td>
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<td>GBS</td>
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<td>M, 54</td>
<td>GBS</td>
<td>Mechanical ventilation (4 days) 0.4 g/kg/day IVIg (5 days)</td>
<td>Fever, weakness and areflexia. No respiratory failure. Dry cough and fever (38.2°C)</td>
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**Clinical features**

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**Blood and CSF analyses**

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<td>M, 65</td>
<td>GBS</td>
<td>0.4 g/kg/day IVIg (5 days)</td>
<td>Fever (39°C), cough, diarrhea, dyspnea, weakness and areflexia in all limbs</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>COVID-19</td>
<td>Respiratory symptoms and upper-limb weakness resolved but lower-limb weakness persisted</td>
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<td>Azithromycin</td>
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<td></td>
<td></td>
<td>HCQ</td>
<td>Poor outcomes, including persistence of severe upper-limb weakness, dysphagia, and lower-limb paralysis</td>
</tr>
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<td></td>
<td></td>
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<td>LPV/RTV</td>
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</tr>
<tr>
<td>Toscano/Italy</td>
<td></td>
<td></td>
<td>F, 77</td>
<td>GBS</td>
<td>400 mg/kg IVig (2 cycles) 400 mg/kg IVig (5 days)</td>
<td>Fever, pharyngitis. Facial diplegia and generalized areflexia evolving to lower-limb paresthesia with ataxia</td>
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<td>COVID-19</td>
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<td></td>
<td>None</td>
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<tr>
<td>Toscano/Italy</td>
<td></td>
<td></td>
<td>M, 23</td>
<td>GBS</td>
<td>400 mg/kg IVig</td>
<td>Fever, pharyngitis. Facial diplegia and generalized areflexia evolving to lower-limb paresthesia with ataxia</td>
</tr>
</tbody>
</table>

**Blood and CSF analyses**

<table>
<thead>
<tr>
<th>First author/Country</th>
<th>COVID-19 diagnosis</th>
<th>COVID-19 symptoms onset</th>
<th>Sex and age</th>
<th>GBS</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhao/China</td>
<td></td>
<td></td>
<td>F, 61</td>
<td>GBS</td>
<td>IVIg</td>
<td>All symptoms resolved over a 30-day course</td>
</tr>
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<td>COVID-19</td>
<td>Respiratory symptoms and upper-limb weakness resolved but lower-limb weakness persisted</td>
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<td>None</td>
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<tr>
<td>Virani/United States of America</td>
<td></td>
<td></td>
<td>M, 54</td>
<td>GBS</td>
<td>Mechanical ventilation (4 days) 0.4 g/kg/day IVIg (5 days)</td>
<td>Fever, weakness and areflexia. No respiratory failure. Dry cough and fever (38.2°C)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>HCQ</td>
<td>COVID-19</td>
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<td>Azithromycin</td>
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<tr>
<td>Sedaghat/Iran</td>
<td></td>
<td></td>
<td>M, 65</td>
<td>GBS</td>
<td>0.4 g/kg/day IVIg (5 days)</td>
<td>Fever (39°C), cough, diarrhea, dyspnea, weakness and areflexia in all limbs</td>
</tr>
<tr>
<td></td>
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<tr>
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<td>GBS</td>
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<td>LPV/RTV</td>
<td>COVID-19</td>
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<td></td>
</tr>
<tr>
<td>Toscano/Italy</td>
<td></td>
<td></td>
<td>M, 23</td>
<td>GBS</td>
<td>400 mg/kg IVig</td>
<td>Fever, pharyngitis. Facial diplegia and generalized areflexia evolving to lower-limb paresthesia with ataxia</td>
</tr>
</tbody>
</table>
### Table 1. Relevant data extracted from the case reports (Continued)

<table>
<thead>
<tr>
<th>First author/Country</th>
<th>Sex and age</th>
<th>COVID-19 symptoms onset</th>
<th>COVID-19 diagnosis</th>
<th>Blood and CSF analyses</th>
<th>Clinical features</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toscano/Italy (Patient 3)</td>
<td>M, 55</td>
<td>10 days before GBS onset</td>
<td>− RT-PCR (nasopharyngeal) − Chest CT (bilateral, GGOs compatible with interstitial pneumonia)</td>
<td><strong>Blood</strong> Lymphocytopenia (value not reported) <strong>CSF</strong> − PL: 193 mg/dL − RT-PCR: negative for SARS-CoV-2</td>
<td>Fever, cough. Flaccid tetraparesis and facial weakness evolving to areflexia. Respiratory failure</td>
<td>GBS − 400 mg/kg IVIg (2 cycles) − Mechanical ventilation COVID-19 Azithromycin</td>
<td>Poor outcomes, including ICU admission owing to neuromuscular respiratory failure and flaccid tetraplegia</td>
</tr>
<tr>
<td>Toscano/Italy (Patient 4)</td>
<td>M, 76</td>
<td>5 days before GBS onset</td>
<td>− RT-PCR (nasopharyngeal) − Normal thorax imaging</td>
<td><strong>Blood</strong> Lymphocytopenia (value not reported) <strong>CSF</strong> − Normal results − RT-PCR: negative for SARS-CoV-2</td>
<td>Cough, hyposmia. Flaccid areflexic tetraparesis and ataxia</td>
<td>GBS 400 mg/kg IVIg COVID-19 None</td>
<td>Mild improvement but unable to stand a month after onset</td>
</tr>
<tr>
<td>Toscano/Italy (Patient 5)</td>
<td>M, 61</td>
<td>7 days before GBS onset</td>
<td>− RT-PCR (negative in nasopharyngeal swabs and BAL) − Serology: positive SARS-CoV-2 IgG − Chest CT (interstitial pneumonia, no parenchymal opacities)</td>
<td><strong>Blood</strong> WCC: 10.4 × 10⁹/mm³ (LC: 13.4%) <strong>CSF</strong> − PL: 40 mg/dL − WCC: 3/mm³ − RT-PCR: negative for SARS-CoV-2</td>
<td>Cough, anosmia, ageusia. Facial weakness, flaccid areflexic paraplegia. Respiratory failure</td>
<td>GBS − 400 mg/kg IVIg − Plasmapheresis − Mechanical ventilation COVID-19 None</td>
<td>Flaccid tetraplegia, dysphagia (enteral nutrition), mechanical invasive ventilation. He had bacterial pneumonia during IVIg treatment, which delayed plasma exchange</td>
</tr>
<tr>
<td>Guitiérrez-Ortiz/Spain</td>
<td>M, 50</td>
<td>5 days before GBS onset (Miller-Fisher syndrome)</td>
<td>− rRT-PCR (oropharyngeal) − Normal chest X-ray</td>
<td><strong>Blood</strong> − LC: 1000/mm³ − Positive for the antibody GQ1b-IgG in the serum <strong>CSF</strong> − PL: 80 mg/dL − RT-PCR: negative for SARS-CoV-2</td>
<td>Cough, malaise, headache, fever. Anosmia, ageusia, right internuclear ophthalmoparesis, right oculomotor palsy, ataxia, areflexia</td>
<td>GBS 0.4 g/kg IVIg COVID-19 (5 days) COVID-19 None</td>
<td>Cranial neuropathies and ataxia improved significantly until solution of all neurological complications. Residual anosmia and ageusia</td>
</tr>
<tr>
<td>Guitiérrez-Ortiz/Spain</td>
<td>M, 39</td>
<td>3 days before GBS onset</td>
<td>− rRT-PCR (oropharyngeal) − Normal chest X-ray</td>
<td><strong>Blood</strong> WCC: 3.1 × 10⁹/mm³ <strong>CSF</strong> − PL: 62 mg/dL − WCC: 2/mm³ − rRT-PCR: negative for SARS-CoV-2</td>
<td>Diarrhea, fever. No dyspnea or respiratory symptoms. Ageusia, bilateral abducens palsy, areflexia</td>
<td>GBS and COVID-19 Telemedicine monitoring (due to a complete hospital saturation) COVID-19 Acetaminophen</td>
<td>Complete neurological recovery</td>
</tr>
</tbody>
</table>

*(Continues)*
<table>
<thead>
<tr>
<th>First author/ Country</th>
<th>Sex and age</th>
<th>COVID-19 symptoms onset</th>
<th>COVID-19 diagnosis</th>
<th>Blood and CSF analyses</th>
<th>Clinical features</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Padroni</td>
<td>F, 70</td>
<td>24 days before GBS onset</td>
<td>RT-PCR (nasopharyngeal) - Chest CT (small GGOs in both lungs)</td>
<td>Blood - WCC: 10.41 × 10^9/L (N: 8.15 × 10^9/L) CSF - PL: 48 mg/dL - WCC: 1 × 10^9/L - RT-PCR: negative for SARS-CoV-2</td>
<td>Fever, cough. Weakness and areflexia in all limbs. Respiratory failure</td>
<td>It was not reported</td>
<td>Day 8: patient remained at ICU with mechanical invasive ventilation</td>
</tr>
<tr>
<td>Camdessanche</td>
<td>M, 64</td>
<td>11 days before GBS onset</td>
<td>RT-PCR (oropharyngeal) - Chest CT (GGOs)</td>
<td>Blood - It was not reported CSF - PL: 166 mg/dL - RT-PCR: negative for SARS-CoV-2</td>
<td>Fever, cough. Flaccid severe tetraparesis. Respiratory failure</td>
<td>GBS - 400 mg/kg IVIg (5 days) - Mechanical ventilation COVID-19 - Acetaminophen - Low molecular weight heparin - LPV/RTV (400/100 mg twice a day for 10 days)</td>
<td>It was not reported</td>
</tr>
<tr>
<td>Alberti</td>
<td>M, 71</td>
<td>7 days before GBS onset, without resolution when GBS started</td>
<td>RT-PCR (nasopharyngeal) - Chest CT (bilateral GGOs and consolidations)</td>
<td>Blood - It was not reported CSF - PL: 54 mg/dL - WCC: 9/mm^3 - RT-PCR: negative for SARS-CoV-2</td>
<td>Fever. Flaccid tetraparesis. Respiratory failure complicated by COVID-19 pneumonia</td>
<td>GBS - 400 mg/kg IVIg (5 days) COVID-19 - HCQ - LPV/RTV</td>
<td>Severe respiratory failure developed during the first 24 h, leading the patient to his death</td>
</tr>
<tr>
<td>Scheidl</td>
<td>F, 54</td>
<td>3 weeks before GBS onset</td>
<td>RT-PCR (oropharyngeal) - Normal chest X-ray</td>
<td>Blood Normal results (values not reported) CSF - PL: 140 g/L - RT-PCR: negative for SARS-CoV-2</td>
<td>No respiratory symptoms or fever. Ageusia, anosmia. Manifestations of a demyelinating inflammatory polyneuropathy. Dysphagia</td>
<td>GBS 400 mg/kg IVIg (5 days) COVID-19 None</td>
<td>Almost complete recovery after IVIg treatment</td>
</tr>
</tbody>
</table>

and steroids. He subsequently developed diarrhea due to *Clostridium difficile* colitis that had been diagnosed 2 days before (symptoms improved after starting on treatment). While still undergoing initial workup, the patient reported urinary retention, prompting magnetic resonance imaging (MRI) of the thoracic, and lumbar spine ( incidental findings of bilateral basilar opacities in the lungs were only revealed). He was evaluated by the neurology team and noted to have 2/5 strength in his lower limbs, with 3/5 in his upper limbs, according to the MRC scale. Deep tendon reflexes (DTRs) were absent. A diagnosis of GBS was made (Table 1)\(^8\).

Sedaghat et al. reported a 65-year-old male patient who was admitted with symptoms of acute progressive symmetric ascending quadruparesis. Neurological manifestations of the patient began with acute progressive weakness of distal lower limbs, 5 days before admission. At that time, symptoms progressed from distal to proximal limbs, until the onset of quadruplegia a day before admission. There was bilateral facial paresis as well. Two weeks before hospitalization, the patient had had a cough, a fever, and sometimes suffered from dyspnea. The patient was a well-known case of type 2 diabetes mellitus, treated with metformin medication. Muscle strength examination showed weakness in the four limbs with an MRC scale of 2/5 in proximal and 3/5 in distal upper limbs; and 1/5 in proximal and 2/5 in distal lower limbs. DTRs were absent. There was a reduction in the vibration and fine touch sensation distally to the ankle joints, and also bifacial nerve palsy ( House-Brackmann Grade 3). On day 9, the neurophysiological study delayed acute motor-sensory axonal neuropathy (Table 1)\(^16\).

From February 28 to March 21, 2020, in three hospitals in Northern Italy, five patients who had GBS after the onset of COVID-19 were examined. Toscano et al. reported that the first symptoms of GBS were lower-limb weakness and paresthesia in four patients, and facial diplegia, followed by ataxia and paresthesia in one patient. Generalized, flaccid tetraparesis or tetraplegia evolved over a period of 36 h to 4 days in four patients; three patients received mechanical ventilation. The results of electrophysiological studies showed that compound muscle action potential amplitudes were low but could be obtained; two patients had prolonged motor distal latencies. On electromyography, fibrillation potentials were present in three patients initially. In another patient, they were absent initially but later present at 12 days. The findings were generally consistent with an axonal variant of GBS in three patients, and with a demyelinating process in two patients. MRIs, performed with administration of gadolinium, showed enhancement of caudal nerve roots in two patients, enhancement of the facial nerve in one patient, and no signal changes in nerves in two patients. This observational series could not determine whether severe deficits and axonal involvement are typical features of COVID-19-associated GBS (Table 1)\(^8,19\).

Gutiérrez-Ortiz and collaborators reported two male patients, who were 50 and 39 years old, respectively. The first one was admitted because of a 2-day history of vertical diplopia, perioral paraesthesia, and gait instability. His medical history was remarkable for bronchial asthma. Five days prior, he had developed a cough, malaise, a headache, low-back pain, and a fever. Neurological examination revealed: absent DTRs in upper and lower limbs, right internuclear ophthalmoplegia, and right fasical oculomotor palsy. These findings were consistent with Miller-Fisher syndrome (a variant of GBS). The youngest patient, on the other hand, presented acute-onset diplopia. Three days before, he had presented diarrhea, a low-grade fever, and a generally poor condition, without any headache, respiratory symptoms, or dyspnea. He did not report nausea or vomiting but noted the presence of ageusia. He was diagnosed with polynéuritis cranialis (another variant of GBS). Neurological examination showed generalized absence of DTRs, as well as bilateral abducens palsy (Table 1)\(^20\).

Padroni et al. reported a 70-year-old woman who complained of asthenia, hands, and feet paresthesia, and gait difficulties progressing within a day. Twenty-four days prior, she had developed a fever and a dry cough. Neurological examination disclosed moderate (MRC scale: 4/5) symmetric distal upper and lower-limb weakness, loss of DTRs, and preserved light touch and pinprick sensation. Neurophysiologic findings were consistent with a diagnosis of GBS (Table 1)\(^21\).

Camdessanche et al. described the case of a 64-year-old French man who was admitted after he fell and hurt his left shoulder leading to a tear of the rotator cuff. He had a fever and a cough for 2 days. Eleven days after, the patient complained of paresthesia in feet and hands. In 3 days, he showed flaccid severe tetraparesis. MRC strength evaluation was 2/5 in legs, 2/5 in arms, 3/5 in forearms, and 4/5 in hands. DTRs were abolished in the four limbs. Five days after neurological symptom onset, electrodiagnostic tests disclosed a demyelinating pattern in accordance with GBS (Table 1)\(^22\).
Alberti et al. reported a 71-year-old male patient with subacute onset of paresthesia at limb extremities, followed by distal weakness rapidly evolving to severe, flaccid tetraparesis over the previous 3 days. He had had a low-grade fever for few days the week prior. Relevant conditions in his medical history included hypertension, abdominal aortic aneurysm treated with endovascular repair in 2017, and lung cancer exclusively treated with surgery. Neurological examination showed: symmetric limb weakness (MRC scale: 3/5 in upper limbs and 2/5 in lower limbs), symmetric and extensive stocking-glove hypoesthesia in the four limbs (more pronounced in lower limbs), and absent DTRs. The patient complained of severe paresthesia in both hands and feet. Moderate dyspnea and moderate low-back pain were present at the time of the first evaluation. He showed hemodynamic disturbances with severe drug-resistant hypertension. Electrodiagnostic tests disclosed a severe form of acute polyradiculoneuritis with prominent demyelinating features (Table 1).

In Germany, Scheidl et al. reported a 54-year-old woman with typical clinical and electrophysiological manifestations of acute demyelinating inflammatory polyneuropathy (the most common type of GBS in Europe). She did not experience a preceding fever or respiratory symptoms, but a transient loss of smell and taste was present. At the moment of admission, a progressive proximally-pronounced paraparesis, areflexia, and sensory loss with tingling in all limbs were found, which had begun 10 days before. The modified Erasmus GBS outcome score was 3/9 at admission and 1/12 on day 7 of hospitalization. The electrophysiological assessment proved a segmental demyelinating polyneuropathy (Table 1).

Conclusions

GBS is emerging as a relevant neurological complication in COVID-19 patients, though their association is still to be proven by more in-depth studies. While the current evidence is not enough to confirm a causal relationship between COVID-19 and GBS, it does justify the verisimilitude of such association, which does not seem to be a fortuitous one. Future studies on the physiopathology and clinical/electrophysiological features of the COVID-19-associated GBS will provide biomedical personnel with a more complete understanding of the performance of GBS in patients with COVID-19 as well as information regarding how to successfully treat it.

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Conflicts of interest

This research has not received any specific grant from public, commercial, or nonprofit agencies.

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