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New era of the Revista Mexicana de Neurociencia

Antonio Arauz¹ and Luis Dávila-Maldonado²
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The Revista Mexicana de Neurociencia emerged as an informative bulletin of the Mexican Academy of Neurology. In 1999, its first issue appeared as Revista Mexicana de Neurociencia with Dr. Lilia Núñez-Orozco as Editor-in-Chief and who directed it until Volume 11, Number 1, published in January-February 2010. Key events during this period were the incorporation of the journal by the International Federation of Neurological Journals, the reservation of its title, the ISSN number that made it a formal periodical publication and the inclusion in the EBSCO, IMBIOMED, Lilacs, and Artemisa index.

In 2010, Dr. Carlos Cantú-Brito assumed the editorial leadership of the journal and during that period, the journal was renewed and achieved the CONACYT journal index. In 2017, Dr. Idelfonso Rodríguez Leyva is appointed Editor-in-Chief and during this period, the Mexican Academy of Neurology decides to give our journal a new impetus, incorporating it into the Permanyer publishing house, changing its content to English, incorporating electronic submissions and manuscript processing, all with the purpose of achieving indexation.

Over the past 23 years, Revista Mexicana de Neurociencia growth has been tremendous and is in a position to continue climbing new goals and objectives as the official journal of the Mexican Academy of Neurology. As incoming Editor-in-Chief, I will build on a strong foundation. However, our most important challenge continues to be convincing the community dedicated to neurological sciences of the importance of contributing to the journal, mainly with original research. Convince them of the need and advantages of having a strengthened journal, with the best quality standards and indexed. What cannot be achieved without the support of all members of the Mexican Academy of Neurology and the neuroscience research community.

In the next years, Revista Mexicana de Neurociencia must be influential and must attract the articles that address basic and clinical research that advances our understanding of neurological diseases. The new editorial board will work to simplify the submission of manuscripts, expedite the editorial decision-making process, and continue improving all editorial processes that will not only help us make editorial decisions but also help authors improve their manuscripts. We have changed the editorial body, modifying the editorial structure and including pediatric neurologists, neurologist, neurosurgeons, basic neuroscience researchers, neuropsychiatrists, endovascular therapy, and colleagues with biostatistical training. The number of editors increased and the editorial masthead now includes 14 editors in various capacities. Incoming coeditors include Fernando Barinagarrementeria and Sergio Iván Valdes, and eleven Associate Editors will serve in important advisory roles: Minerva López and Elma Paredes as Associate Editors in Neurology; Pablo León and Ramiro Ruiz-Garcia as Associate editors of Neuropsychiatry; Edgar Nathal as Associate Editor of Neurosurgery; Francisco Pellicer as Associate Editor of Basic Neuroscience; Fabiola Serrano-Arias and Juan Manuel Márquez-Romero as Associate editor of Endovascular therapy; Melissa Chávez-Castillo as Associate Editor of...
Neuropediatrics; and Miguel Barboza and Miguel García-Grimshaw as Associate Editors of Biostatistics. We are all planning the new sections that will be incorporated into the journal.

*Revista Mexicana de Neurociencia* must also play a role educating the next generations, so we are working on resident and fellow section that will include the participation of residents in the editorial process.

We have also invited recognized authors to contribute with reviews and original articles of specific topics. This number of the *Revista Mexicana de Neurociencia* includes an update of stroke and atrial fibrillation by Nicole Beaton Sur and José Romano of the University of Miami and a review of Neurological complications of interatrial blocks and Bayes’ Syndrome by Adrian Baranchuck and cols. of the Queen’s University of Canada. Both, atrial fibrillation, interatrial block and Bayes’ syndrome are conditions that increase the incidence of stroke ischemic events, cognitive impairment, and dementia. Therefore, looking for AF in ischemic stroke patients is mandatory, mainly in those older than 60 years. Atrial block and Bayes’ syndrome are easily detectable on an electrocardiogram and could explain several cases classified as embolic stroke of undetermined source. Therefore, it is highly recommended that neurologists return to review electrocardiograms in search of specific alterations of the p wave, especially in patients with suspected cardioembolic cerebral infarction, without AF.

It is a great honor to be the Editor-in-Chief of *Revista Mexicana de Neurociencia*, the leading Mexican Journal of Neuroscience, for the next 5 years. My goal is for the journal to be at the forefront of disseminating neurological research and educational articles, to improve medical care for each of the six people in the world affected by neurological conditions.

It is for all of the above that we believe that *Revista Mexicana de Neurociencia*, supported by our board of directors and with the strengths of this great group of editors, will achieve a new and better stage. We invite you to participate with scientific and academic collaborations. Grounded in experience, we dare to establish the necessary changes for the future of neuroscience. Together, we can continue to grow our journal.
Pitfalls and caveats in the diagnostic pathway of people with Parkinson’s disease

Amin Cervantes-Arriaga1,2, Cynthia Sarabia-Tapia1, Oscar Esquivel-Zapata1, Susana López-Alamillo1, Etienne Reséndiz-Henríquez1, Teresa Corona1, and Mayela Rodríguez-Violante1,2*

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Abstract

Objective: We carried out a cross-sectional study to identify the factors involved in each stage of the diagnosis pathway that may lead to a diagnostic delay in persons with Parkinson’s disease (PD). Materials and Methods: Consecutive patients with PD were included. A questionnaire assessing the recognition of the initial symptoms, pathway to seek attention diagnosis and perception on the diagnostic time and identified barriers was applied. Diagnosis delay was defined as ≥ 12 months between initial recognition of the symptom and the definitive diagnosis of PD. Results: A total of 114 patients (57.9% male) with PD were included in the study. The overall median time of the diagnosis pathway was 14.5 (interquartile range [IQR] 31) months and the longest time in this pathway was between the first medical consultation and the definitive diagnosis of PD, a median of 9 (IQR 14) months. The main appraisal of the first symptom was being “not worried” (48.2%). The mains reasons for seeking medical attention were symptom worsening (42.1%). Patient’s perception on the diagnostic time was reported as very adequate/adequate in 52.7%. Barriers delaying the diagnosis identified included the belief of spontaneous symptoms relief and lack of trust in their doctor. Conclusion: Both the person with PD and the physician play a shared role in the diagnosis of PD. Improving the awareness of the disease, as well as improving medical education on PD, could result in a timely diagnosis.

Keywords: Parkinson's disease. Delayed diagnosis. Diagnosis pathway. Primary health care. Diagnosis.

Resumen

Objetivo. Se llevó a cabo un estudio transversal para identificar los factores involucrados en cada etapa del camino diagnóstico que pueden conducir a un retraso diagnóstico en personas con enfermedad de Parkinson (EP). Material y métodos. Se incluyeron pacientes consecutivos con EP. Se aplicó un cuestionario que evaluó el reconocimiento de los síntomas iniciales, la vía para buscar el diagnóstico de atención y la percepción sobre el tiempo de diagnóstico y las barreras identificadas. El retraso en el diagnóstico se definió como ≥12 meses entre el reconocimiento inicial de los síntomas y el diagnóstico definitivo de EP. Resultados. Se incluyeron a 114 pacientes (57.9% hombres) con EP. El tiempo medio del diagnóstico fue de 14.5 (RIC 31) meses y el tiempo más largo en este proceso fue entre la primera consulta médica y el
Introduction

Parkinson’s disease (PD) is a complex multisystemic neurodegenerative disorder affecting over 6 million people globally. PD is hallmarked by their cardinal motor symptoms, but also non-motor symptoms are part of the disease.

The diagnostic pathway can be divided into three milestones. The first stage is the recognition of the symptoms by the subject. Second, the subject needs to make the decision to seek medical attention. Finally, the primary care physician (PCP) who provides the first contact must suspect and confirm the diagnosis or, if needed, refer the patient to the proper specialist. Research has shown that it takes patients more time to recognize their motor symptoms and to realize they need medical attention, than it takes the general practitioner (GP) to diagnose PD. The median time from motor symptom onset to seeking a PCP has been reported to be around 7-11 months; while the time from the first visit to a final diagnosis varies from 1 to 12 months.

Factors currently known to delay the diagnosis include young onset of motor symptoms, postural instability and gait disorder subtype, and female gender. This diagnostic pathway is full of experiences some of them can be negative leading to loss of trust in the doctor, resulting in a lengthy and uncertain process. Benefits of a timely diagnosis include an early initiation of symptomatic treatment, improved functionality, and better quality of life. Data regarding the patient’s experiences in their diagnostic pathway are scarce. Gaining insight into the possible factors that delay the diagnosis process may lead to developing effective strategies. This study aims to improve our understanding of the factors involved in each of the stages of the diagnostic pathway of persons with PD (PwP).

Methods

A cross-sectional study was carried out. PwP attending the Movement Disorders Clinic at the National Institute of Neurology and Neurosurgery in Mexico City from July to August 2019 were included in the study. Participants considered for this study were diagnosed with PD using the International Parkinson and Movement Disorders Society clinical criteria.

Data collected included demographic variables such as gender, date of birth, current marital status, employment status, and years of education, and whether they had any access to social security. A semi-structured questionnaire containing both open-ended and closed-ended questions was designed to assess time from the first identification of motor symptoms to the time of definitive diagnosis. At present, no specific validated questionnaire for this purpose is available for PD, consequently, a questionnaire was designed based on instruments used on other diseases, mainly cancer. Selection of the time intervals and main correlated factors was based on critically assessment of literature, conceptual framework, and expert opinion.

A pilot testing was carried out to test the content validity (relevance, acceptability, and feasibility). A total of two rounds of pilot testing were performed. This resulted in changes in the order of the items and clarification of wording or phrasing.

The final questionnaire was divided into three parts. The first part considered the recognition of the initial symptom of PD; PwP provided information regarding their first identified symptom. The second part included a series of questions that intended to understand the patient’s pathway to seek attention with a health-care provider. The second part included the time of the first medical consultation, the patient’s main reason for seeking for medical attention, selected factors with potential influence on the symptom experience, and healthcare-seeking behaviors. The time of diagnosis, as well as the year of referral to tertiary center, were also collected. Finally, the last part intended to assess the patient’s perception on the diagnostic time, if it was considered timely, as well the main reasons for a delayed diagnosis and identified barriers.
In addition, the Movement Disorder Society Unified PD rating scale at the first visit was used to define the motor subtype into tremor dominant (TD), postural instability and gait disturbance (PIGD), and indeterminate according to Stebbins et al. PD onset was classified as classic PD (age of onset 41-59), early-onset PD (EOPD) if age of onset was ≤ 40 years, and late-onset PD (LOPD) if age of onset was ≥ 60 years.

The index time was defined for the study purposes as the month and year the PwP recalled noticing the motor symptoms associated with the disease for the first time. The first milestone collected was externalization defined as the process of thoughts or worries into an external form such as writing or speaking to a third party. The second milestone was seeking medical attention. The last milestone was definitive PD diagnosis. Time between the milestones was measured in months in all cases.

Delay in diagnosis for the study purpose was defined as a span of 12 or more months between the initial recognition of the symptoms and the definitive diagnosis of PD or the beginning of PD treatment.

All PwP attending the clinic within the study period were invited to participate. Those who voluntarily agreed to participate were given a full explanation of the study and signed an informed consent form. The study was approved by the local ethics committee.

**Statistical analysis**

Kolmogorov–Smirnov test was used to test normality. Data were described in measures of central tendency (mean or median) and dispersion as standard deviation (SD) or interquartile range (IQR) accordingly to their distribution. Student’s t and analysis of variance (ANOVA) tests were used for the comparison of continuous variables between groups. Mann–Whitney U or Kruskal–Wallis test was used for non-parametric variables analysis. When needed, Bonferroni correction for multiple comparisons was used to adjust the p values. For comparison between categorical variables, Chi-square test was used. Statistical significance was considered as p < 0.05.

**Results**

A total of 66 men (57.9%) and 48 women (42.1%) were included in the study. The mean age was 65.4 ± 12.9 years, and the mean disease duration was 9.5 ± 5.2 years. The mean years of education were 9.7 ± 5.9 years. A total of 76 PwP (66.6%) were married/free union. Fifty-three (46.5%) had access to social security, and only 33 (28.9%) were currently employed. In addition, 24 (21.1%) had a family history of PD.

Regarding PD, a total of 43 PwP (37.7%) were considered classic, 19 (16.7%) EOPD, and 52 (56.6%) LOPD. The most common motor subtype was PIGD (50.9%) followed by TD (36.8%).

Regarding the time elapsed between milestones, the median time from symptom onset to externalization was 1 month with a range of 1-96 months. The median time from the first milestone to seeking medical attention was 2.5 (IQR 10.9) months. The median time from the second milestone to diagnosis was 9 (IQR 14) months. Overall, the median time from noticing the motor symptom onset to the final PD diagnosis was 14.5 (IQR 31) months. Table 1 shows the comparison of the time in months for each milestone according to the main demographic and clinical variables. In summary, age of onset was statistically different across two of the time milestones. PwP with EOPD had a greater time to seek medical attention and time to final diagnosis. For PwP with EOPD, the overall diagnosis pathway (median 48, IQR 57) was longer when compared to the classic onset (median, 15, IQR 32, p = 0.01) and LOPD (median 12, IQR 18, p = 0.01).

The first part of the questionnaire assessing the recognition of the initial symptom showed that tremor was the most frequent motor symptom noticed by the subject (59.6%) followed by bradykinesia and rigidity (27.2%). Moreover, the main appraisal of the first symptom was being “not worried” (48.2%) followed by “worried or stressed” (43.9%).

The second part of the questionnaire assessed the pathway to seek attention with a health-care provider and final diagnosis. The main reasons for seeking medical attention were symptom worsening (42.1%) followed by symptom onset (29.8%) and symptom persistence (26.3%). The first contact physician was a GP in 36.8%, a movement disorders specialist in 18%, and a general neurologist also in 18% of the cases. The specialty of the first contact physician did not had an impact on the time from the first medical consultation to the PD diagnosis (p = 0.16).

Finally, the third part of the questionnaire assessed the PwP perception on the diagnostic time and its timeliness. A total of 54 (47.4%) PwP were timely diagnosed according to the study criteria, while 60 (52.6%) had a delay on diagnosis. The only variables with a statistically significant difference between groups were age and age at onset. PwP timely diagnosed were older than those with a delay.
(68.4 ± 11.1 vs. 62.7 ± 13.9, p = 0.02) and had an older age of onset (59.7 ± 12.4 vs. 52.4 ± 14.7, p = 0.01).

Finally, patient’s perception on the diagnostic time was reported as very adequate/adequate in 52.7%, average in 21.1%, and inadequate/very inadequate in 26.3%. When comparing those PwP with a time from onset to diagnosis < 12 months with those ≥ 12 months, no statistically significant difference was found in the very adequate/adequate perception (61.1% vs. 45%, p = 0.13). Similarly, no statistical difference was found regarding the very inadequate/inadequate perception between groups (22.2% vs. 30%, p = 0.47). Moreover, the percentage of agreement between very adequate/adequate perception and actual time to diagnosis < 12 months was only 50%.

The main reason for a delayed diagnosis given by those PwP who responded average or worst (n = 54) was misdiagnosis in 63%, followed by economical constraints in 11.1%, belief of spontaneous symptoms relief in 7.4%, and lack of interest by the PwP in 7.4%.

On the other hand, the main barriers that might have delayed seeking medical attention identified by the PwP were belief of spontaneous symptoms relief in 28.9%, lack of trust in their doctor in 17.6%, fear of a diagnosis in 11.4%, and limited access to health services in 7.9%. Table 2 compares the main factors assessed in the questionnaire between PwP diagnosed before or after 1 year from symptom onset.

### Discussion

PD is a chronic neurodegenerative disease affecting activities of daily living as well as the health-related quality of life of the persons with the disease. While no cure has been found yet, it has been shown that symptomatic treatment has a benefit in the PwP life, thus supporting the need for an earlier diagnosis. The diagnostic pathway begins in the patient’s end by recognizing the symptoms, acknowledging their relevance, and deciding to seek medical consultation. On the

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**Table 1. Time milestones (months) according to the main demographic and clinical variables of the study sample**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Time to externalize Median (IQR)</th>
<th>Time to seek medical attention Median (IQR)</th>
<th>Time to diagnosis Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n = 66)</td>
<td>1 (0.25)</td>
<td>6 (11.25)</td>
<td>14 (30)</td>
</tr>
<tr>
<td>Female (n = 48)</td>
<td>1 (0)</td>
<td>5 (11)</td>
<td>14.5 (42)</td>
</tr>
<tr>
<td>p†</td>
<td>0.244</td>
<td>0.654</td>
<td>0.856</td>
</tr>
<tr>
<td><strong>Age at onset Median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic (n = 43)</td>
<td>1 (3)</td>
<td>7 (13)</td>
<td>15 (32)</td>
</tr>
<tr>
<td>EOPD (n = 19)</td>
<td>1 (0)</td>
<td>18 (20)</td>
<td>48 (57)</td>
</tr>
<tr>
<td>LOPD (n = 52)</td>
<td>1 (0)</td>
<td>2 (11)</td>
<td>12 (18)</td>
</tr>
<tr>
<td>p†</td>
<td>0.177</td>
<td>0.003</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Family history Median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (n = 82)</td>
<td>1 (0)</td>
<td>6 (11)</td>
<td>12.5 (30)</td>
</tr>
<tr>
<td>Parkinson’s disease (n = 24)</td>
<td>1 (0)</td>
<td>5 (11)</td>
<td>14.5 (50)</td>
</tr>
<tr>
<td>Essential tremor (n = 8)</td>
<td>1 (0)</td>
<td>13 (39.75)</td>
<td>27 (79)</td>
</tr>
<tr>
<td>p†</td>
<td>0.722</td>
<td>0.474</td>
<td>0.235</td>
</tr>
<tr>
<td><strong>Comorbidities Median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 68)</td>
<td>4.6 ± 13.8</td>
<td>13.4 ± 17</td>
<td>30.6 ± 31.5</td>
</tr>
<tr>
<td>Yes (n = 46)</td>
<td>2.8 ± 4.5</td>
<td>12.2 ± 23.8</td>
<td>21.5 ± 30.8</td>
</tr>
<tr>
<td>p†</td>
<td>0.94</td>
<td>0.19</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Motor subtype Median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIGD (n = 58)</td>
<td>1 (0)</td>
<td>6 (18.5)</td>
<td>12 (26)</td>
</tr>
<tr>
<td>Tremor dominant (n = 42)</td>
<td>1 (0.25)</td>
<td>4.5 (11)</td>
<td>16 (31)</td>
</tr>
<tr>
<td>Indeterminate (n = 14)</td>
<td>1 (6.5)</td>
<td>12 (10.25)</td>
<td>30.5 (60)</td>
</tr>
<tr>
<td>p†</td>
<td>0.238</td>
<td>0.692</td>
<td>0.150</td>
</tr>
<tr>
<td><strong>Education (years) Median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 12 (n = 71)</td>
<td>1 (0)</td>
<td>7 (13)</td>
<td>13 (30)</td>
</tr>
<tr>
<td>≥ 12 (n = 43)</td>
<td>1 (0)</td>
<td>4 (11)</td>
<td>18 (42)</td>
</tr>
<tr>
<td>p†</td>
<td>0.301</td>
<td>0.122</td>
<td>0.879</td>
</tr>
</tbody>
</table>

EOPD: early-onset Parkinson’s disease; IQR: interquartile range; LOPD: late-onset Parkinson’s disease; PIGD: postural instability and gait disturbance.

1Mann–Whitney U-test; 2Kruskal–Wallis test.
other hand, the journey to diagnosis ends at the doctor’s side with a definitive diagnosis and the therapeutic shared decision-making. Nevertheless, between these two milestones, there are several, sometimes burdensome, factors that can result in a diagnosis delay. We aimed to identify some of these factors resulting in a timely or delayed diagnosis in PwP.

In our study, the time from symptom onset to the diagnosis of PD had a median of 14.5 months which is within the range reported in the literature which is between 12 and 19 months.

The demographic and clinical determinants of the diagnosis delay reported in the literature include gender, age at onset, and motor subtype. Regarding gender, some authors report a longer time in men compared to women, while other have found no difference. Interestingly, Vlaanderen et al. reported similar finding stating that while no significant differences were found in neurologist consultations, women with PD visited GP more often than men. In our study sample, no difference in the diagnosis pathway between men and women was found. It has also been reported that PwP with PIGD subtype had a longer time to seek medical care. In our study, no difference in the time to seek medical care between motor subtypes was found. Finally, a longer time to diagnosis has been reported in PwP with EOPD ranging from 25 to 60 months. Our study confirmed this finding. This can be partially explained by the still common belief, in both general population and health providers, that PD is a disease only seen in the elderly, thus not considering the possibility, and delaying medical consultation. Another point to consider is that tremor in younger persons has more differential diagnosis, requiring longer diagnosis work-up process.

Regarding the symptom recognition, tremor was the most common symptom identified which might be

<table>
<thead>
<tr>
<th>Variables</th>
<th>Time from onset to diagnosis ≤ 1 year</th>
<th>Time from onset to diagnosis &gt; 1 year</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom at onset</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>31 (57.4)</td>
<td>37 (61.7)</td>
<td>0.64</td>
</tr>
<tr>
<td>Rigidity/bradykinesia</td>
<td>16 (29.6)</td>
<td>15 (25)</td>
<td>0.99</td>
</tr>
<tr>
<td>Gait disorder</td>
<td>3 (5.6)</td>
<td>2 (3.3)</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>Symptom appraisal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not worried</td>
<td>24 (44.4)</td>
<td>31 (51.7)</td>
<td>0.44</td>
</tr>
<tr>
<td>Worried/stressed</td>
<td>27 (50)</td>
<td>23 (38.3)</td>
<td>0.21</td>
</tr>
<tr>
<td>Fear</td>
<td>2 (3.7)</td>
<td>5 (8.3)</td>
<td>0.30</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.9)</td>
<td>1 (1.7)</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>Reason for seeking medical care</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom onset</td>
<td>26 (48.1)</td>
<td>8 (13.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptom persistence</td>
<td>15 (27.8)</td>
<td>15 (25)</td>
<td>0.74</td>
</tr>
<tr>
<td>Symptom worsening</td>
<td>12 (22.2)</td>
<td>36 (60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.9)</td>
<td>1 (1.7)</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>First contact physician</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General practitioner</td>
<td>18 (33.3)</td>
<td>24 (40)</td>
<td>0.46</td>
</tr>
<tr>
<td>Internist/geriatrist</td>
<td>3 (5.6)</td>
<td>4 (6.7)</td>
<td>0.80</td>
</tr>
<tr>
<td>Neurologist</td>
<td>13 (24.1)</td>
<td>13 (21.7)</td>
<td>0.76</td>
</tr>
<tr>
<td>Movement disorder specialist</td>
<td>14 (25.9)</td>
<td>12 (20)</td>
<td>0.45</td>
</tr>
<tr>
<td>Other</td>
<td>6 (11.1)</td>
<td>7 (11.7)</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Previous knowledge of the disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>32 (59.3)</td>
<td>28 (46.7)</td>
<td>0.18</td>
</tr>
<tr>
<td>No</td>
<td>22 (40.7)</td>
<td>32 (53.3)</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Diagnostic time perception</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very inadequate</td>
<td>6 (11)</td>
<td>8 (13.3)</td>
<td>0.71</td>
</tr>
<tr>
<td>Inadequate</td>
<td>6 (11.1)</td>
<td>10 (16.7)</td>
<td>0.39</td>
</tr>
<tr>
<td>Acceptable</td>
<td>9 (16.7)</td>
<td>15 (25)</td>
<td>0.29</td>
</tr>
<tr>
<td>Adequate</td>
<td>20 (37)</td>
<td>17 (28.3)</td>
<td>0.32</td>
</tr>
<tr>
<td>Very adequate</td>
<td>13 (24.1)</td>
<td>10 (16.7)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

†Chi-square test.
expected since it can usually be more easily identifiable by the patient and their family. Interestingly, the most common appraisal was being now worried in almost half of the patients. Providing better health education might lead to improvement in this stage of the diagnosis pathway.

Regarding the reasons for seeking medical attention, symptom worsening rather than its onset or persistence was the most reported by the PwP. Again, rising awareness of the relevance of the onset and persistence of parkinsonism and tremor is needed. Almost 40% of the subjects went to GP, while 36% went to neurologist/movement disorder specialist. The choice of the first contact health provider did not have an impact in the time to diagnosis, although it might have been expected it to be shorter in the specialist group. It might be possible that PwP seen by a GP had the full-blown clinical picture while those attending a specialist had a more atypical presentation, but our study design does not allow to reach that conclusion and further studies on this matter are needed.

Regarding the perception of the time to diagnosis, half of the PwP reported a very adequate/adequate. In contrast, Plouvier et al. reported that only 4.8% of their patients reported being satisfied with their diagnosis pathway. This striking difference is probably the result of different constructs; Plouvier et al. assessed the satisfaction with the whole diagnostic pathway. In contrast, our study assessed the perception of the amount of time from symptom onset to diagnosis. More studies using a standardized measure are needed on this matter. In addition, the percentage of agreement between the study definition of a timely diagnosis and a positive perception by the PwP was only 50% which highlights the difficulty of this construct as Rees et al. have stated.

When the PwP considered the diagnosis not being timely, the main reason was misdiagnosis in over 60%. Unfortunately, the number of doctors or number of diagnosis received before PD was not assessed in our study. Still, misdiagnosis rate as reported by the PwP was remarkably high underscoring the need for better training at the health provider end. Other reasons attributable to the PwP were belief of spontaneous symptoms relief and lack of interest but their frequency was much lower.

Finally, the barriers delaying the diagnosis identified by the PwP also included the belief of spontaneous symptoms relief in a third of the cases, but also lack of trust in their doctor. Patient-doctor relationship and shared decision-making are a critical part of the diagnosis pathway; also, it has been reported that when PwP gets engaged in the process of their disease, correlates to a greater quality of life.

Our study has limitations. First, the lack of a disease specific validated tool for PD; our questionnaire was based and adapted from instruments used in other diseases. Efforts should be taken in developing these tools for PwP exploring more in depth some of the issues highlighted in our study. Second, recall bias cannot be avoided with some variables, such as the time of first motor symptom and the time of PD diagnosis. Some cases were diagnosed at our center but other were diagnosed elsewhere and then referred.

Conclusion

Factors in both the PwP and the doctor side play a role in delaying the diagnosis. Improving awareness of the disease as well as improving medical education are needed. The diagnosis pathway in PD can be improved with combined efforts by the PwP and the health providers that should lead to a shorter time to diagnosis and better quality of life.

Funding

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that 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.
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Cognitive impairment in people with COVID-19 with mild-moderate symptoms in Ecuador

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Abstract

Background: Complications of COVID-19 can include neurological, psychiatric, psychological, and psychosocial sequelae. Little is known about the consequences of COVID-19 on the cognitive functions of patients in the subacute phase of the disease. Objective: The objective of the study was to determine if there is an incidence of cognitive impairment in patients with COVID-19 with mild to moderate symptoms in the remission phase. Method: This is a cross-sectional study conducted between April 2021 and August 2021 at the Eugenio Espejo Hospital in Quito, Ecuador. The Montreal Cognitive Assessment test was applied to COVID-19 patients with mild to moderate symptoms. Results: A total of 50 subjects were recruited; 88% (n = 44) presented cognitive deterioration and only 12% (n = 6) showed a normal score. Conclusions: In our cohort study, patients with COVID-19 with mild-moderate symptoms are at high risk of cognitive impairment.

Keywords: COVID-19. Cognitive impairment. Mild to moderate.

Deterioro cognitivo en personas con COVID-19 con síntomas leves-moderados en Ecuador

Resumen

Antecedentes: Las complicaciones de COVID-19 pueden incluir secuelas neurológicas, psiquiátricas, psicológicas y psicosociales. Se sabe poco sobre las consecuencias del COVID-19 en las funciones cognitivas de los pacientes en la fase subaguda de la enfermedad. Objetivo: Determinar si existe incidencia de deterioro cognitivo en pacientes con COVID-19 con síntomas leves a moderados en la fase de remisión. Método: Se trata de un estudio de tipo transversal realizado entre abril de 2021 y agosto de 2021 en el Hospital Eugenio Espejo de Quito, Ecuador. Se aplicó el MoCA test a los pacientes con COVID-19 con síntomas de leve a moderado. Resultados: Un total de 50 sujetos fueron reclutados, el 88% (n = 44) presentó deterioro cognitivo y apenas el 12% (n = 6) evidenció una puntuación normal. Conclusiones: En nuestro estudio de cohorte los pacientes con COVID-19 con sintomatología leve-moderada tienen un alto riesgo de presentar deterioro cognitivo.


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Introduction

As the coronavirus disease (COVID-19) pandemic continues to be a multidimensional threat to humanity, more evidence has emerged of the neurological involvement associated with it. The neuroinvasive properties of COVID-19 have allowed the hypothesis of several pathogenic mechanisms related to acute and chronic neurological sequelae. Neuroimmune interaction may be important not only in the pathogenesis of neurological manifestations, but also in the implications of systemic hyperinflammation and its consequences at the cognitive level. While COVID-19 primarily affects the respiratory system, other organs, including the brain, may be involved. In Western clinical studies, relatively mild neurological dysfunction, such as anosmia and dysgeusia, is common, while severe neurological disorders such as stroke and meningoencephalitis are less common. It is unclear how much COVID-19 infection contributes to the incidence of central nervous system damage due to comorbidities in the affected population. Clinically defined cases of acute disseminated encephalomyelitis have been rarely verified, cases of Guillain-Barré syndrome and acute necrotizing encephalopathy have been reported in patients with COVID-19. Common neuropathological findings in patients include microglial activation with microglial nodules in a subset, lymphoid inflammation, acute hypoxic-ischemic changes, and astrogliosis; subacute cerebral infarcts, spontaneous hemorrhage and microthrombi, and occasional infarcts of the anterior pituitary have also been noted. Complications of COVID-19 can include neurological, psychiatric, psychological, and psychosocial sequelae. Little is known about the consequences of COVID-19 on the cognitive functions of patients in the subacute phase of the disease. Much remains to be learned about the effects of direct viral infection of brain cells and whether COVID-19 persists in the long term, contributing to chronic symptoms. More research is needed to understand the causal mechanisms of a probable cognitive deterioration associated with this pathology, so our study proposal focuses on investigating the cognitive profile of the hospitalized patient with COVID-19, which would be an important contribution in the understanding of disease and a better understanding of the interaction of COVID-19 with its human host.

Subjects and methods

This was a cross-sectional study, conducted between April 2021 and August 2021 at the Eugenio Espejo Hospital in Quito, Ecuador. This hospital has been one of those designated for the care of patients with COVID-19 by the Ministry of Public Health. The study has the approval of the competent entities and the informed consent of all the participants was obtained before the beginning of the symptoms were invited to participate in the research; all subjects had a positive polymerase chain reaction test for COVID-19 performed at the institution designated by the Ministry of Public Health of Ecuador. After signing the informed consent, the participants were evaluated using the Montreal Cognitive Assessment (MoCA) test. The test was applied by a neuro-psychologist and two resident physicians in psychiatry. The participants were between 18 and 65 years of age. The captured data were entered into an electronic database and descriptive statistics, the statistical analysis contemplated a 95% confidence interval, using Chi-square, for which the SPSS version 23 program was used. In all cases, a p < 0.05 is significant.

Results

A total of 50 subjects were recruited, mostly men. 58% (n = 29), of which 86.21% (n = 25) had cognitive impairment and only four participants had a normal test. As for the female sex, 90.48% (n = 19) showed cognitive deterioration and only 9.52% (n = 2) had a normal performance. The participants who were between 51 and 65 years old are 34% (n = 17), whereas the subjects between 36 and 50 years old were 46% (n = 23) and the remaining 20% (n = 10) between 18 and 35 years old. Of the participants between 51 and 65 years old, 82.35% (n = 14) presented cognitive deterioration in relation to their counterpart without deterioration 17.64% (n = 3), on the other hand, of the group between 36 and 50 years old 95% (n = 22) present cognitive deterioration and only one subject presented the normal test, finally, of the participants between 18
and 35 years old, 80% (n = 8) were impaired and 20%
(n = 2) it is not.

The patients with university education were 50%
(n = 25), of these 88% (n = 23) presented cognitive
deterioration. Those with secondary education were
36% (n = 18), of which 83.33% (n = 15) had some de-
gree of deterioration and only 14% (n = 7) had primary
education, all showing deterioration cognitive.

Of the sample collected, 88% (n = 44) presented
cognitive deterioration and only 12% (n = 6) showed a
normal score. Of the 44 subjects with cognitive impair-
ment, 58.81% n = (25) had a score between 20 and 25
in the MoCA test, 34.09% n = (15) had a score between
10 and 19 in the test and in 9.09% n = (4) a score lower
than 9 was found.

There was no statistically significant relationship after
applying the Chi-square test between cognitive impairment
and sex (p = 0.647), nor was there evidence of a
relationship between age and cognitive impairment
(p = 0.302), in the same way there was no relationship
between education and cognitive impairment (p = 0.515).

Discussion
In this study, it has been possible to verify a preva-
lence of 88% of cognitive impairment in patients treated
at the Eugenio Espejo Hospital in Quito, Ecuador, sim-
ilar incidences can be verified in studies where the
same test has been applied in the population under
similar conditions10. In this sense, it is important to
mention that most of these patients did not report cog-
nitive alterations and therefore these types of problems
go unnoticed.

The sequelae of cognitive disorders are increasingly
seen as a major challenge in the COVID-19 pandemic.
However, most of the evidence of cognitive alterations
after COVID-19 infection and invasion of the virus by
the central nervous system comes from severely affect-
ed individuals in the acute phase of the disease11 in this
study is verified the presence of cognitive impairment
in patients with mild and moderate symptoms.

It is believed that direct viral entry and systemic
mechanisms such as cytokine storm contribute to neu-
roinflammation in patients with COVID-19, the etiology
of cognitive impairment would be multifactorial, among
these factors would be age12. Age seems to be a risk
factor13. However, in this study, there seems to be no
statistically significant relationship associated with age,
which is clinically significant since there is the same
incidence in young and old patients.

The clinical presentation of COVID-19 and its long-term
effects are still a matter of study, the implications on men-
tal health in the short and long term require clarification14,
it is not clear if the cognitive deterioration persists over
time or if there is remission of symptoms. COVID-19 in-
fecion can cause long-term effects on immune processes
within the CNS by causing microglial dysfunction15. Our
study shows that there is cognitive impairment in the re-
mission phase of symptoms. Therefore, it is necessary to
continue investigating relatively recent onset pathology.

Apparently, there are no significant differences in the
incidence of cognitive impairment in people with
COVID-19 related to sex16, however studies on the sub-
ject are scarce, in any case our data show that there
is no difference.

As has been noted, there is a similar prevalence of
cognitive impairment in patients with different levels
of education, so it does not seem to be a protective factor.
No scientific literature could be found in this regard, so
data must be taken with caution.

Although it is true that the use of the psychometric
instrument could have increased the number of diag-
nosed patients, we believe that the criteria used allowed
us to select the most clinically significant cases. We
consider as a serious limitation that it was not possible
to increase the sample due to the considerable decrease
in diagnosed cases due to vaccination against COVID-19
in Ecuador and there was no control group either. In any
case, our data support the fact that there is a high inci-
dence of cognitive impairment in patients with COVID-19
with mild to moderate symptoms in the remission phase.

Conclusions
In our cohort study, patients with COVID-19 with mild
to moderate symptoms have a high risk of presenting
cognitive impairment, a better understanding of the
causal processes and evolution over time is required
to develop preventive and therapeutic interventions.

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the Mental Health Unit of the Hospital de Especiali-
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has been received from any other entity.

Conflicts of interest
The authors declare that they have no conflict of
interest.
Ethical disclosures

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

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

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

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Clinical and environmental risks factors associated with Parkinson’s disease in Yucatan

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1Autonomous University of Yucatan, Department of Neurosciences, Centro de Investigaciones Regionales Dr. Hideyo Noguchi; Neurology Service at: 2Hospital Faro del Mayab; 3Hospital Regional del ISSSTE Elvia Carrillo Puerto. Mérida, Yucatan, Mexico

Abstract

Objective: The objective of the study is to identify the risk and protective factors associated with Parkinson's disease (PD) in inhabitants of Yucatan. Methods: Case control study. A questionnaire with the main risk and protective factors for PD described in the literature was applied to cases and controls. Results: The sample consisted of 85 cases and 124 controls. In the univariate logistic regression analyzes, it was found that the following factors were significantly associated with a higher risk of developing PD: family history of PD (OR = 5.28, p = 0.001), personal history of diabetes (OR = 2.35, p = 0.01), the number of head trauma (OR = 1.35, p = 0.02), number of general anesthesia received (OR = 1.27, p = 0.050), exposure to organic solvents (OR = 2.73, p = 0.02) and the years of exposure to organic solvents (OR = 1.05, p = 0.01): Conclusions: The findings of this research indicate that the inhabitants of the state of Yucatan are exposed to the following risk factors: having a relative with PD, personal history of diabetes, number of head traumas, exposure to organic solvents, years of exposure to organic solvents and number of general anesthesia received.

Keywords: Case-control study. Parkinson's disease. Risk and protection factors. Head trauma. General anesthesia.

Factores de riesgo clínicos y ambientales asociados a la enfermedad de Parkinson en Yucatán

Resumen

Objetivo: Identificar los factores de riesgo y de protección asociados con padecer la enfermedad de Parkinson (EP) en habitantes de Yucatán. Métodos: Estudio de casos y controles. Se aplicó un cuestionario con los principales factores de riesgo y protección de EP descritos en la literatura tanto a los casos como a los controles. Resultados: La muestra estuvo constituida por 85 casos y 124 controles. En los análisis de regresión logística univariados se encontró que los siguientes factores se asociaron significativamente a un mayor riesgo de desarrollar la EP: antecedente familiar de EP (RM = 5.28, p = 0.001), antecedentes de diabetes (RM = 2.35, p = 0.01), el número traumatismos craneoencefálicos (RM = 1.35, p = 0.02), número de anestesias generales recibidas (RM = 1.27, p = 0.050), la exposición a solventes orgánicos (RM = 2.73, p = 0.02) y los años de exposición a solventes orgánicos (RM = 1.05, p = 0.01): Conclusiones: Los hallazgos de esta investigación indican que los habitantes del estado de Yucatán están expuestos a los siguientes factores de riesgo: tener un familiar con EP, antecedentes personales de diabetes, el número de traumatismos.
Introduction

It is estimated that there are approximately 6.2 million people with Parkinson's disease (PD) in the world, by the time 2040 there will be 14.2 million people with PD and due to its rapid increase, some authors have considered declaring it a non-infectious pandemic. Two hundred years have passed after the first description of PD by James Parkinson and various hypotheses have been put forward about its cause, but none have been conclusively proven.

PD is currently believed to have a multifactorial origin, being the result of a complex interaction between genetic and environmental factors, some of which confer risk, while others provide protection. Among the clinical risk factors associated with the development of PD, the following have been frequently described: family history of PD and essential tremor, a personal history of diabetes, head trauma, general anesthesia, and other factors. Among the environmental risk factors associated with PD, the following have been described: exposure to organic solvents, pesticides, herbicides, consumption of well water, and others. As protective factors, caffeine consumption, smoking, and sports have been found, among others.

The Mexican population is aging, which allows us to suppose that, in the future, PD could be a public health problem, so it is necessary to have epidemiological data on this disease to anticipate trends and plan care needs. Likewise, each region has its own social, cultural, and environmental characteristics. Yucatan is a region with a high impact of water contamination due to its karst type soil favoring contaminants entry into the phreatic level. There is evidence of contamination of the Yucatan aquifer, the only source of fresh water in the area, by organochlorine pesticides, as well as its bioaccumulation in the blood of women with cancer and breast milk, due to agricultural activities.

This would be the second on risk and protective factors associated with PD in Mexico, which could provide knowledge about the study dynamics of PD in different regions of Mexico, allowing the identification of people who would be at risk of Parkinson.

Objective

The objective of the study is to identify the risk and protective factors associated with Parkinson's disease in inhabitants of the state of Yucatan.

Material and methods

This is an epidemiological, observational, analytical, retrospective, case-control study. The protocol was reviewed and approved by the Ethics Committee of the Research Center "Dr. Hideyo Noguchi" in Mérida. Participants who met the inclusion criteria and who agreed to participate by signing an informed consent were included in the study. The study was conducted from May 2016 to May 2019. This was a non-probability convenience sample. The sample consisted of patients diagnosed with Parkinson's disease by a neurologist. In the original design, it was intended to gather a sample of 100 patients and 100 controls, if the number of cases was less than 100, two controls would be used for each case. However, in the study period, only 85 cases and 124 controls were interviewed. A questionnaire designed to collect data on clinical and environmental variables considered as possible risk or protective factors for Parkinson's disease was applied to the cases and controls. The inclusion criteria were: patients diagnosed with PD by a neurologist; patients who have resided in Yucatan for at least 10 years prior to the date of their PD diagnosis; patients who signed an informed consent letter to participate in the study. The elimination criteria were: patients who did not respond completely and correctly to the questionnaire designed for the study; patients who decided to withdraw voluntarily before completing the questionnaire; patients whose diagnosis was reversed or modified by a neurologist.

The control group was made up of participants matched with the group of cases by sex and age (± 3 years). Their inclusion criteria were: people who do not have PD, people who have resided in Yucatan for at least 10 years before the date of the PD diagnosis of their respective control; people who signed an informed consent letter to participate in the study. The elimination criteria were: people who did not respond completely and correctly to the questionnaire designed...
for the study; people who decided to withdraw voluntarily before completing the questionnaire.

The clinical and environmental variables that were analyzed as possible risk factors associated with PD were: family history of PD, family history of essential tremor, head trauma, number of head trauma, number of times of unconsciousness due to head trauma, having been exposed to general anesthesia and the number of times this occurred, using pesticides, herbicides, and organic solvents, as well as the number of years of exposure to these, and well water consumption. The variables that were analyzed as possible protective factors were: smoking, consumption of caffeinated beverages, and physical activity.

Statistics analysis

The statistical analysis of the risk factors was carried out using the statistical package Statistical Package for the Social Sciences (SPSS). Univariate and multivariate logistic regression analyzes were performed on the variables under study to determine their contribution as possible risk and protection factors for PD. To calculate the strength of the association between each of factors and PD, the odds ratio (OR) was used, with a 95% confidence interval. In all cases, a test was considered significant when it was \( p < 0.05 \).

In the first phase, to estimate the relative risk of each of the variables, a univariate logistic regression analysis was performed individually with each one of them. Finally, with those factors that were significant in the univariate analysis, multiple logistic regression models were made in order to create models with those variables that remained significant and to be able to adjust for those confounding factors that could affect the risk estimation.

Results

The sample consisted of 85 cases and 124 controls. The mean age (± standard deviation) of the cases was 65.6 ± 10.1 years and the age of the controls was 64.3 ± 10.5 years. Fifty-one patients had two controls, 22 patients only one control, matched by age and sex, the remaining 12 patients had no control by age and sex. In the cases, 58 (68.2%) were men and 27 (31.7%) were women, which corresponds to a ratio of 2.1 men for every woman.

Univariate logistic regression

Table 1 shows the results of the univariate logistic regression analysis of clinical and environmental risk factors that in previous studies have been associated with a higher risk of developing PD, and Table 2 shows the results of univariate logistic analyzes of protective factors frequently associated with a lower risk of developing PD. The relative risk estimates revealed that a higher risk of developing PD was significantly associated with family history of PD, personal history of diabetes, the number of head trauma, the number of general anesthesia received, organic solvents exposure and number of years of organic solvents exposure. Due to head trauma may be associated with reverse causality bias, only head trauma occurring 10 or more years before the diagnosis of PD were considered in the analyzes. In the case of controls, only trauma that preceded 10 years to the age of diagnosis of their respective peers with PD were considered. In this study, none of the factors that are considered protective for the development of PD had a significant association (Table 2). Table 3 summarizes the risk factors associated with Parkinson’s disease resulting from the univariate logistic regression analysis.

Multiple logistic regression

In the conditional multiple logistic regression analyzes, a model was created (Table 4) that included the following variables: family history of PD (OR = 5.84) and number of years of solvents exposure (OR = 1.05). Variables that were not significant were not included in the model.

As mentioned in the background, having a history of smoking or consuming coffee has been shown to be associated with a lower risk of developing PD. Although in the present study neither of these two variables were associated with a reduced risk of developing Parkinson’s disease, two multiple logistic regression models were made with the variables that were associated with a higher risk of PD but adjusting for the history of smoking and caffeine consumption (Table 5). Making this adjustment, in both models having a relative with PD and the number of years of exposure to solvents were maintained as risk factors.

Discussion

Various epidemiological studies reinforce the hypothesis that PD is a neurodegenerative disorder of
multifactorial origin, which results from a complex interaction between the genetic characteristics of individuals, the chronic degenerative pathologies they suffer from, various habits, and multiple environmental factors, which can increase or reduce the risk of Parkinson’s disease\textsuperscript{2,3,5}.

### Table 1. Estimation of the association of clinical and environmental factors with the risk of PD resulting from the univariate logistic regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>CI (95%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of PD</td>
<td>5.28</td>
<td>2.00-13.95</td>
<td>0.001</td>
</tr>
<tr>
<td>Family history of essential tremor</td>
<td>0.65</td>
<td>0.24-1.67</td>
<td>0.37</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.35</td>
<td>1.15-4.81</td>
<td>0.01</td>
</tr>
<tr>
<td>Head trauma</td>
<td>1.43</td>
<td>0.82-2.49</td>
<td>0.20</td>
</tr>
<tr>
<td>Number of head trauma</td>
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<td>1.03-1.77</td>
<td>0.02</td>
</tr>
<tr>
<td>Unconsciousness due to head trauma</td>
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<td>0.77-4.55</td>
<td>0.16</td>
</tr>
<tr>
<td>Number of times of unconsciousness due to head trauma</td>
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<td>0.75-3.10</td>
<td>0.23</td>
</tr>
<tr>
<td>Personal history of receiving general anesthesia</td>
<td>1.58</td>
<td>0.90-2.75</td>
<td>0.10</td>
</tr>
<tr>
<td>Number of general anesthesia received</td>
<td>1.27</td>
<td>1.00-1.61</td>
<td>0.050</td>
</tr>
<tr>
<td>Environmental risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solvents exposure</td>
<td>2.73</td>
<td>1.13-6.58</td>
<td>0.02</td>
</tr>
<tr>
<td>Number of years of solvents exposure</td>
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<td>1.00-1.09</td>
<td>0.01</td>
</tr>
<tr>
<td>Pesticides exposure</td>
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<td>0.51-1.80</td>
<td>0.96</td>
</tr>
<tr>
<td>Number of years of pesticides exposure</td>
<td>1.01</td>
<td>0.98-1.03</td>
<td>0.31</td>
</tr>
<tr>
<td>Herbicides exposure</td>
<td>1.68</td>
<td>0.78-3.62</td>
<td>0.18</td>
</tr>
<tr>
<td>Number of years of herbicides exposure</td>
<td>1.03</td>
<td>0.96-1.07</td>
<td>0.19</td>
</tr>
<tr>
<td>Well water consumption</td>
<td>0.65</td>
<td>0.37-1.14</td>
<td>0.13</td>
</tr>
</tbody>
</table>

### Table 3. Summary of risk factors associated with PD resulting from the univariate logistic regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>CI (95%)</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Family history of PD</td>
<td>5.28</td>
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<tr>
<td>Number of head trauma</td>
<td>1.35</td>
<td>1.03-1.77</td>
<td>0.02</td>
</tr>
<tr>
<td>Number of general anesthesia received</td>
<td>1.27</td>
<td>1.00-1.61</td>
<td>0.050</td>
</tr>
<tr>
<td>Solvents exposure</td>
<td>2.73</td>
<td>1.13-6.58</td>
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</tr>
<tr>
<td>Number of years of solvents exposure</td>
<td>1.05</td>
<td>1.00-1.09</td>
<td>0.01</td>
</tr>
</tbody>
</table>

### Table 4. Multiple logistic regression model of the association of risk factors with the presence of PD

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>CI (95%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of PD</td>
<td>5.83</td>
<td>2.18-15.54</td>
<td>0.000</td>
</tr>
<tr>
<td>Number of years of solvents exposure</td>
<td>1.05</td>
<td>1.01-1.10</td>
<td>0.008</td>
</tr>
</tbody>
</table>

### Table 5. Multiple logistic regression model of the factors associated with a higher risk of PD adjusted for tobacco and coffee consumption

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>CI (95%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of PD</td>
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<td>2.15-15.36</td>
<td>0.000</td>
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<tr>
<td>Number of years of solvents exposure</td>
<td>1.05</td>
<td>1.01-1.10</td>
<td>0.008</td>
</tr>
</tbody>
</table>

### Family history of Parkinson’s disease

Having a family history PD was associated with a 5.28 times higher risk of PD, which was approximately 1.6 times higher than the risk reported in other studies in various parts of the world\textsuperscript{5,17,18} but six times lower than the risk of a study conducted in Italy\textsuperscript{5}. A study in Cuba reported an odds ratio of 7.22, being 1.3 times higher than that reported in our study\textsuperscript{19}.

In the multivariate analyzes, having a relative with PD remained a risk factor for developing PD with an OR of 5.83, which is approximately three and seven times...
lower compared to the multivariate analyzes of studies carried out in India (OR: 21.40) and Italy (OR: 41.70) respectively5,9.

In the meta-analysis by Noyce et al., which added 26 case-control studies, reported a significant association between having a first-degree relative with PD and the risk of developing the disease, with a pooled odds ratio of 3.23 (95% CI 2.65-3.93)20, which is approximately half the risk reported in our study.

**Solvents exposure**

Solvents are substances found in fuels, paints, glues, lubricants, degreasers, and cleaning products, all of which have been linked to an increased risk of PD, in part due to anecdotal reports of parkinsonism in people highly exposed to solvents21.

The association between solvents and the development of PD has been studied mostly in epidemiological studies of the case-control type22. Most of the relative risk estimates are reported in a range of 1.0 to 1.8, but in these studies the solvents were treated, as in our study, as a single entity without distinguishing the chemicals10,22-25. In general, the observed associations of PD with solvents have been modest and very similar to those reported in our work, and apparently, there are only reports of univariate analysis.

The only study to date that has evaluated the association between PD and exposure to different types of organic solvents present in chemical products is a case-control study conducted with 99 pairs of twins (49 monozygotic and 50 heterozygotes), where for each pair one had Parkinson's disease and the other did not, finding that the most suggestive solvents as possible etiological agents were trichlorethylene (TCE), perchlorethylene (PERC) and carbon tetrachloride (CCl4)21. A significantly higher risk of PE was associated with trichlorethylene exposure (OR = 6.1, 95% CI: 1.2-33; p=0.034), while perchlorethylene exposure (OR = 10.5, 95% CI 0.97-113, p = 0.053;) and carbon tetrachloride (RM = 2.3, 95% CI 0.9-6.1, p = 0.088) had tendencies to be significant. However, the risk estimates were based on a very small number of exposed subjects22. TCE, PERC, and CCl4 have been used extensively around the world for decades. TCE has been used as a degreasing, cleaning agent, additive in many common household products, including correction fluid for typewriters, adhesives, paints and carpet cleaners, and stain removers21.

For future studies, we suggest identifying frequently used chemicals in our country that contain some of the possible etiological agents associated with the development of PD. We also recommend the use of protection in people exposed to this class of substances.

**Personal history of diabetes mellitus**

In the present study, a 2.35 times higher risk of developing PD was found when the participants had a history of diabetes, which is higher than the study by Schernhammer et al. who found a 1.33 higher risk of PD and is contradictory with the study by Powers et al., who reported that diabetes is a protective factor8,26.

**Traumatic brain injuries**

In the univariate analysis, we found a 1.3 times higher risk of developing PD associated with the number of times they received head trauma (one or more times), which is consistent with two similar studies with multivariate analyzes. In the Goldman's study, it is reported that people who have received one head injury had a 2.8 times greater risk of developing PD. While Gao's study was found a risk similar to the present study, with an odds ratio of 1.40 when the subjects had received a single head trauma and an OR of 2.33 when they had received two or more head trauma27,28. No univariate analysis reports were found.

Postural instability, stiffness, and bradykinesia are diagnostic criteria for PD and, naturally, the presence of these motor symptoms can cause falls in patients, reporting that up to 90% have fallen at least once29. Consequently, studies evaluating head trauma as a risk factor for developing PD will only consider trauma before the onset of motor symptoms of the disease, since failure to do so could incur a reverse causality bias by including in the analysis of head trauma that occurred as a consequence of the early motor disorders of PD5,29-31. In a nested case-control study carried out with 24,412 people with a diagnosis of PD and 243,363 controls, an increase in the risk of falls was found up to 10 years before the diagnosis of PD32, which could cause head trauma. Finally, studies that seek to establish whether head injuries represent a risk factor for the development of PD should eliminate head trauma that occurred 10 years before the diagnosis of the disease.

**General anesthesia**

In the univariate analysis, a 1.2 times higher risk of developing PD was found associated with the number of general anesthesia received (one or more times), which agrees with De Michele's univariate analysis,
which reported an odds ratio of 1.05, while Zorzon in their multivariate analysis reported a odds ratio of 2.25,33. 

General anesthesia has been suggested as a risk factor associated with Parkinson’s disease in some case-control studies, but not all5,34. A meta-analysis with 6 case-control studies found no association of general anesthesia with Parkinson’s disease25. In a retrospective cohort study that included 490,156 anesthesiologists and 499,388 interns, anesthesiologists were found to have a higher risk of dying from Parkinson’s disease than interns.7 In experimental models, mechanisms have been described that relate exposure to anesthetic gases such as halothane, isoflurane, and nitrous oxide with the development of PD35.

Study limitations

Due to the coronavirus pandemic (COVID-19) it was not possible to reach the sample size (n = 100). The small sample size of the cases (n = 86) reduces the power of the statistical analyses. To compensate for the above, in some cases two controls were used for each one, which is recommended by Gail, using the case saving rule. Therefore, it is suggested to increase the sample size for future studies36.

Epidemiological case-control studies have been used successfully to investigate possible associations between various variables and the risk of developing certain multifactorial diseases, such as PD. However, they have biases inherent in their methodology, such as memory bias in elderly patients and reverse causality by not considering that the possible factors associated with PD could be a consequence and not a cause of the disease. In addition, another potential source of bias in this type of study is related to the collection of data in the interviews, where the interviewers, knowing the hypotheses, can, consciously or not, influence the interviewees to provide answers consistent with those hypotheses.

It is necessary to reach a consensus regarding the methodology of epidemiological studies of risk and protective factors associated with PD, to avoid or reduce biases. For greater veracity in future studies, it is suggested to increase the sample size if feasible, the intensity and duration of the factors associated with PD should be estimated, such as exposure to pesticides and organic solvents, tobacco, and caffeine consumption. Likewise, to reduce the reverse causality bias, only factors before the onset of the prodromal phase of PD should be considered, which is conservatively estimated to begin about 10 years before diagnosis, so this value could be used as a point cut-off point51.

Conclusions

The findings of this research indicate that the inhabitants of the state of Yucatan are exposed to the following risk factors for developing PD: family history of PD, personal history of diabetes, the number of head trauma, exposure to solvents organics, number of years of exposure to organic solvents, and the number of general anesthesia received. It is necessary to reach a consensus regarding the methodology of epidemiological studies of risk and protective factors associated with PD, to avoid or reduce biases.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that 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

Somatodyspraxia: A novel term proposition as a primary factor of apraxia and its applicability in the PAINT Neuropsychological Rehabilitation Model for brain injury

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Abstract

This article proposes the term Somatodyspraxia to refer to the difficulties in body management and postural adjustments for performing actions, due to alterations in somatosensory and proprioceptive processing, as a consequence of acquired brain injury. In addition, we propose Somatoapraxia as a primary factor for apraxia and describe its applicability for a Neuropsychological Rehabilitation Model for apraxia. The explanatory models of apraxia, the somatosensory and proprioceptive alterations underlying various types of apraxia, and their manifestation in different neurological conditions, are taken into consideration. Recognizing Somatodyspraxia as a clinical component of patient’s life allows its integration for the improvement of current existing rehabilitation programs.

Keywords: Somatodyspraxia. Apraxia. Acquired brain injury.

Somatoapraxia: una nueva propuesta de término como factor principal de la apraxia y su aplicabilidad en el modelo de rehabilitación neuropsicológica PAINT para lesiones cerebrales

Resumen

En este artículo se presenta el término “somatoapraxia” para referirse a la dificultad en el manejo corporal y ajustes posturales en la realización de acciones, debido a alteración en el procesamiento somatosensorial y propioceptivo como consecuencia de daño cerebral adquirido. Además, se plantea la somatoapraxia como un factor primario de las apraxia y su aplicabilidad en un modelo de rehabilitación neuropsicológica. Se consideran las alteraciones somatosensoriales y propioceptivas como subyacentes a varios tipos de apraxia y su manifestación en diferentes patologías neurológicas. El reconocimiento de la somatoapraxia como componente clínico de la apraxia y la afección a la vida de los pacientes, permite mejorar los programas de rehabilitación existentes.

Palabras clave: Somatoapraxia. Apraxia. Lesión cerebral adquirida.

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Introduction

We propose the novel term “Somatoapraxia” to be the alteration in somatosensory and proprioceptive processing, after acquired brain injury, which makes it problematic to manage the body schema and carry out the necessary postural adjustments for the execution of tasks or actions. It differs from apraxia, since apraxia has been defined as a disorder that involves the inability to execute learned and purposeful movements, on command or by imitation, due to alteration in the concept of movement or in the logical motor sequence of previously learned movements1,2.

In adults, different descriptive models for apraxia have been proposed, which encompass different etiologies: failure in visual input, memory, semantics, or in the management of space and time3. In children with learning disabilities, Ayres proposed a similar term, somatodyspraxia4, to refer to the inability to interpret and organize sensory information that allows an adequate and effective response to multiple environmental stimuli5. However, this only considers the origin of the problem to be due to planning and conceptualization factors of ideational apraxia. Furthermore, in adults with acquired brain injury, alterations in sensory and proprioceptive processing that impact daily living activities have been described1; however, they have not been considered as part of a theoretical model.

A somatosensory and proprioceptive core concept, which explains the complexity of the different types of apraxia after acquired brain injury, has not been proposed. Therefore, is our objective to present the term “Somatoapraxia” as a novel core concept that exists as principal factor in apraxia. We will also highlight the terms applicability in a Neuropsychological Rehabilitation Model for apraxia.

History of apraxia

The term apraxia was proposed by Steinthal in 1871, to refer exclusively to the set of disorders that had as the common characteristic, the inability to correctly execute a motor activity on command6. However, the most important person responsible for its recognition was Hugo Karl Liepmann (1863-1925), who distinguished different functional components responsible for praxis processing. He believed that the learning of motor skills required the acquisition of “movement formulas,” “innervation patterns,” and “kinetic memories”7. Thus, Liepmann characterized ideational apraxia, ideomotor apraxia, and limb or kinetic apraxia as consequences of brain injury in adults7. Liepmann proposed ideational or conceptual apraxia as an interruption in the activation of the space-time plan, therefore, the idea of movement is not possible. Conversely, in an ideomotor apraxia the spatio-temporal plans are preserved, but they cannot guide the innervation engrams to execute movements because they are disconnected from them; the patient knows what to do, but not how to do it. Finally, when the interruption of the innervation engrams interferes with the selection of muscular synergies to perform movements, there is kinetic apraxia of the limbs7.

Even then, Liepman considered that praxis requires the idea or plan of movement, which must be recovered and associated through the left sensorimotor cortical connections, which in turn carry information to the left primary motor areas. When the left limb performs the movement, the information is transmitted from left to right through the corpus callosum and activates the right motor cortex8.

Explanatory models of apraxia

In recent decades, complex cognitive models of praxis processing have been developed to explain and classify apraxia. The description of the mechanisms underlying this disorder has been diverse. Heilman, González Rothi and Valenstein9 in 1982, and González Rothi, Heilman, and Warson10 in 1985, proposed that there are at least two types of mechanisms that describe apraxia: (1) a degraded memory trace that produces difficulties in the reception and production of gestures, and (2) a memory discharge dysfunction that generates alterations in their production3.

Roy and Square, in 1985, proposed that praxis processing is mediated by a system that involves two components, both conceptual and of production9. The first includes three types of knowledge: (1) about the operation of tools and objects, (2) about the independent actions of objects, and (3) about the sequential organization of actions. They considered that movements are dependent on the interaction between the conceptual knowledge of the tools, objects and actions (semantic action), and the structural information contained in the motor programs. In this context, apraxia is the result of a failure in the production system, while an alteration in the conceptual system implies difficulties in the recognition of the specific utility of tools and the mechanical requirements of an action that allows us to achieve an objective10,11.

Similarly, a model of apraxia was proposed by Geschwind12 in 1965, based on the disconnection of
the left premotor cortex and Wernicke’s area\textsuperscript{13}. According to this model, apraxia is the result of lesions in the supramarginal gyrus or the arcuate fasciculus.

Ayres\textsuperscript{4} based on her studies in children, identified a population with learning disabilities who showed difficulties in interpreting the sensory information of their bodies and their environment. Based on her research and clinical experience, she described how the nervous system translates somatosensory information into action, and postulates that proper integration of proprioception and the vestibular aspect are critical for adaptive behavior\textsuperscript{14}. Ayres emphasized somatosensation and its relationship with the body schema as the basis for praxis in children; however, she proposes that praxis is based of only three components: ideation (conceptualization of actions), motor planning, and motor execution. Furthermore, she describes somatodyspraxia as a problem in the organization of the motor plan, such as, ideational apraxia.

Although different models have been described to explain apraxia, somatoapraxia has not been considered as a primary factor of the different apraxia. We consider that when somatosensory and proprioceptive processing is altered, after acquired brain injury, the management of the body schema and the necessary postural adjustments to carry out tasks or actions, (praxis), becomes difficult. Based on this theory, we present the term somatodyspraxia as a primary factor in apraxia and its applicability in a Neuropsychological Rehabilitation Model for apraxia.

**Somatodyspraxia as a primary factor in apraxia**

In somatodyspraxia the ability to execute an action is altered. This ability requires that the brain is capable of knowing bodily functions and conceptualize the objective of a motor action. In somatodyspraxia, the management of the body schema and postural adjustment is absent. In the execution of praxis, the processing of information from the proprioceptive, somatosensory, kinesthetic, and vestibular systems is required to determine how the body is designed and how it will function for the performance of a task or action. This sensory processing allows using exteroceptive and interoceptive information to regulate and adapt movement and give appropriate motor and postural responses\textsuperscript{15} necessary in performing praxis.

In Somatodyspraxia, the integration of proprioceptive, somatosensory signals, as well as body scheme that allow estimating body movements is altered, resulting in **gait apraxia**\textsuperscript{16}. The proprioceptive system allows us to perceive the movements of the joints, to know the position of the body, the force generated by the muscles, and the speed and direction of our movements\textsuperscript{17}. System alterations complicate the reception of normal impulses from the muscles and joints\textsuperscript{18}. Processing alterations of proprioceptive sensations result in disruption of postural stability and lack of knowledge of the body’s position in space\textsuperscript{19,20}. In addition, neuronal principles show that for adequate postural control of the head, the interaction of the vestibulospinal tracts, which selectively activate the muscles of the neck and trunk, are crucial\textsuperscript{21}. Information that travels from the skin to the central nervous system (CNS) is useful to generate human balance. When the cutaneous afferent inputs are not transmitted to the CNS, it can cause an imbalance\textsuperscript{22}, and subsequently gait apraxia.

In somatodyspraxia, there is alteration of tactile information, which contributes to the manipulation and grasping of objects, plays a role in linking present and past sensations necessary for the performance of praxis\textsuperscript{23}. These difficulties can lead to **apraxic agraphia**, in which the subject struggles in the simple task of properly grasping a pencil and guiding movements to trace letters. The same can happen in adult patients with acquired brain injury, who experience difficulties to adequately perform activities of daily living\textsuperscript{24}.

Somatodyspraxia can cause problems in the body schema and in postural adjustments necessary for **dressing**. The patient may have problems when trying to put on a sweater, having difficulty in placing arms in the corresponding sleeves, for example, because he does not make the necessary postural adjustments. It is also common for the patient to carry out the steps to put on a garment incorrectly or in the wrong order, for example, putting the pants on the arms, or putting on a sweater first and then the shirt, or not knowing whether to tie their shoelaces or button a shirt. In addition, they have difficulty in fastening and unbuttoning\textsuperscript{25}, causing **dressing apraxia**.

In somatodyspraxia, the internal and updated representation of the position of the body and movement in space are affected\textsuperscript{26}. Clinical observations show that patients with somatosensory and vestibular alterations often make errors in movement trajectory and may have trouble detecting and estimating body displacement\textsuperscript{26}. Signals from muscles, joints, skin, and eyes are continuously integrated with vestibular input and evoke postural and oculomotor responses. Alterations present at this level, can lead to a **constructional apraxia**, a concept that describes an alteration present when
carrying out activities such as assembling, building, or
drawing\textsuperscript{27}.

Somatodyspraxia may be the primary factor in limb apraxia, since a patient with acquired brain injury may have problems in the body schema management and postural adjustments to orient utensils and move it properly, or he cannot use the appropriate cutlery for the type of food or associate the object with the action (e.g., using a knife instead of a spoon for soup or adding salt instead of sugar to the coffee). Furthermore, the subject may have difficulties in using objects, such as the toothbrush and razor, trying to use the toothbrush to comb his hair. Furthermore, they may have difficulties in properly orienting and positioning their body, for example, to properly manipulate a hairband to make a ponytail.

Orofacial apraxia, or buccofacial apraxia is characterized by a loss of voluntary control of facial, lingual, and masticatory muscles in association to somatosensory and proprioceptive disturbance. The typical patient fails to produce the correct movement in response to verbal command or to imitate correctly a movement performed by the examiner due to Somatodyspraxia. Sometimes, the person needs to use his hands to help introduce food completely into the mouth and thus be able to swallow. It may also happen that the patient does not find the proper position of the phonation apparatus for the correct articulation of language, producing an afferent motor aphasia\textsuperscript{27}. Similarly, patients with Somatodyspraxia may experience difficulties in the body schema and sense of the body itself. Compound sensory, proprioceptive, exteroceptive, and interoceptive data, are required for sphincter control\textsuperscript{28}. Like all body Functions, sphincter control is regulated by the Nervous System. At the level of the entire lower urinary tract (bladder and urethra) there are a series of sensory endings or exteroceptive (tactile, painful, and thermal) and interoceptive (visceral or abdominal distension) neuroreceptors located mainly in the trigone and urethral meatus\textsuperscript{29}. Patients barely know what position their body is in and, therefore, cannot receive afferent information from the sphincters.

In summary, the functional implications of somatodyspraxia are reflected in different activities such as walking, dressing, the construction of letters and drawings, in the adequate movement of the organs of the mouth for the articulation of language and swallowing, and sphincter control, due to the lack of adequate integration of somatosensory and proprioceptive information, body schema and postural adjustments for the execution of praxis (Fig. 1). The novel term plays an important role in the mechanisms responsible for the previously mentioned apraxias.

**Somatodyspraxia in acquired brain injury**

In praxis, movements are complex and seem to involve several brain regions, such as the premotor, prefrontal, temporal, and parietal areas. The parietal lobe has been shown to be involved in the acquisition of movements for the use of tools\textsuperscript{13}. In addition, the parietal cortex seems to be relevant in abnormalities of the somatosensory and proprioceptive systems, which have been found altered in disturbances that affect the CNS, such as a cerebrovascular event (stroke)\textsuperscript{30}, Traumatic brain injury (TBI)\textsuperscript{31}, or neurocognitive impairment\textsuperscript{32}. Therefore, the somatosensory and proprioceptive alterations in acquired brain injury lead to the presence of somatodyspraxia.

Because somatosensory and proprioceptive deficiencies are common in somatodyspraxia patients after stroke, deterioration in postural function and level of independence may be present\textsuperscript{32}. They often require assistance during bathing, shaving, and getting dressed\textsuperscript{32}. Neuroimaging studies, which include positron emission tomography and functional magnetic resonance imaging, have shown that lesions to the lower left and upper parietal lobe seem to be involved in the alteration of movements for the use of tools\textsuperscript{13}.

Alzheimer’s disease is associated with somatosensory processing and discrimination\textsuperscript{32} that can lead to somatodyspraxia which impacts daily living activities, such as meals, housework, or driving. Commonly, in mild cognitive impairment, significant decline in the
performance of these activities is observed, which may progress rapidly into Alzheimer’s disease. The problems in carrying out these activities, observed in this population, may be related to the deterioration in praxis due to a primary somatodyspraxia factor, which causes struggles in action executing such as the use of cutlery or judging how close the food is to the mouth.

Similarly, patients with Parkinson’s disease experience somatosensory alterations and problems in proprioceptive processing causing somatodyspraxia, due to an affection of the basal nuclei and their connections with postcentral and premotor areas. These alterations cause lack of precision in goal-directed movements and altered postural reflexes that lead to problems in gait and balance. We observe temporal or spatial errors, such as interrupted slow movements apraxic substitution errors, such as brushing teeth with a hairbrush, or using a part of the body as an object.

It is common that after a TBI, patients present disorders of the somatosensory and proprioceptive systems. Deficiencies in the ability to integrate information from the sensory, motor and skeletal-muscular systems can generate somatodyspraxia in patients with TBI. This causes difficulties in grasping or thumb orientation for proper use of tools, due to alterations in the postcentral and premotor areas of the contralateral hemisphere to the injury. Therefore, daily living activities become arduous.

Cerebellar ataxia arises due damage or dysfunction affecting the cerebellum and/or its input/output pathways cerebellar dysfunction may result in significant functional difficulties with upper and lower limb movement, oculo-motor control, balance and walking. Contrary to somatodyspraxia, ataxia is associated with dysmetria, cerebellar tremor, nystagmus, and dysarthria. Its rehabilitation is centered in coordination and balance training, multifaceted inpatient rehabilitation, a cycling regime, balance training, treadmill training, occupational therapy, and inspiratory muscle training.

After brain injury, patients require neuropsychological rehabilitation, which is a theoretical framework of interventions designed to improve cognitive, emotional, and psychosocial functioning, due to changes in the brain. The goal is to promote greater functional independence in a wide variety of situations of daily life. So far, few studies have investigated the effectiveness of different apraxia methods of intervention. This may be caused by the erroneous belief that apraxia only occurs during imitation, verbal command, and in the absence of the object, without influencing daily life activities. There are some interventions proposed in the literature, which focus mainly on syndromic management strategies such as ideomotor apraxia, orofacial apraxia, or dressing apraxia. In addition, other rehabilitation techniques have focused on the execution of gestures. However, improvement was observed only in the symptoms, without generalization. Conversely, Durand, Gago Galvagno and Elgier, treated neuropsychological ability and not the symptom, they based the rehabilitation on the body schema in patients with dressing apraxia, during which they provide Kinesthetic-tactile, proprioceptive and spatial stimuli to guide the upper limb during movement.

**Functional neuroanatomical bases for our somatodyspraxia rehabilitation model**

In praxis, movement depends on simple processes integrated and organized in learned motor patterns. Therefore, execution of a praxis pattern requires a constant flow of information between the cortical and subcortical areas; thereby being a mechanism in which the cortex serves as a station where information is classified and integrated, while the subcortical structures provide feedback to the entire system, rectifying input information and the commands that will result in the execution of specific responses.

The spinal cord acts as a communication bridge between the brain and the sensations received by the body from the external world and the internal environment. Thus, the sensory information of different submodalities is sent to the brain through the spinal tract. Sensory nerve fibers of different sizes and functions are arranged and distributed in nerve bundles or tracts. Below, we show the most relevant afferent pathways that reach the medulla and their function; this, to show the relationships they maintain with the production of action (praxis) and our proposal for neuropsychological rehabilitation of praxis (Table 1). Somatodyspraxia patients show alterations in recognition and association of multiple somatosensory and proprioceptive stimuli. For rehabilitation, we suggest applying tactile stimuli to the subject, such as pain, temperature, pressure, texture and vibration. We also seek to place him in uncomfortable positions and carry out tasks such as pulling, loading and pushing, in order to stimulate the sensations of the muscles and joints leading to the goal of movement and to promote knowledge of the parts of the body to solve a task (praxia).

The brainstem has an important sensory and motor function and acts as a primary distributor for somatosensory information from the spinal cord and the
motor pathways of the cerebral cortex. The movements produced by the brainstem involve the entire body and are important for walking, eating, drinking, swimming, grooming, and sexual behavior. The central part of the brainstem contains the nuclei of the cranial nerves and bundles of sensory and motor fibers. It is summarize the cranial nerves that related to the brainstem and their function; this, to show the relationship they have to produce action (praxis) and our proposal for neuropsychological rehabilitation of praxis (Table 2).

The cerebellum is involved in the synergy of movement through the spinocerebellar, vestibulocerebellar, and cerebrocerebellar bundles, by means of which movements are grouped correctly for the execution of acts that require special adjustments to establish and maintain balance and to regulate muscle tone, necessary for praxis. Our proposal for the rehabilitation of somatodyspraxia recommends working on the control of static and dynamic balance with the use of balance boards, balls and unstable surfaces. In addition, we suggest working on regulating motor rhythm, through activities for motor coordination of hands, fingers and feet. The most relevant pathways that reach the cerebellum and their function are shown, to specify the relationship they maintain with the production of action (praxis) and our proposal for neuropsychological rehabilitation of praxis (Table 3).

Sensory information from the brainstem (somatosensory, auditory, vestibular, and taste) reaches the thalamus and information from visual and olfactory pathways is added. The thalamus is associated with the integration of somatosensory information (touch, pressure, pain, and temperature), which is processed in the ventral posteromedial nuclei (head and neck) and ventral posterolateral nuclei (body). Then, it is transmitted to the somatosensory cortex of the parietal lobe. Auditory information is processed in the medial geniculate nuclei and sent to the auditory cortex in the temporal lobe. Vestibular information reaches the posterior ventral nuclei and is directed to the somatosensory cortex of the parietal lobe. The posteromedial ventral nuclei receive information from the sense of taste, which is directed to the gustatory area in the parietal lobe. Visual information reaches the lateral geniculate nuclei and is subsequently projected into the visual cortex in the occipital lobe. The olfactory information is received in the central part of the dorsal medial nuclei, and then it is projected toward the orbitofrontal cortex. For the rehabilitation of somatoparalexia, according to our model, we suggest that the subject performs an activity that integrates proprioceptive stimuli of the head and body, vestibular, visual, and auditory. For example, standing on a balance board that forces him to make postural adjustments against gravitational force; throwing bags of different weights, textures, and shapes into a

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### Table 1. Functions and sensations of the Ascending pathways of the spinal cord and proposal for neuropsychological rehabilitation in somatodyspraxia

<table>
<thead>
<tr>
<th>Ascending pathways</th>
<th>Sensation</th>
<th>Fiber connections</th>
<th>Terminate in</th>
<th>Proposal for neuropsychological rehabilitation of somatodyspraxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral spinothalamic tract</td>
<td>Pain and temperature</td>
<td>Reticular formation Ventral posterolateral nucleus of the thalamus Somesthetic area (postcentral gyrus of the cerebral cortex)</td>
<td>Postcentral gyrus</td>
<td>Apply uncomfortable/painful stimuli to feet and hands, due to their cortical representation Apply ice to the parts of the body where you want to increase muscle tone</td>
</tr>
<tr>
<td>Anterior spinothalamic tract</td>
<td>Slight touch and pressure</td>
<td>Superior cerebellar peduncle Cerebellum</td>
<td>Postcentral gyrus</td>
<td>Apply large heavy cushions to the entire body Use soft objects of different weights as stimuli</td>
</tr>
<tr>
<td>Gracile and cuneate fasciculi medial lemniscus</td>
<td>Discriminatory touch, vibratory sensitivity, conscious sensation of muscles and joints</td>
<td>Inferior cerebellar peduncle Cerebellum</td>
<td>Postcentral gyrus</td>
<td>Use objects with vibration Loading, Pulling, and Pushing Tasks</td>
</tr>
<tr>
<td>Anterior and posterior spinocerebellar tract</td>
<td>Musculo-articular unconscious sensation</td>
<td></td>
<td>Cerebral cortex</td>
<td>Working on unstable surfaces that require postural adjustments against gravitational force</td>
</tr>
</tbody>
</table>

---

**Note:** Table 2 and Table 3 are not explicitly shown in the provided text but are referenced in the narrative. The tables would typically contain detailed information about the pathways and their functions as described in the text.
container, to see where the stimulus is directed and to listen when it falls, all integrated into a single action (praxis)\textsuperscript{48}. The most relevant nuclei of the thalamus and their functions are shown, as well as their relationship with the production of action (praxis) and our proposal for neuropsychological rehabilitation of praxis (Table 4).

The basal nuclei are important in motor learning\textsuperscript{39}. They play an important role in inhibiting unwanted movements and promoting the desired ones, initiating the production of movements directed toward a goal, and modulating the force of the movements\textsuperscript{13} necessary for the execution of praxis. For neuropsychological rehabilitation of somatopraxis, according to our model, we suggest performing activities to inhibit movement, processing speed, and modulation of movement. Shown, are the basal nuclei, as well as their functions and the relationship they maintain with the production of action (praxis), as well as our proposal for neuropsychological rehabilitation of praxis (Table 5).

Regarding the cortical areas involved, the parietal lobe comprises a multiplicity of areas and can vary in different parts of the parietal cortex. The most important are involved with the trajectory of movement of various parts of the body, orientation of the extremities, the control of body parts, the identification, size, and shape of objects, as well as the location and orientation of the object. For the rehabilitation of somatopraxis, we propose using objects of different textures and sizes to stimulate different parts of the patient’s body. We also suggest using objects with different temperatures, for example ice to stimulate cold, and others that stimulate pain. In addition, in our neuropsychological rehabilitation model, we propose carrying out activities that stimulate the internal representation of the body or body schema, such as jumping around, rolling your body on the floor or on a large cushion. Activities that require pulling, loading, and pushing, for proprioceptive stimulation, should also be included, for example, moving therapy equipment, huge cushions, and/or supporting your own weight from a trapeze\textsuperscript{48}.

As mentioned above, praxis is an integrative function, in which the harmonious work of different neural systems promotes learning and maturation of each of the aspects involved in the production of voluntary and involuntary movement. The execution of praxis must be

**Table 2. Functions and quality of the cranial nerves and proposal for neuropsychological rehabilitation in somatodyspraxia**

<table>
<thead>
<tr>
<th>Cranial nerves</th>
<th>Function</th>
<th>Quality</th>
<th>Proposal for neuropsychological rehabilitation of somatodyspraxia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arousal/consciousness</td>
<td>Reticular formation</td>
<td>Activities to improve alertness</td>
</tr>
<tr>
<td>Oculomotor nerve (III)</td>
<td>Motor function, involved in the muscular control of the eyes</td>
<td>Motor</td>
<td>Visual tracking activities</td>
</tr>
<tr>
<td>Trochlear nerve (IV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abducens nerve (VI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facial nerve (VII)</td>
<td>Facial expression, gland discharge and taste sensation</td>
<td>Sensitive</td>
<td>Facial muscle massage Somatosensory stimuli in the facial oral tract Orofacial movements</td>
</tr>
<tr>
<td>Trigeminal nerve (V)</td>
<td>Sensitivity of the face, nose, teeth, jaw movements</td>
<td>Mixed</td>
<td>Tongue proprioceptive exercises, such as pushing to the front, to the sides, pulling the tongue, or carrying an object, like a pencil</td>
</tr>
<tr>
<td>Vestibulocochlear nerve (VIII)</td>
<td>Vestibular Information</td>
<td>Sensitive</td>
<td>Exercises, such as going up a ramp, going down, head down to pick up balls</td>
</tr>
<tr>
<td>Glossopharyngeal nerve (IX)</td>
<td>Sensitivity and movement of the tongue and pharynx</td>
<td>Mixed</td>
<td>Stimulate the inside of the cheeks and gums with cotton swabs, tongue depressors, teethers, or vibration brushes</td>
</tr>
<tr>
<td>Vagus nerve (X)</td>
<td>Sensory and motor actions of organs, such as the heart, blood vessels, and viscera</td>
<td>Mixed</td>
<td>Cardiovascular exercises that favor inhalation and expiration</td>
</tr>
<tr>
<td>Accessory nerve (XI)</td>
<td>Control of neck and tongue muscles</td>
<td>Motor</td>
<td>Stimulate muscle tone of the neck with proprioceptive exercises Swallowing exercises</td>
</tr>
<tr>
<td>Hypoglossal nerve (XII)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
analyzed as a functional system, which requires the communication of the cortex, subcortex, and spinal cord. The integrated system forms a neural network involved in different actions, which when suffering selective damage through a pathological process can produce Somatopraxis.

**Proposal of a neuropsychological rehabilitation model for apraxia**

Based on the definition of somatodyspraxia, alterations in the processing of somatosensory and proprioceptive information lead to difficulties in understanding the body schema and the relationship of the body itself with respect to objects, making postural adjustments for the correct execution of movements, and therefore carrying out many of the activities of daily living, such as dressing, eating, or combing hair.

In this article, we propose that somatodyspraxia is the primary factor of apraxia and we present a neuropsychological intervention model for Apraxia and Somatodyspraxia that focuses on the stimulation of the somatosensory and proprioceptive systems, body schema, and postural adjustments.

The intervention program in this approach is based on a neuroanatomical and neurophysiological theory.

<table>
<thead>
<tr>
<th>Thalamic Nuclei</th>
<th>Function</th>
<th>Fiber connections</th>
<th>Proposal for neuropsychological rehabilitation of somatoapraxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>Emotional tone, recent memory mechanisms</td>
<td>Mamilothalamic tract, cingulate gyrus, hypothalamus</td>
<td>Use stimuli that have emotional value</td>
</tr>
<tr>
<td>Dorsomedial</td>
<td>Integration of somatic, visceral and olfactory information, and relationship with emotional sensations</td>
<td>Prefrontal cortex, hypothalamus, other thalamic nuclei</td>
<td>Proprioceptive stimuli that stimulate interoception</td>
</tr>
<tr>
<td>Dorsolateral, posterolateral, pulvinar</td>
<td>Unknown</td>
<td>Cerebral cortex, other thalamic nuclei</td>
<td></td>
</tr>
<tr>
<td>Ventral anterior</td>
<td>Influences the activity of the motor cortex</td>
<td>Reticular formation, substantia nigra, striatum, premotor cortex, other thalamic nuclei</td>
<td>Motor activities that stimulate body schema</td>
</tr>
<tr>
<td>Ventral lateral</td>
<td>Influences the motor activity of the motor cortex</td>
<td>Reticular formation, substantia nigra, striatum, premotor cortex, other nuclei of the thalamus, cerebellum, and red nucleus</td>
<td>Apply motor activities that seek the integration of vestibular, visual and proprioceptive senses</td>
</tr>
<tr>
<td>Ventral posteromedial (VPM)</td>
<td>Relay for common sensations toward consciousness</td>
<td>Trigeminal lemniscus, taste fibers</td>
<td>Promote the recognition and expression of the sensations experienced with the material</td>
</tr>
<tr>
<td>Ventral posterolateral (VPL)</td>
<td>Relay for common sensations towards consciousness</td>
<td>Medial and spinal lemniscus</td>
<td>Promote the recognition and expression of the sensations experienced with the material</td>
</tr>
<tr>
<td>Intralaminar</td>
<td>Influences states of consciousness and alertness</td>
<td>Reticular formation, spinothalamic and trigeminothalamic tracts</td>
<td>Vertical vestibular, like jumping and hopping</td>
</tr>
<tr>
<td>Midline</td>
<td>Unknown</td>
<td>Reticular formation</td>
<td></td>
</tr>
<tr>
<td>Reticular</td>
<td>The cortex regulates the thalamus</td>
<td>Cerebral cortex, reticular formation</td>
<td>Stimulate the state of attention</td>
</tr>
<tr>
<td>Medial geniculate body</td>
<td>Hearing</td>
<td>Inferior colliculus</td>
<td>Apply auditory stimuli during the integrated activity</td>
</tr>
<tr>
<td>Lateral geniculate body</td>
<td></td>
<td>Optic tract</td>
<td></td>
</tr>
</tbody>
</table>
We recommend focusing on the stimulation the proprioceptive and somatosensory systems, because this specific information, after traveling through the somatosensory pathway and the thalamus, reaches parietal areas which communicate with primary motor areas. The integration of this information in the CNS helps regulate the production of adequate motor responses for performing praxis. In addition to stimulating the somatosensory and proprioceptive systems, the patient’s movement is guided and regulated through language.

By stimulating the somatosensory system with touch, pain, pressure, vibration, and temperature stimuli, one favors the understanding of the body schema, which is necessary for the execution of movements such as writing, dressing, eating and swallowing, the articulation of words or sphincter control. Muscle and joint activation by stimulating mouth and phonation apparatus movements favor for proprioception. Intervention through the vestibular system and management of postural adjustments is necessary for the adequate head and eyes movements for drawing, the integration of two-dimensional and three-dimensional visual stimuli, walking, handling objects, and even getting dressed.

In this section, we propose a neuropsychological rehabilitation model for apraxia, based on the PAINT Model. Our model proposes conducting a comprehensive

<table>
<thead>
<tr>
<th>Area</th>
<th>Function</th>
<th>Fiber connections</th>
<th>Terminate in</th>
<th>Proposal for neuropsychological rehabilitation of somatodyspraxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinocerebellum</td>
<td>Regulation of face and hand movements</td>
<td>Medial (vermis)</td>
<td>Dorsal nucleus</td>
<td>Motor activities using balance boards, balls and swings</td>
</tr>
<tr>
<td></td>
<td>Coordination of extremities (hands, fingers, and feet).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vestibulocerebellum</td>
<td>Control of static and dynamic balance</td>
<td>Vermian regions, flocculonodular lobe, fastigial nucleus</td>
<td>Spinal cord and motor nuclei</td>
<td>Visual tracking activities favoring the vestibular system</td>
</tr>
<tr>
<td></td>
<td>Eye movement</td>
<td>Anterior spinotthalamic tract</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrocerebellum</td>
<td>Learning and maintenance of motor skills</td>
<td>Cerebral cortex</td>
<td>Lateral areas of the contralateral hemisphere</td>
<td>Encourage adaptive responses</td>
</tr>
<tr>
<td></td>
<td>Error correction</td>
<td>Ventral lateral nucleus of the thalamus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rhythm regulation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Area</th>
<th>Function</th>
<th>Pathways</th>
<th>Fiber connections</th>
<th>Terminate in</th>
<th>Proposal for neuropsychological rehabilitation of somatodyspraxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate nucleus</td>
<td>Static and dynamic balance control</td>
<td>Medial (vermis)</td>
<td>Ipsilateral spinal cord</td>
<td>Visual tracking activities favoring the vestibular system</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eye movement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Putamen</td>
<td>Generation of speed and range of motion</td>
<td>Vermian regions, flocculonodular lobe, fastigial nucleus</td>
<td>Vestibular nucleus</td>
<td>Spinal cord and motor nuclei</td>
<td>Throw balls and sacks, following a trajectory</td>
</tr>
<tr>
<td></td>
<td>Action control, motivation and cognition</td>
<td>Anterior spinotthalamic tract</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>Motor control and coordination</td>
<td>Excitatory-inhibitory</td>
<td>Caudate nucleus and putamen</td>
<td>Motor and prefrontal cortex</td>
<td>Promote the inhibition of motor stimuli upon verbal command</td>
</tr>
</tbody>
</table>
rehabilitation program based on the stimulation of the somatosensory and proprioceptive systems, body schema and postural adjustments involved for the execution of praxis, as part of a complex functional system45 (Fig. 2).

One of the main objectives of our PAINT Neuropsychological Rehabilitation Model is to stimulate the somatosensory system through all its functions: pain, touch, temperature, pressure, texture, and proprioception, since the nervous system requires somatosensory feedback to control voluntary movement. We base this on the fact that, during voluntary movement, the CNS is continuously receiving information from both, somatosensory signals derived from changes in the external environment and from the person’s postural changes46. The integration of somatosensory information is critical for motor control and movement recognition, and the correct performance of movements that involve manipulating objects and purposive actions.

Another of the main objectives of our PAINT Neuropsychological Rehabilitation Model is to stimulate the proprioceptive system, and perception or awareness of the position and movement of body. Proprioception is the body’s self-awareness that tells the body where it is in space. We receive proprioceptive input from our sensory receptors located in muscles, tendons, joints and internal organs47, and it is crucial to the brain, as it plays a large role in posture, body awareness, use of tools and purposive actions. This information is processed in the somatosensory areas of the posterior parietal cortex. We propose activities that stimulate proprioceptive senses, such as pushing and pulling with the patient’s own weight, pulling a rope or heavy mat; or resistance exercises that involve different body segments, including the tongue48.

The PAINT Neuropsychological Rehabilitation Model for apraxia also pursues the stimulation of the body schema and postural adjustments of the subject. The goal is to promote mobility of the upper and lower limbs, as well as the use of both hands and feet in praxis. This model for apraxia proposes stimulation of the body schema by providing tactile-kinesthetic stimuli to the upper and lower limbs. The therapist guides the movements by placing him or herself behind the patient, so that the actions are natural, while simultaneously giving a verbal description of the movements, thus favoring the correct connection between the movement and its execution with the use of objects. Regarding the problems of managing the body in space, we seek to work on understanding the place the body occupies in space in relation to an object.

Our PAINT Neuropsychological Rehabilitation model aims to stimulate postural adjustments by making different movements with the body or putting it in awkward positions from which patients must move several body segments such as the arm, leg or, even the head. This allows the stimulation of postural adjustments against gravitational force, through movements of the head and body on surfaces such as balls, seesaws or suspended equipment, with the goal of causing linear accelerations and angular accelerations. Our Rehabilitation Model seeks to integrate proprioceptive and visual information, to establish diagrams of the position and dynamics of body movements, the verticality within the three-dimensional gravitational field49, the position of the head with respect to gravity and the detection of changes in its movement45, as well as determining speed and direction of the movements.

By understanding the concept of somatodyspraxia, one can exploit it during patient rehabilitation after acquired brain injury. The rehabilitation of the different proprioceptive and somatosensory components allows the patient to recover vital neurological pathways for the re-establishment of daily life activities. Our proposed term of somatodyspraxia and its importance in the PAINT Neuropsychological Rehabilitation model will allow medical and rehabilitation personnel to have a better understanding of the neurological and neuropsychological concepts that ultimately affect a patients quality of life.

**Conclusion**

Acquired brain injury commonly causes alterations in different cognitive functions. Adults with brain injury
can present a form of apraxia, which we have called somatodyspraxia; an alteration in somatosensory and proprioceptive processing, after acquired brain injury, which makes it difficult to manage the body schema and the postural adjustments necessary for the execution of tasks or actions. Patients with these types of alterations have difficulty in carrying out activities of daily life, which impacts their quality of life. The precise recognition of somatodyspraxia in adults is relevant because it can guide the establishment of a rehabilitation program focused on the stimulation of the somatosensory system, proprioceptive system, body schema, and postural adjustments.

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

**References**

Stroke and atrial fibrillation: An update

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Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice. AF is associated with an increased risk of cardiovascular disease, heart failure, stroke, cognitive impairment and dementia, and mortality. Individuals with AF have a 5-fold risk of ischemic stroke, and AF-related strokes are associated with greater disability and mortality compared with strokes from other causes. Moreover, the burden of AF and AF-related stroke on patients, their caregivers, health-care systems, and society is significant and projected to increase in the coming decades due to the rapid growth of the ageing population. The care and management of patients with AF and AF-related stroke are challenging, often involving complex decision-making to weigh the risks and benefits of various treatment and prevention strategies. This topical review focuses on the latest science and advances in AF and AF-related stroke and identifies knowledge gaps and future directions of continued research.


Actualización en ictus y fibrilación auricular

Resumen

La Fibrilación Auricular (FA) es la arritmia sostenida más común en la práctica clínica. La FA se asocia a un riesgo incrementado de enfermedad cardiovascular, falla cardiaca, enfermedad cerebrovascular, deterioro cognitivo y demencia. Los individuos con FA tienen un riesgo cinco veces mayor de ictus, y los infartos isquémicos asociados a la FA causan mayor discapacidad y mortalidad comparado con otras causas de ictus isquémico. Se estima que las consecuencias y la carga de la FA y el ictus ocasionado por la FA en pacientes, sus familias, la sociedad y el sistema de salud, se incrementa de manera importante en las próximas décadas dado el aumento en la población anciana, lo cual tiene un riesgo aumentado de FA. El manejo de los pacientes con ictus y FA es complejo dado el riesgo de hemorragia en pacientes con enfermedad cerebrovascular, particularmente en las etapas tempranas después del ictus. Esta revisión temática se enfoca en avances recientes en la terapéutica del ictus asociado a FA e identifica direcciones futuras de investigación.

Introduction

Atrial fibrillation (AF) is common, affecting an estimated 37.6 million individuals globally in 2017\(^1\), an increase from 33.5 million individuals in 2010\(^2\). The prevalence of AF increases with age, nearly doubling every decade after age 60 years\(^3\). As people are living longer and the ageing population continues to grow rapidly, the prevalence of AF is projected to nearly triple by the year 2050\(^4\). Similarly, the burden of AF posed by the increased risk of cardiovascular disease, heart failure, stroke, cognitive impairment and dementia, and mortality is also expected to increase in parallel over the ensuing decades\(^4\).

The treatment of patients with AF and AF-related stroke is complex, and the burden on patients, caregivers, health-care systems, and society is high. Although there have been significant scientific advances in the area of AF and cardioembolic stroke recently, many key knowledge gaps remain. In this topical review, an overview of AF and AF-related stroke will be discussed, with an emphasis on treatment, prevention, screening, special considerations, and future research directions.

Risk factors for AF and stroke

Increased age and male sex are the strongest non-modifiable risk factors for AF. Male sex is associated with a 1.5-fold risk of developing AF and 2-fold higher incidence compared with female sex\(^5,6\). Although the overall incidence, prevalence, and age-adjusted lifetime risk of AF is higher in men, there are more women than men with AF due to differences in Regarding other non-modifiable risk factors, the literature suggests that white men have a higher incidence of AF; however, black patients have a higher risk of death related to AF and a higher risk of AF-related stroke\(^7\).

Common modifiable risk factors for AF include hypertension, diabetes, obesity, cardiovascular disease, smoking, and alcohol use. Similarly, these same risk factors increase the risk of stroke in patients with AF. Women with AF tend to be older and have more hypertension, hyperlipidemia, and obesity, while men with AF tend to have more coronary artery disease, left ventricular dysfunction, and chronic obstructive pulmonary disease\(^8\).

AF is associated with a 5-fold risk of ischemic stroke\(^9\), one of the most feared and debilitating sequelae of the arrhythmia. AF accounts for approximately 20-25% of all ischemic strokes, though the frequency of AF increases to approximately 40% in ischemic stroke patients ≥ 80 years old\(^9\). Risk factors for stroke in the setting of AF include increased age, female sex, hypertension, heart failure, diabetes, and history of cardiovascular or cerebrovascular ischemic events. Women with AF have a higher risk of stroke compared with men, which is thought to be mediated by increased age and vascular risk factors\(^10-14\). Moreover, AF-related stroke tends to be more severe in women, and more women than men die or are disabled from AF-related stroke every year\(^15\).

Risk stratification schemes, such as the CHA\(_2\)DS\(_2\)-VASc score, assist in assessing the risk of stroke and systemic embolism in AF patients, giving weight to common risk factors (Table 1). The American Heart Association and American Stroke Association guidelines recommend using the CHA\(_2\)DS\(_2\)-VASc score for risk stratification to guide the use of anticoagulants for the prevention of stroke and systemic embolism\(^16\).

Mechanisms and clinical presentation of stroke in AF

AF is characterized by irregular atrial activity, resulting in abnormal and irregular atrial contractions. Several factors, such as enlarged atrial size, atrial fibrosis, chronic inflammation, and upregulation of ion channel subunits, contribute to the development and maintenance of AF. Irregularities in atrial contraction associated with AF increase the risk of stasis of blood flow and thrombus formation, thereby predisposing to stroke and systemic embolism. Over 90% of thrombi secondary to AF arise from the left atrial appendage\(^17\). There is emerging evidence suggesting that atrial cardiopathy, characterized by structural, contractile, architectural, or electrophysiological changes within the atria, may contribute to stroke through thrombus formation even in the absence of AF\(^18,19\). The lack of temporal association between implantable device-detected AF and stroke events supports the notion that the thrombi may arise from the dysfunctional atria and atrial appendage rather than from the AF itself\(^20,21\). In some cases, the stroke itself may contribute to the development of AF, and AF detected after stroke may have a different risk profile for recurrent thromboembolic events\(^19,22\).

AF can be paroxysmal or sustained; however, the risk of stroke is similar regardless of AF type. Although generally considered a “silent” condition, up to 60% of individuals report symptoms such as fatigue, dizziness, palpitations, dyspnea, chest pain, generalized weakness, and other less common symptoms\(^23\). Women tend to be more symptomatic compared with men and they report higher burden of symptoms and lower quality of
life compared with men. Accordingly, women are more likely than men to seek care for AF. Given the relatively silent and potentially paroxysmal nature of AF, it can be challenging to detect. It is estimated that approximately 13% of individuals with AF have undetected AF.

In up to 37% of cases, stroke is the first sign of AF. The symptoms of stroke secondary to AF are characterized by the sudden onset of neurological deficits that are typically maximal at onset. The course of symptoms is less likely to be progressive or stuttering as is sometimes the case in strokes due to small or large vessel disease. Patients with AF-related stroke present with greater severity and higher frequency of large vessel occlusion strokes compared to strokes from other causes.

Infarct patterns in AF-related stroke include large territory wedge-shaped infarcts and/or smaller multifocal infarcts in multiple arterial territories (Fig. 1). In addition, patients with AF tend to have a higher burden of white matter hyperintensities and evidence of cerebral small vessel disease, including microhemorrhages. Vessel imaging in the acute stroke setting may show large vessel occlusion. Hemorrhagic transformation of the infarcted tissue is more common in cardioembolic strokes, likely due to larger infarct size and increased patient age.

### Treatment and outcomes of AF-related stroke

Population-based studies in the US and Canada suggest that ischemic stroke admissions with comorbid AF have been steadily increasing over the past decade. Thrombolytic therapy and endovascular therapy remain the hallmark of acute ischemic stroke treatment for eligible patients, regardless of the presence of AF. One caveat is that patients with known AF who are on anticoagulation for stroke prevention may not be eligible for intravenous thrombolysis, thus endovascular therapy may be the only acute treatment option. In addition, blood pressure management, heart rate and rhythm control, and management of post-stroke complications are crucial to in-hospital treatment of AF-related stroke. Several studies have shown that rate control is not inferior to rhythm control regarding cardiovascular outcomes and mortality for the treatment of AF, and the focus of this section will be the use of anticoagulants for stroke prevention.

### Oral anticoagulants (OACs) for secondary stroke prevention

Initiation of anticoagulation therapy in patients with AF-related stroke is paramount for secondary stroke prevention. Decision-making in this setting is challenging, given the risk of hemorrhage in the immediate post-stroke period, weighed against the risk of recurrent ischemic stroke, or other ischemic events. The estimated risk of a recurrent ischemic stroke is 1.5% per day in the first 2 weeks after an acute stroke, while the risk of any radiographic hemorrhagic

### Table 1. The CHA2DS2-VASc score components and estimated yearly risk of stroke and systemic embolism

<table>
<thead>
<tr>
<th>CHA2DS2-VASc Risk Factor</th>
<th>Points</th>
<th>CHA2DS2-VASc Score</th>
<th>Yearly risk of ischemic stroke (%)</th>
<th>Yearly risk of stroke/TIA and systemic embolism (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>+1</td>
<td>0</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+1</td>
<td>1</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Age &lt; 65 years</td>
<td>0</td>
<td>2</td>
<td>2.2</td>
<td>2.9</td>
</tr>
<tr>
<td>Age 65-74 years</td>
<td>+1</td>
<td>3</td>
<td>3.2</td>
<td>4.6</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>+2</td>
<td>4</td>
<td>4.8</td>
<td>6.7</td>
</tr>
<tr>
<td>Diabetes</td>
<td>+1</td>
<td>5</td>
<td>7.2</td>
<td>10.0</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>+1</td>
<td>6</td>
<td>9.7</td>
<td>13.6</td>
</tr>
<tr>
<td>Male sex</td>
<td>0</td>
<td>7</td>
<td>11.2</td>
<td>15.7</td>
</tr>
<tr>
<td>Female sex</td>
<td>+1</td>
<td>8</td>
<td>10.8</td>
<td>15.2</td>
</tr>
<tr>
<td>Stroke/TIA/thromboembolism</td>
<td>+2</td>
<td>9</td>
<td>12.2</td>
<td>17.4</td>
</tr>
</tbody>
</table>

Adapted from Friberg et al. 2012. TIA signifies transient ischemic attack.
transformation ranges from 3.2% to 44% in the first 5 days depending on the use of thrombolytic therapy

Vitamin K antagonists (VKAs) and direct OACs (DOACs) are the mainstay of stroke prevention in patients with AF, each with their unique set of advantages and risks (Table 2)32-36. Although VKAs, such as warfarin, have been used for decades and are associated with a two-thirds relative risk reduction of stroke and systemic embolism compared with aspirin, the need for constant serum level monitoring and multiple food and drug interactions makes warfarin difficult to use. Patients with AF on warfarin tend to have suboptimal time in the therapeutic range37, and women tend to be more at risk of stroke than men while on warfarin due to differences in metabolism5.

DOACs, such as dabigatran, rivaroxaban, apixaban, and edoxaban, have emerged into clinical practice in the past decade. DOACs are as effective, if not more effective, than warfarin for stroke and systemic embolism prevention33-36. In addition, DOACs have a more favorable safety profile and do not require constant blood level monitoring, making them easier to use. In 2019, the American College of Cardiology and American Heart Association published updated guidelines recommending DOACs as first line for eligible patients with AF23. The main contraindication to DOACs includes patients with mechanical heart valves and moderate-to-severe mitral valve stenosis23.

Timing of initiation of OACs

The timing of initiation of OACs for secondary stroke prevention after acute stroke depends on many factors, mainly the size of the infarct and the presence of hemorrhage on brain imaging. One decision-making algorithm is illustrated in figure 2. As patients with recent ischemic stroke were excluded from the clinical trials on anticoagulation, much of the evidence is based on observational studies and robust evidence is lacking in this patient population. The AHA/ASA guidelines suggest initiation of OACs immediately after TIA and 14 days after acute ischemic stroke event in most cases, apart from very large infarcts (defined as either NIHSS > 15 or an infarct involving the complete territory of a vessel) with severe hemorrhagic transformation in which delaying OAC initiation beyond 2 weeks is reasonable. European guidelines from the pre-DOAC era suggest a more granular approach to initiating OACs depending on stroke severity, recommending initiation of OACs 1 day after a transient ischemic attack, 3 days after minor stroke (NIHSS < 8), 6 days in mild stroke (NIHSS 8-15), and 12 days after severe stroke (NIHSS > 15)38.

Data from observational studies suggest that in clinical practice, DOACs are started on average 4-11 days after ischemic stroke. Early start of DOACs in these studies was associated with an average risk of intracerebral hemorrhage (ICH) of 2.2% per year, which was 3-fold lower than the risk of ischemic stroke events over the same time39.

Despite current guidelines, an estimated 50% of patients with acute stroke and AF are discharged from the hospital without OAC, with evidence of sex and race/ethnic differences in OAC utilization40. Risk of bleeding, risk for falls, and goals of care (comfort measures/hospice care) are commonly cited reasons for not starting OACs at stroke hospital discharge, and the rate of OAC use may increase over time after hospital discharge.

At present, there are several randomized controlled trials underway evaluating various OAC initiation
Table 2. Oral anticoagulants recommended for stroke prevention in AF

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Benefits</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K antagonists</td>
<td><strong>67% relative risk reduction versus aspirin</strong> 26% reduction in mortality versus aspirin Can be used in patients with mechanical valves and mod-severe mitral stenosis Point of care confirmation of anticoagulation Reversible</td>
<td>Significant food and drug interactions Need for blood level monitoring Suboptimal time in therapeutic range Low patient adherence</td>
</tr>
<tr>
<td>Warfarin</td>
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<td></td>
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<tr>
<td>Direct oral anticoagulants (DOACs)</td>
<td><strong>About 19% relative risk reduction compared with warfarin</strong> 10% reduction in mortality compared with warfarin Easy to use, less food/drug interactions Lower rates of hemorrhage Reversible</td>
<td>Contraindicated in mechanical valves and moderate-to-severe mitral stenosis Reversal agents less readily available, costly Caution in renal and hepatic impairment</td>
</tr>
<tr>
<td>Direct thrombin inhibitors</td>
<td></td>
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<td>Dabigatran</td>
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<tr>
<td>Factor Xa inhibitors</td>
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<tr>
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<td></td>
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<tr>
<td>Rivaroxaban</td>
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<tr>
<td>Edoxaban</td>
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</table>

**Figure 2.** One evaluation and management algorithm for decision-making in patients with acute stroke with indications for anticoagulation. AC: anticoagulation; OAC: oral anticoagulation; CAA: cerebral amyloid angiopathy; CMB: cerebral microbleed; HAS-BLED: Hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile INR, elderly, and drug/alcohol usage; ICH: intracerebral hemorrhage; IVC: inferior vena cava; DVT: deep venous thrombosis; PE: pulmonary embolism; NIHSS: National Institutes of Health Stroke Scale.

protocols after acute ischemic stroke for patients with AF (ELAN, [Switzerland/International NCT03148457]; TIMING [Sweden, NCT02961348]; OPTIMAS [United Kingdom, EduraCT 2018-003859-38]; START [United States, NCT03021928]; and AREST [United States, NCT02283294]).
**Left atrial appendage occlusion (LAAO)**

Since approximately 90% of thrombi in AF arise from the left atrial appendage, LAAO is an attractive approach to secondary prevention in patients with AF in which long-term anticoagulation is contraindicated. The PROTECT AF trial showed non-inferiority of LAAO with the WATCHMAN device compared with warfarin for the endpoint of stroke, systemic embolism, and cardiovascular death. Similarly, the PREVAIL trial showed significantly lower complication rates (2.2%), and non-inferiority of the WATCHMAN device for LAAO versus warfarin for stroke and systemic embolism > 7 days post-randomization. Although there is an upfront risk of periprocedural complications (such as cardiac tamponade) and a long-term risk of ischemic stroke with LAAO, the overall risk seems to be offset by significantly lower rates of hemorrhage in the long-term. In patients with AF undergoing cardiac surgery for other reasons, surgical LAAO has also been shown to reduce the risk of stroke and systemic embolism compared to those randomized not to have LAAO, though the majority of these patients also remained on anticoagulation during follow-up. The updated American and European guidelines indicate LAAO as a Class IIb indication for stroke prevention in AF patients undergoing cardiac surgery or with a contraindication to long-term anticoagulation. It remains challenging to identify those patients at such a high risk of stroke in whom LAAO is preferred to anticoagulation. For example, recent data suggest that even patients with AF and falls, dementia, or microhemorrhages have a relatively low risk of subsequent ICH and a greater risk of recurrent ischemic stroke.

**ICH and anticoagulants in AF**

The management of ICH in patients with AF who require anticoagulation is another challenging scenario, specifically if and when to resume anticoagulants. Observational data suggest that resumption of OAC after ICH is associated with reduced ischemic events and mortality, without a significant increase in hemorrhagic events. Moreover, observational studies suggest that the optimal timing of resumption of OAC after ICH is within 4-8 weeks, depending on individual patient characteristics, the size, and location of the ICH. However, the SoSTART randomized trial of 203 participants in the UK was unable to show non-inferiority for resumption versus avoidance of OAC after ICH (median time 115 days post-ICH): although there was no significant difference in ICH recurrence, the mortality in the start-OAC group was twice that in the avoid-OAC group. Several randomized clinical trials are currently underway and expected to provide more robust data on outcomes after resumption of OAC initiation and LAAO versus best medical care after ICH: ASPIRE (NCT03968393); PRESTIGE-AF (NCT03996772); STATICH (NCT03186729); A3ICH (NCT03243175); and ENRICH-AF (NCT03950076); STROKECLOSE (NCT02830152).

**Screening for AF**

Current US Preventive Services Task Force recommendations state that there is an insufficient evidence to support widespread screening given the low frequency of AF in the general unselected population and in individuals over age 50 years. Nevertheless, significant technological advances over the past decade have yielded newer devices which are easy to use, commercially available and have high sensitivity and specificity for detecting AF. Given that the risk factors for stroke and AF are similar, the role of screening for AF in high-risk populations (increased age and high-risk CHA2DS2-VASc score) has become a recent research focus, especially in post-stroke patients with various stroke subtypes. The CRYSTAL-AF study of cryptogenic stroke patients (mean age 62 years) showed an AF detection rate of 12% at 1 year with implantable loop recorders versus 2% with standard of care. In the EMBRACE trial, also in patients with cryptogenic stroke with a mean age of 73 years, the AF detection rate with a 30-day external monitor was 16% versus 3% in the control group. More recently, the STROKE-AF and PER DIEM studies have shown significantly higher AF detection rates with the use of implantable loop recorders in post-stroke patients with various non-AF stroke etiologies, compared with the standard of care or 30-day external loop recorder monitoring, respectively. Several studies have also shown favorable results in screening high-risk patients for AF in the absence of recent stroke with various protocols, from intermittent electrocardiogram screening to implantable loop recorders. One question that remains to be answered, however, is the amount or burden of device-detected AF that would warrant initiation of anticoagulation. In other words, is the risk-benefit balance the same for a patient with a 30-s episode of AF compared with a patient with > 24 h of AF detected during screening?
Future directions

Significant scientific advances have been made in the past few decades regarding the screening, prevention, and treatment of patients with AF and AF-related stroke. Nevertheless, the prevalence of both AF and AF-related stroke, and the burden associated with each, are steadily increasing with the rapid growth of the ageing population. Several questions remain unanswered and are the focus of ongoing and future clinical trials. First, is screening for AF in high-risk populations for the primary prevention of stroke effective and cost-efficient? Second, what is the minimum burden of device-detected AF necessary to warrant anticoagulation? Third, should all non-AF post-stroke patients be screened for AF with implantable loop recorders, regardless of stroke subtype? Fourth, when is the optimal time to initiate oral anticoagulation in patients with recent AF-related stroke (both ischemic and hemorrhagic stroke)? Finally, the association between AF, stroke, and the development of cognitive impairment and dementia has been well established in observational studies, and the underlying pathophysiological mechanisms, and strategies for prevention, are also the focus of ongoing research.

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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).

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Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective and observational study.

References

Neurological complications of interatrial blocks and Bayes' syndrome

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Abstract

Interatrial blocks (IABs) are a variety of abnormalities in the interatrial conduction. Bayes' syndrome is a clinical entity based on the association between advanced IABs and supraventricular tachyarrhythmias, being atrial fibrillation (AF) the most frequent. Due to its negative effects on left atrial electromechanical function, both IABs and Bayes’ syndrome are associated with thromboembolic phenomena, causing cardiovascular and neurological complications. In regard to neurological involvement, patients with these conditions have an increased incidence of ischemic events, cognitive impairment, and dementia. These observations triggered the question whether the use of early anticoagulation therapy (before the documentation of AF) could prevent thromboembolic events in patients with IABs diagnosis. This review aims to summarize the most recent evidence describing the association of IABs and Bayes’ syndrome with neurological events. Potential early therapeutic options to prevent these undesirable clinical consequences will be also discussed.

Keywords: Interatrial block. Bayes’ syndrome. Stroke. Dementia.

Complicaciones neurológicas en los bloqueos interauriculares y el síndrome de Bayés

Resumen

Los bloqueos interauriculares son una variedad de anomalías en la conducción interauricular. El síndrome de Bayés es una entidad clínica basada en la asociación entre bloqueo interauricular avanzado y taquiarritmias supraventriculares, siendo la fibrilación auricular la más frecuente. Debido a sus efectos negativos sobre la función electromecánica de la aurícula izquierda, tanto el bloqueo interauricular como el síndrome de Bayés se asocian a fenómenos tromboembólicos, provocando complicaciones cardiovasculares y neurológicas. En cuanto a la afectación neurológica, los pacientes con estas condiciones tienen una mayor incidencia de eventos isquémicos, deterioro cognitivo y demencia. Estas observaciones generaron la pregunta de si el uso de la terapia de anticoagulación temprana (antes de la documentación de la fibrilación auricular) podría prevenir eventos tromboembólicos en pacientes con diagnóstico de bloqueo interauricular. Esta revisión tiene como objetivo resumir la evidencia más reciente que describe la asociación del bloqueo interauricular y el síndrome de Bayés con eventos neurológicos. También se discutirán posibles opciones terapéuticas tempranas para prevenir estas consecuencias clínicas indeseables.

Introduction

Interatrial blocks (IABs) include a variety of disturbances in interatrial conduction and are the most frequent and well-known blocks at the atrial level. IAB is more frequently found in elderly patients (with a prevalence of 8% in septuagenarians) and patients with structural heart disease. These rhythm abnormalities result in varying refractory periods and slower conduction velocities within the atrial myocardium, a potential substrate for the development of atrial arrhythmias.

IABs are classified as (Fig. 1):
- Partial IAB (first degree): The ECG shows that the P-wave duration is ≥ 120 ms, and usually is bimodal (“notched”) in leads I, II, III, and aVF.
- Advanced IAB (third degree): The diagnosis is made when a P-wave duration is ≥ 120 ms, and the morphology of the P-wave in the inferior leads (II, III, and aVF) is biphasic or “positive-negative.”
- Intermittent IAB (second degree): IAB may occur transiently on a beat-to-beat basis or associated with changes in heart rate or following pauses induced by premature contractions. The P-wave morphology may show transient morphological changes in the same recording.

Advanced IAB is an increasingly recognized surrogate of atrial dysfunction and a trigger of atrial dysrhythmias, mainly atrial fibrillation (AF). The combination between IAB and supraventricular arrhythmias is known as Bayes’ syndrome.

Recent studies have demonstrated a strong relationship between IAB or Bayes’ syndrome and thromboembolic phenomena, with cardiovascular and neurological consequences. Regarding neurological involvement, patients with IAB or Bayes’ syndrome have an increased incidence of ischemic events, cognitive impairment, and dementia. These observations triggered the hypothesis that the early use of anticoagulation and antiarrhythmic therapy could have benefits in patients with IAB before the documentation of AF.

This review aims to summarize the most recent evidence describing the association of IAB (and Bayes’ syndrome) with neurological events, focusing on stroke, dementia, and cognitive impairment. Potential early therapeutic options to prevent these undesirable clinical consequences will also be discussed.

IABs and stroke

Cardiac embolism is a common cause of ischemic stroke. Pathophysiological mechanisms that can explain the link between IABs and stroke are multiple and are mainly related to the potential development of supraventricular arrhythmias and impaired left atrium contractility.

Advanced IAB was shown to be a significant predictor of both new-onset and recurrent AF. As is known, AF is one of the most frequent causes of stroke and can be detected in nearly 25% of all patients with stroke by sequentially combining different electrocardiographic methods. The rationale for the association between IAB and AF is probably related with atrial remodeling and fibrosis seen in both conditions; in IAB the delayed atrial activation produces an abnormal contraction against a closed mitral valve, increasing left atrium pressure. This leads to progressive dilation, more fibrosis, an increase in pro-inflammatory markers and favors the occurrence of AF.

Furthermore, IAB has shown to be a predictor of embolic stroke even when there is no documentation of AF. In a big-scale study, the incidence of ischemic stroke was more than two-fold in patients with advanced IAB as compared to those without, even after the adjustment for traditional risk factors and symptomatic AF. Similar investigations found a significantly high frequency (between 61 and 80%) of IAB in patients with sinus rhythm and a history of stroke. This link between stroke and IAB in the absence of documented AF (or other atrial arrhythmias) can be explained by the specific electromechanical disorders in this condition. In advanced IAB, depolarization follows a caudo-cranial route, first toward the AV node and then in a retrograde direction through the left atrium resulting in poor left atrial electromechanical function. This impaired functioning of the left atrium can predispose to clot formation and embolic phenomena, even in the absence of other atrial arrhythmias.

The association between advanced IAB and stroke has been demonstrated in different settings and conditions, including the general population, very elderly patients, and patients with high CHADS2 score. Also in patients with a history of an embolic stroke of unknown source, advanced IAB predicted the recurrence of a cerebrovascular event.

The detection of IAB should be considered in the risk stratification of patients in sinus rhythm that are at high risk of stroke, even if they have no documented AF. In addition, in patients that present with ischemic stroke and IAB is present in the ECG, the search for AF must be intensified.

IABs and silent cerebrovascular disease

Clinical implications of silent cerebrovascular disease include an increased risk for future symptomatic ischemic stroke, memory impairment, and cognitive...
In a case–control study, IAB was significantly associated with the incidence of asymptomatic cerebrovascular disease using Magnetic Resonance Imaging (MRI) examination. IAB was present in 59% of the patients with silent brain ischemia. Older age, uncontrolled hypertension, and higher CHA2DS2-VASc were significantly more common in patients with silent vascular disease16.

A cross-sectional study observed an association between advanced IAB and the total burden of asymptomatic cerebral small vessel disease in 499 patients with no documented AF. This association was independent of left atrium diameters, left ventricle ejection fraction, left ventricle wall thickness, and other possible confounding factors. Interestingly, this study constructed a small vessel disease score to better represent the burden of cerebral damage, instead of a single MRI manifestation17.

Screening for IAB might help to improve risk stratification of individuals at an elevated risk of subclinical cerebrovascular diseases.

**IABs and cognitive impairment**

The association of AF with cognitive impairment and dementia has been previously described18. In patients in sinus rhythm with IAB and in those with Bayes’ syndrome the association seems to be very similar. In fact, recently published data confirm the association of P-wave duration with cognitive impairment and dementia19. Pathophysiological mechanisms that explain these associations are probably multifactorial and include symptomatic ischemic stroke and silent cerebral infarcts, but also hemorrhages and hypoperfusion due to hemodynamic alterations that lead to reduced cardiac output and decreased diastolic cerebral arterial flow4,20.

In the prospective BAYES registry, which included patients aged 70 years and older with structural heart disease in sinus rhythm, an association (independent of age, sex, and other confounding factors) between IAB and cognitive impairment was found5. Interestingly, the relationship between IAB and cognitive impairment was also present during follow-up and was independent of AF and the history of stroke.

The Advanced Characterization of Cognitive Impairment in Elderly with IABs (CAMBIAD study) was a case–control multicenter study conducted in 265 subjects aged 70 years and older in sinus rhythm without significant structural heart disease. This study included 143 cases with mild cognitive impairment (Mini-Mental State Examination score 20-25) and 122 controls with normal cognitive
function. Patients with cognitive impairment had longer P-wave duration, higher prevalence of IAB, and higher prevalence of advanced IAB when compared to controls. IAB was independently associated with mild cognitive impairment, both for partial and advanced IAB but with a stronger association in the case of advanced IAB. An association with dementia has also been suggested, particularly in patients with advanced IAB. In the Cardiac and Clinical Characterization of Centenarians study, the prevalence of dementia progressively increased when passing from normal P-wave, to partial IAB, advanced IAB, and AF. Therefore, a systematic assessment of the cognitive status at baseline and during follow-up in patients with advanced IAB or Bayes’ syndrome should be considered.

**Role of early therapeutic interventions**

The rationale of considering anticoagulation in patients with IAB and no documentation of AF relies on several observations. First, some studies using implantable devices have demonstrated a lack of a clear temporal relationship between cryptogenic stroke and paroxysmal AF, supporting the hypothesis of the importance of a prothrombogenic state in the left atrium, even in the absence of AF. Furthermore, advanced IAB and AF share multiple clinical and pathophysiological similarities; both processes present the same anatomical substrate (fibrotic atrial cardiomyopathy) which can induce blood stasis, hypercoagulation, and more atrial fibrosis. Finally, IABs have demonstrated to be a risk factor for stroke and cerebrovascular diseases even in the absence of AF. There are ongoing studies aiming to compare the efficacy of anticoagulation in patients with advanced IAB with no prior documentation of AF. The results of these studies will allow determining the efficacy of this early therapeutic intervention in patients with advanced IAB and no demonstrated AF. If positive results are
found, a global strategy for anticoagulation to prevent stroke in patients without AF should be considered.

Regarding antiarrhythmic treatment in IAB with no AF documentation the current situation is similar. Considering the clear and strong association of IAB with atrial arrhythmias, the idea of considering antiarrhythmic treatment when IABs are detected seems reasonable. Indeed, this idea was suggested in a small series, and anti-arrhythmic treatment of patients with advanced IAB has shown to reduce AF occurrence. However, no randomized data are available at present times and whether antiarrhythmic treatment should be used to prevent arrhythmias in asymptomatic patients with IAB needs still to be tested in large prospective trials.

Conclusion

The presence of IABs is strongly associated with negative neurological consequences, mainly as a result of cardioembolic events. These conduction abnormalities need to be included in the diagnosis work-up when there is no clear cause for neurological symptoms. The use of early anticoagulation and antiarrhythmic treatment to prevent these undesirable consequences needs to be further evaluated in large trials.

Conflicts of interest

None.

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