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## My point of view

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We are now living in complex times where corruption is criticized and yet practiced daily, where values are spoken about, but human life itself seems to not be respected, where we speak of fraternity and yet we put up walls that separate us, and where we speak of science but put a price and charge for sharing it.

With this Editorial Committee, the Mexican Journal for Neuroscience has attempted for peer evaluation to be practiced on a daily basis, thus seeking that those who consider this publication for making their findings known feel appreciated and not criticized, and evaluated more than put down.

However, clarity in communication, as in science itself, is not reached rapidly, nor does the scope that a publication may have grown exponentially. It is perseverance and daily work that makes the difference.

This Journal is gradually attempting to place itself as a publication of high impact not only in the Spanish-Speaking Neuroscientific Community but also in its whole orb. This is the reason why publications are made in the scientific and academic current language, English.

Every work which is made brick by brick, step by step, and gear after gear may suffer sudden destruction if its value is not appreciated, petty interests appear and its future is non-favorable. However, hope goes beyond life itself and confidence that the goodwill remains continue to exist.

The reader may ask the reason for these remarks. Our country, where considerable advances in health had been reached, especially in the management of women's and infant's health, as well as in the prevention and treatment of cancer; is currently suffering a political

transition that is having a negative impact in that which had already been achieved. Suddenly, and with a simple memorandum, programs disappeared and the health of many that had hope was undermined. The lack of continuity in programs and the little institutional respect result tragic for a country that goes little steps forward and then all at once goes back decades. There is little that those of us who work in the Public Sector can do for changing measures that were taken vertically by the powerful authority, yet we know that by remaining silent, we would be agreeing to be complicit in it.

Many of us have had the experience to live decades, in which the variability in each new government results from changes in emblems, paperwork, and phrases to remember to changes in superiors, directors, secretaries, etc. All of this, is possibly expected and tolerated, but that which is truly preoccupying is that suddenly the health of those most in need is undermined. The actual government prides itself in working for the poor, and yet this sector of the population that we are honored to serve in public hospitals is suddenly the most affected. Those who are not living in our country will probably wonder why they are not raising their voice. The answer is simple: by living marginalized and with little education, they do not demand what they deserve.

This editorial is meant to simply be a reflection, and whoever reads it may or may not agree with it, but I hope that in the search of truth that those of us who write, work on research and mostly education do, infect those who come in making that which is good more solid and that we do not allow changes to tumble it and much less to destroy it.

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# Factores asociados a la enfermedad de Parkinson en pacientes de la Comarca Lagunera, México

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## Resumen

**Introducción:** La enfermedad de Parkinson (EP) es un padecimiento neurodegenerativo progresivo, incapacitante e incurable; en el 90% de los casos es de etiología poligénica y multifactorial. La Comarca Lagunera es la novena zona más poblada de México, está ubicada en el centro-norte; aquí las concentraciones de arsénico, cadmio y plomo superan en 1-3 órdenes de magnitud los niveles aceptables. **Objetivo:** El objetivo de esta investigación fue evaluar la asociación de los factores ambientales en el desarrollo de la EP en esta región. **Material y métodos:** Se incluyeron pacientes y sujetos controles de más de 18 años que aceptaron participar firmando el consentimiento informado escrito, oriundos y residentes de la Comarca Lagunera; el diagnóstico de EP se determinó de acuerdo con los Criterios diagnósticos del Banco de Cerebros del Reino Unido; los controles fueron personas sanas y sin antecedentes de enfermedad neurológica. En todos se realizó una evaluación neurológica completa. **Resultados:** Se incluyeron 204 personas: 60 con diagnóstico de EP y 144 controles; encontramos que el consumo de tabaco, café y té se asociaban negativamente con el desarrollo de EP, en tanto que la ubicación de la vivienda, la fuente del agua de consumo, y el contacto con pesticidas y plomo no mostraron asociación. **Conclusiones:** En concordancia con otros estudios, el tabaquismo, el consumo de café y de té se asociaron negativamente al desarrollo de EP, en tanto que el consumo de agua de pozo, exposición a pesticidas y/o plomo, y tipo de vivienda rural no tuvieron asociación; así, su presunta participación como «detonadores» de la enfermedad sigue siendo controvertida.

**Palabras clave:** Enfermedad de Parkinson. Factores ambientales. Área de la Comarca Lagunera.

## Factors associated with Parkinson's disease in patients from the Comarca Lagunera, Mexico

### Abstract

**Introduction:** Parkinson's disease (PD) is a progressive, incapacitating and incurable neurodegenerative disease; in 90% of cases its etiology is polygenic and multifactorial. Comarca Lagunera is the ninth most populated area of Mexico, located in

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the center-north; its concentrations of arsenic, cadmium and lead exceed in 1-3 orders of magnitude acceptable levels. **Objective:** To evaluate the association of environmental factors with the development of PD in this region. **Materials and Methods:** Patients and controls were more of 18 years old, they agreed to participate with the signature of the informed consent; they were natives and residents of Lagunera region; PD diagnosis was made according Diagnostic Criteria of the Brain Bank of the United Kingdom; controls were healthy people without history of neurological disease. All of them underwent neurological evaluation. **Results:** 204 people were included: 60 persons with PD diagnoses and 144 controls; consumption of tobacco, coffee and tea were associated to negative effect to develop PD, while rural housing, source of water consumption, and the exposition to pesticides and lead were not associated to PD. **Conclusions:** In accordance with other studies, smoking, consumption of coffee and tea were protective factors for the development of PE, while consumption water well, exposure to pesticides and/or lead, and rural housing were not associated to PD; so, their presumed participation as “triggers” of the disease remains controversial.

**Key words:** Parkinson's disease. Environmental factors. Comarca Lagunera area.

## Introducción

La enfermedad de Parkinson (EP) se considera, dentro de los padecimientos neurodegenerativos, la más frecuente después de la enfermedad de Alzheimer. Es una enfermedad progresiva, incapacitante e incurable; sin embargo, la calidad de vida y la expectativa han mejorado con los tratamientos actuales<sup>1</sup>. La prevalencia estimada de la EP es del 0.3% en población general y del 3% en mayores de 60 años. En México la prevalencia varía de 40 a 50 casos por 100,000 habitantes/año<sup>2</sup>.

En el 10% de los casos el origen es genético, de transmisión mendeliana; la gran mayoría, el 90%, se cataloga como EP esporádica, definida como poligénica y multifactorial. La hipótesis ecogenética explica la interacción entre ambos tipos<sup>3,4</sup>.

La Comarca Lagunera es la novena zona más poblada de México, ubicada en el centro-norte incluye parte de los Estados de Coahuila y Durango, y debe su nombre a los cuerpos de agua alimentados por los ríos Nazas y Aguanaval, ahora remplazados por las presas Lázaro Cárdenas y Francisco Zarco<sup>5</sup>. El agua tiene los siguientes usos: agrario (89%), público urbano (7%), pecuario (2%) e industrial (2%). El 60.6% se extrae del subsuelo y el resto de aguas superficiales (Comisión Nacional del Agua [CNA], 2005)<sup>6-8</sup>. Dada la diversidad de contaminantes ambientales en la Comarca Lagunera, se debe analizar si dichas condiciones participan en la presentación de la EP<sup>9</sup>.

Si bien la predisposición genética es relevante en la EP los detonantes parecen ser ambientales, mismos que aún faltan por identificar<sup>10</sup> para cada población. Los factores de riesgo reconocidos para desarrollar EP son: la edad mayor a 60 años<sup>11</sup>, el sexo (varones)<sup>12</sup> y el efecto protector del tabaquismo<sup>13</sup>, la ingesta de café o té<sup>14,15</sup>; otros factores de riesgo menos claros son el

traumatismo craneoencefálico<sup>16</sup>, el consumo de alcohol<sup>17,18</sup>, vivir en comunidades rurales, el contacto con herbicidas o pesticidas, la ingestión de agua de pozo<sup>19</sup>, la exposición a metales (manganeso<sup>20</sup>, plomo<sup>19</sup>, y arsénico<sup>21,22</sup>), la dieta<sup>23,24</sup> y el uso de tamoxifeno<sup>25</sup>. El uso de levodopa y su impacto en el curso de la EP sigue siendo controvertido<sup>26</sup>.

La Comarca Lagunera es la región más afectada de México por el hidroarsenicismo agudo. En 1962 en Torreón se notificaron 40 casos graves y una defunción; actualmente se manifiesta como hidroarsenicismo crónico endémico<sup>27,28</sup>. Las concentraciones de arsénico, cadmio y plomo en la región superan en uno, dos y hasta tres órdenes de magnitud los niveles considerados como aceptables para sitios contaminados, lo que incrementa los riesgos de efectos adversos en la salud en las poblaciones vecinas<sup>11</sup>.

El objetivo de esta investigación fue evaluar la asociación de los factores ambientales en el desarrollo de la EP en una población del norte (Comarca Lagunera) de México.

## Material y métodos

Se realizó un estudio observacional, transversal, analítico, comparativo y abierto. La muestra de casos se obtuvo de manera consecutiva en la consulta externa del Servicio de Neurología de la Unidad Médica de Alta Especialidad n.º 71 del IMSS, unidad de concentración de pacientes de la Comarca Lagunera. Se incluyeron pacientes de más de 18 años, oriundos y residentes de la Comarca Lagunera, con diagnóstico de EP de acuerdo con los Criterios diagnósticos del Banco de Cerebros de la Sociedad de la enfermedad de Parkinson del Reino Unido (UKPDSBB)<sup>29</sup> y que aceptaron participar en el estudio firmando el consentimiento informado. Las personas controles fueron acompañantes

de las salas de espera de consulta externa y seleccionadas por aleatorización simple, sin antecedente o enfermedad neurológica y por lo demás con las mismas características demográficas que los pacientes con EP y que aceptaron participar en el estudio firmando el consentimiento informado.

En todos se realizó una evaluación médica neurológica completa. Los enfermos con EP se estratificaron de acuerdo con la *Unified Parkinson's Disease Rating Scale* (UPDRS)<sup>30</sup>. El análisis de la información fue procesado mediante el SPSS® 15, se realizó estadística descriptiva y razón de Momios (RM) e intervalo de confianza (IC) del 95%.

## Resultados

Fueron incluidos 204 individuos, de los cuales 60 tenían el diagnóstico de EP de acuerdo con los criterios del UKPDSBB y 144 personas clínicamente sanas; todos los participantes tenían su residencia en el área de la Comarca Lagunera durante al menos 5 años en el momento del estudio; se clasificaron por grupos etarios, en décadas. En el grupo de controles se observa que son significativamente más jóvenes. Analizados por sexo, antecedente familiar de EP y tipo de vivienda no se observaron diferencias (Tabla 1). El tiempo de evolución de la enfermedad fue de 1 a 30 años, media de  $7.5 \pm 6.24$  años. A excepción de la edad, los grupos eran comparables. Obtener la anuencia de personas sin EP mayores para participar en el estudio fue una limitación en este trabajo, por otro lado, y como fortaleza de la investigación, la relación casos/controles fue 1:2.4.

Se analizaron los factores asociados a la EP (Tabla 2); de este análisis destaca que el consumo de tabaco, de café y de té estuvo asociado a un efecto protector para desarrollar EP, en tanto que factores ambientales como la ubicación de la vivienda, la fuente del agua de consumo, y el contacto con pesticidas y plomo no mostraron asociación alguna.

A partir de estos datos, evaluamos si el tiempo de consumo de tabaco o la cantidad de ingesta de café o té se asociaron al efecto protector, encontrando que para el tabaco y la ingesta de té hubo una relación estadísticamente significativa (Tabla 3).

## Discusión

El grupo de pacientes estudiados tenían  $62.5 \pm 11.19$  años de edad, había más varones que mujeres, y más o menos una década antes les había sido diagnosticada la enfermedad ( $54.98 \pm 12.03$ ), datos que concuerdan

**Tabla 1.** Características demográficas por grupo

	Casos	Controles	Total
Edad			p=0.04
30 a 40 años	3	24	27
41 a 50 años	4	24	28
51 a 60 años	15	34	49
61 a 70 años	23	38	61
71 a 80 años	12	21	33
81 a 90 años	3	3	6
Total	60	144	204
Sexo			p=0.08
Femenino	31	54	85
Masculino	29	90	119
Total	60	144	204
Tipo de vivienda			p=0.54
Urbana	52	129	181
Rural	8	15	23
Total	60	144	204
Antecedente familiar de EP			p=0.19
Sí	4	4	8
No	56	140	196
Total	60	144	204

EP: enfermedad de Parkinson.

con los estudios epidemiológicos de este padecimiento en diversas poblaciones<sup>31-33</sup>. A excepción de la edad, los controles eran comparables a los enfermos con EP. La relación casos/controles fue 1:2.4, lo que le proporciona robustez al estudio.

Se analizaron algunos factores potencialmente relacionados con la enfermedad; en nuestra investigación el hábito tabáquico se asoció negativamente a la EP (RM: 0.51; IC 95%: 0.28-0.94; p = 0.032), como se ha observado consistentemente en múltiples estudios al respecto<sup>34</sup>; aunque no hay consenso de cómo el tabaquismo protege a la enfermedad, se ha sugerido una relación biológica estrecha entre el receptor nicotínico de acetilcolina y el sistema dopaminérgico estriatal<sup>35</sup>, donde la activación de estos receptores modularía la liberación de dopamina<sup>36</sup>; además parece que la nicotina posee un efecto protector limitando el daño que produce la 1-metil-4-fenil-1,2,3,6-tetrahidropiridina en las neuronas estriatales<sup>37,38</sup>.

Como en otras investigaciones, el consumo de café también se asoció negativamente a la EP (RM: 0.64; IC 95%: 0.51-0.95; p = 0.019)<sup>39,40</sup>, este efecto «beneficioso» se ha atribuido a una acción antagonista selectiva sobre el receptor de adenosina A<sub>2A</sub> en las neuronas estriatopallidales y con ello la atenuación de la neurodegeneración dopaminérgica<sup>41,42</sup>. Análogo a otros estudios<sup>43,44</sup>, el consumo de té tuvo una relación inversa con la EP (RM: 0.64; IC 95%: 0.48-0.85; p = 0.0001).

**Tabla 2.** Factores asociados a la enfermedad de Parkinson (EP)

	N.º EP (%)	N.º controles (%)	RM	IC 95%	Valor de p
Vivienda					
Urbana	52 (86.7)	129 (89.6)	1.2	0.57-2.89	0.628
Rural	8 (13.3)	15 (10.4)			
Fuente del agua					
Pozo	3 (5)	5 (3.5)	1.4	0.338-6.327	0.907
Potable	57 (95)	139 (96.5)			
Tabaquismo					
Positivo	10 (16.7)	47 (32.6)	0.51	0.28-0.94	0.032
Negativo	50 (83.3)	97 (67.4)			
Alcoholismo					
Positivo	12 (20)	19 (13.2)	0.92	0.80-1.62	0.62
Negativo	48 (80)	125 (86.8)			
Consumo de café					
Positivo	33 (55)	52 (36.1)	0.70	0.51-0.95	0.019
Negativo	27 (45)	92 (63.9)			
Exposición a pesticidas					
Positivo	8 (13.3)	12 (8.3)	1.6	0.69-3.71	0.30
Negativo	52 (86.7)	132 (91.7)			
Consumo de té					
Positivo	26 (43.3)	26 (18.1)	0.64	0.48-0.85	0.0001
Negativo	34 (56.7)	118 (81.9)			
Exposición a plomo					
Positivo	5 (8.3)	9 (6.3)	1.23	0.59-2.57	0.55
Negativo	55 (91.7)	135 (93.8)			
Uso de anticonceptivos hormonales					
Negativo	26 (83.9)	50 (92.6)	0.41	0.103-1.683	0.373
Positivo	5 (16.1)	4 (7.4)			

RM: razón de momios.

**Tabla 3.** Relación de tiempo de consumo de tabaco y cantidad de café y té

	Media	Valor de p
Tiempo en años de consumo de tabaco	2.32±6.703	0.006
Casos	7.29±13.273	
Controles		
Tazas estándar de té (236.5 ml)	0.58±0.809	0.001
Casos	0.24±0.594	
Controles		
Tazas estándar de café (236.5 ml)	0.63±0.66	0.39
Casos	0.53±0.78	
Controles		

Este efecto protector se atribuye a sus acciones antioxidante, antiinflamatoria, quelante de hierro, polifenoles, a la teonina y a la cafeína.

La asociación negativa entre tabaco, café y té han sido muy consistentes en diversos estudios y diversas poblaciones, sin embargo, la asociación de EP y eventos

ambientales como exposición a metales, pesticidas, herbicidas, tipo de agua de consumo, vivienda rural y microorganismos no han sido consistentes, por lo que se ha planteado la posibilidad de que dicha exposición sea en edades tempranas<sup>45</sup> y esa sea la razón de tantas discrepancias entre las investigaciones. Nosotros proponemos que los eventos ambientales además sean diferentes en las distintas poblaciones y esta sea otra razón de por qué los resultados no se replican. Como en este estudio, donde la contaminación por metales (arsénico, cadmio y plomo) y del agua han sido documentados en la región geográfica donde se realizó la investigación y, sin embargo, no tuvieron asociación alguna con la EP<sup>9</sup> lo cual deja en entredicho la importancia de los «detonadores» ambientales estudiados en otras investigaciones y su participación en la EP en esta población.

La explicación de la asociación de EP y metales se ha sustentado en algunas evidencias, entre ellas, en que en la sustancia negra de pacientes con EP se ha encontrado mayor cantidad de hierro, cobre y zinc que

en controles, metales que también están presentes en los depósitos amiloides y participan en la formación de placas seniles, ovillos neurofibrilares y están implicados en los procesos de oxidación, la homeostasis del calcio y la muerte neuronal; sin embargo, en los estudios basados en cuestionarios de exposición laboral a metales no se ha hallado la asociación entre exposición laboral a plomo, cobre, hierro, mercurio, zinc o manganeso y el riesgo de EP<sup>46</sup>.

Los habitantes de áreas rurales están estrechamente relacionados con el consumo de agua de pozo y la exposición a herbicidas y pesticidas, que son eventos relacionados al estilo de vida. Un metaanálisis<sup>47</sup> encontró un ligero incremento en el riesgo de desarrollar EP en habitantes de regiones rurales (Riesgo Relativo (RR): 1.17; IC 95%: 1.10-1.24), y consumidores de agua de pozo (Riesgo Relativo RR: 1.30; IC 95%: 1.12-1.51); en este mismo estudio concluyeron que las asociaciones positivas fueron mínimas, que las investigaciones sobre EP y la vida rural, la agricultura y el uso de pesticidas, el gradiente biológico y la temporalidad del inicio de la enfermedad no se han investigado adecuadamente. Y aunque con los pesticidas había una asociación positiva consistente, los resultados carecían plausibilidad biológica, pues ni el gradiente biológico ni el periodo de latencia hasta el diagnóstico de EP después del uso de pesticidas se evaluaron adecuadamente.

Esta investigación tiene algunas debilidades que compartimos con publicaciones similares, la mayoría de nuestros sujetos de estudio (86.7% en EP y 89.6% en controles) eran ciudadanos, con baja frecuencia de exposición a pesticidas (13.3% en EP y 8.2% en controles), y aún más baja frecuencia en el antecedente de consumo de agua de pozo (5% en EP y 3.5% en controles). Sin embargo, a diferencia del café, el té y el tabaco, que de forma consistente están asociados negativamente a la EP, en los resultados de distintas publicaciones sobre el efecto deletéreo de un estilo de vida rural, este no ha sido consistente y el presente estudio abona en ese sentido. Habrá de considerarse que estos factores «detonadores» quizá coparticipen con variantes genéticas específicas de ciertas poblaciones y eso explique resultados diferentes.

Por otro lado, es posible que tanto los sujetos que viven en área rural como los ciudadanos tengan la misma exposición a los metales contaminantes de la región y que por ello no se encuentren dichas diferencias, en cuyo caso deberían verse diferencias en mayor prevalencia e incidencia de la enfermedad en esta región, que no evaluamos en esta investigación.

Otra debilidad fue que los sujetos controles era más jóvenes que los casos, esto aunque se justifica por la dificultad de obtener la anuencia de personas sin EP y mayores para participar en el estudio, debe de tenerse en cuanto a los resultados.

## Conclusiones

En concordancia con otros estudios, el tabaquismo, el consumo de café y té se asociaron negativamente al desarrollo de la EP.

El consumo de agua de pozo, la exposición a pesticidas y plomo, así como la vivienda rural, no tuvieron asociación con la EP, por lo que su presunta participación como «detonadores» de la enfermedad, en concordancia con la literatura científica, sigue siendo controvertida.

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## Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

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# Surgical stress: Cortisol and anxiety in surgeons, patients, and stretcher-bearers

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## Abstract

**Introduction:** Daily stress can cause detrimentally high circulating levels of cortisol. Although habituation to this response can occur, it does not necessarily mean resilience. The operating room may be a natural site for the study of stress. **Objective:** The aim of the present study was to compare the impact of surgical stress in three protagonists of the operating room who play different roles: surgeon, patient, and stretcher-bearer. **Methods:** Twelve triads (patient, stretcher-bearer, and surgeon) of volunteers were selected. Urine samples were taken to determine the level of urinary cortisol as an indicator of stress. The state-trait anxiety inventory (STAI) was applied in all subjects before surgery. **Results:** The statistical analysis indicated that surgeons had the highest urinary cortisol levels, with no difference in cortisol levels between stretcher-bearers and patients. No differences in scores on the STAI-State (which evaluates the level of anxiety in response to a contingency) were found among the three experimental groups, and the lowest STAI-Trait scores (which evaluate anxiety as a personality trait) were found in surgeons. **Conclusion:** These data suggest that surgeons, through years of professional practice, develop a certain degree of resilience to perceived anxiety, but this resilience does not prevent the elevation of biochemical markers of anxiety. Therefore, although outward signs of anxiety are not manifest, strategies should be implemented to reduce anxiety in this group of professionals.

**Key words:** Surgeons. Stretcher-bearers. Surgery. Stress. Urinary cortisol. Anxiety.

## Estrés quirúrgico: cortisol y ansiedad en cirujanos, pacientes y camilleros

### Resumen

**Introducción:** El estrés cotidiano puede causar efectos nocivos relacionados con niveles circulantes elevados de cortisol y aunque pueda ocurrir habituación, no necesariamente significa resiliencia. Es posible que el quirófano sea un sitio natural para el estudio del estrés. **Objetivo:** Se comparó el efecto del estrés quirúrgico en tres protagonistas con diferentes roles. El paciente, el camillero y el cirujano, antes del evento quirúrgico. **Métodos:** Se seleccionaron 12 triadas de voluntarios. Se tomaron

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muestras de orina para determinar el nivel del cortisol urinario como indicador de estrés y el Inventario de Ansiedad Rasgo-Estado se aplicó en todos los sujetos en la primera medición previa a la cirugía. **Resultados:** El análisis estadístico indicó que los niveles urinarios más altos de cortisol correspondieron a los cirujanos y no hubo diferencias entre los camilleros y los pacientes. Mientras que no hubo diferencias en los puntajes de IDARE-Estado (que evalúa el nivel de ansiedad en respuesta a alguna contingencia) entre los tres grupos experimentales, el menor puntaje de la escala IDARE-Rasgo (que evalúa la ansiedad como rasgo de personalidad) se encontró en los cirujanos. **Conclusiones:** Lo que estos datos indican es que el grupo de cirujanos a través de sus años de ejercicio profesional ha desarrollado cierto grado de resiliencia a la ansiedad percibida, lo que no impide que sus marcadores bioquímicos de ansiedad se encuentren elevados. Por lo que es recomendable la instrumentación de procedimientos encaminados a reducir la ansiedad (aunque no manifiesta) en este grupo de profesionales.

**Palabras clave:** Cirujanos. Camilleros. Cirugía. Estrés. Cortisol urinario. Ansiedad.

## Introduction

The quality of life of medical staff can be influenced by stressful situations that are related to daily professional pressures. The life expectancies of obstetrician surgeons and gynecologists are lower than other medical specialists<sup>1</sup> and they are subjected to greater stress<sup>2</sup>. Pressure is perceived as low among psychiatrists, and the uncertainty factor is high among neurologists<sup>3</sup>. However, adaptive processes may result in some resilience to the impact of sustained stress<sup>4,5</sup>.

The spontaneous release of cortisol into plasma is a preparatory response of the organism that allows adaptation to the environment and support for stress situations<sup>6</sup>. However, the continuous presence of cortisol in plasma may be a risk factor for cardiovascular disease<sup>7</sup>. Under normal conditions, stress results in allostasis<sup>8</sup>, a normal response of the body to sustained stress in an attempt to regain homeostasis. If the stressful situation is prolonged, then the organism can undergo so-called allostatic overload<sup>9</sup>, which can be detrimental to health.

The operating room can be considered a natural model for studying stress and the body's response to stress. Urinary cortisol levels are modified in stressful situations that are associated with surgery. The surgeon-patient dyad is subjected to different but nonetheless intense stress that is represented by the surgical procedure. The present study investigated cortisol levels and their possible relationship to indicators of anxiety among surgeons, patients, and stretcher-bearers.

## Methods

The present study employed a transversal, quasi-experimental design. Approval of the experimental protocol was obtained from the Research Committee and Ethics Committee of the Center of Medical Specialties of the State of Veracruz "Dr. Rafael Lucio" (CEMEV),

México. Based on the relatively common and safe procedures that were used during surgery, the present investigation was classified by General Health Law and the Official Mexican Standard as Category II. The participants in the study received a detailed explanation of the protocol. Afterward, they signed an informed consent form. The anonymity of all of the participants was rigorously ensured.

## Experimental groups

Three groups were formed, based on non-probabilistic convenience sampling (n = 12/group), with the common experience of having simultaneously participated in the same surgical event. All of the volunteers were male, solely in an attempt to maintain homogeneity of the sample.

The control group consisted of stretcher-bearers with prior experience in the operating rooms of the hospital. Their primary task was to take the patients to the operating room. The group of patients underwent their first surgical intervention experience. All of the patients had received a diagnosis of inguinal hernia. Under epidural anesthesia, they underwent Lichtenstein's inguinal plasty technique. The group of surgeons had at least 7 years of experience and participated directly in the surgical event. All of the surgeons were certified by the Mexican Council of General Surgery.

In all three groups, participants with a history of metabolic disease, corticosteroid intake in the past 6 months, anxiolytic drug intake in the past 3 months, or a history of adrenal gland disease were excluded from the study.

## Sampling and state-trait anxiety inventory (STAI) application

During surgical procedures, the highest degree of expectation is the preoperative period before surgery.

The pre-operative period began at 8:00 AM. Stretcher-bearers who tend the stretchers play a relatively passive role compared with surgeons and patients. These stretcher-bearers follow a plan, but they are aware that unexpected events can occur that would expose them to a high degree of stress. For these reasons, we collected urine samples and applied the STAI during the pre-operative period.

### **Urinary cortisol**

A urine sample was collected in a clean container with volume measurements and without preservatives. The quantitative determination of urinary cortisol was performed using an electrochemiluminescent immunoassay (Elecsys 1010/2010, MODULAR ANALYTICS E170, and COBAS E). The Elecsys apparatus for cortisol analysis is based on the competition principle using a polyclonal antibody that is specifically directed against cortisol. The total duration of the analysis was 18 min. A 20  $\mu$ l sample was incubated with a specific antibody and a labeled ruthenium complex that was derived from cortisol. Depending on the concentration of the factor to be analyzed in the sample and formation of the respective immune complex, the binding site of the labeled antibody is partially occupied by the factor to be analyzed and partially occupied by the ruthenylated hapten. In the second incubation, after adding streptavidin-coated microparticles, binding of the complex to the solid phase occurs through interaction of biotin and streptavidin. The mixture is aspirated into the measuring cell where the microparticles are magnetically captured on the surface of the electrode. The free substances are removed with ProCell. The application of a voltage to the electrode induces chemiluminescent emission that is measured by a photomultiplier. A calibration curve was generated based on two-point calibration and a curve that was obtained from the bar code of the reagent. The reference values for cortisol that were used in the CEMEV and established by Bayer Diagnostics were in the range of 28.5-213.7 g/dl (78.6-589.6 nmol/L).

### **STAI**

The STAI (n.b., the IDARE is the translated and validated version that is used in Mexico)<sup>10</sup> was previously applied successfully among participants of the surgical procedure<sup>11</sup>. The STAI consists of two self-report scales that are designed to measure anxiety as a present state of anxiety (STAI-S [IDARE-E]) and a trait or personality characteristic (STAI-T [IDARE-R]). The STAI-S measures symptoms of

anxiety that a person experiences under a specific situation. The STAI-T measures the frequency with which people usually experience anxiety symptoms as a personality trait. Both scales consist of 20 items that are scored on a Likert scale with four options that range from “not at all” to “too much.” The STAI has high consistency, validity, and reliability (Cronbach’s  $\alpha = 0.83$  for the STAI-T subscale and 0.92 for the STAI-S subscale), in which its elements and scales are closely related to the constructs of the instrument. The scores are classified as the following: 20-31 (very low anxiety), 32-43 (low anxiety), 44-55 (moderate anxiety), 56-67 (high anxiety), and 68-80 (very high anxiety).

Both the stretcher-bearers and surgeons completed the STAI during the pre-operative period while being comfortably seated. The patients completed the STAI in their bed before taking any medication as part of balanced anesthesia, with the exception of analgesics when indicated.

### **Statistical analysis**

The urinary cortisol data and scores on the two STAI subscales did not follow a parametric distribution; therefore, the results were compared using Kruskal-Wallis nonparametric analysis of variance (ANOVA; Statistica 7, Statsoft), followed by the Wilcoxon *post hoc* test. Values of  $p \leq 0.05$  were considered statistically significant. The Wilcoxon test was chosen due to its ability to compare pairs of data that follow a non-parametric distribution. The results are expressed as the mean  $\pm$  standard error of the mean. The graphs were generated using Kaleidagraph 4.0 software.

### **Results**

The ages of the subjects in the study were not significantly different among groups ( $H^2 = 3.465$ ,  $p < 0.177$ ). The mean age of the stretcher-bearers was  $38.1 \pm 2.907$  years (range: 25-50 years). The mean age of the surgeons was  $44.3 \pm 1.884$  years (range: 36-50 years). The mean age of the patients was  $39.8 \pm 2.396$  years (range: 28-50 years). The surgeons had a mean of  $16.0 \pm 1.969$  years of professional experience (range: 7-24 years).

### **Urinary cortisol**

Significant differences were found in urinary cortisol levels among groups ( $H_2 = 7.564$ ,  $p < 0.023$ ). The lowest cortisol level was found in the group of

stretcher-bearers. Urine from patients and surgeons contained higher urinary cortisol levels, which were significantly different between surgeons and stretcher-bearers (Fig. 1).

### STAI-S

The Kruskal–Wallis test showed that the scores on the STAI-S were not significantly different among the three groups ( $H_2 = 4.598$ ,  $p = 0.100$ ). The Wilcoxon *post hoc* test, which was used to compare data by pairs, detected a significant difference (Fig. 2), in which the group of patients had the highest scores on the STAI-S.

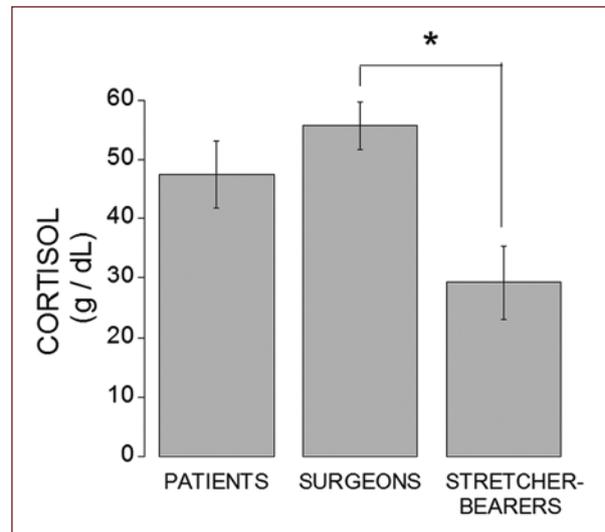
### STAI-T

The Kruskal–Wallis test indicated significant differences in STAI-T scores among the three groups ( $H_2 = 6.333$ ,  $p < 0.042$ ). The surgeons had the lowest STAI-T scores (Fig. 3).

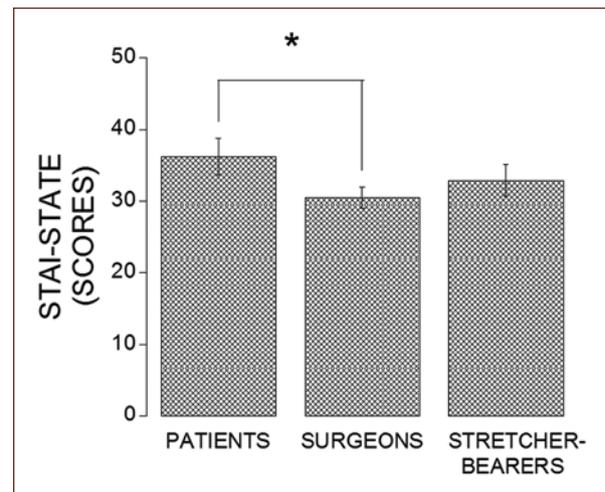
## Discussion

The aim of the present study was to measure and compare urinary cortisol and anxiety levels in individuals who were subjected to surgical stress (stretcher-bearers, patients, and surgeons) before the surgical event. The highest concentration of urinary cortisol was found in surgeons. The patients had slightly higher STAI-S scores. The surgeons had the lowest STAI-T scores.

The measurement of urinary cortisol was performed in the 1<sup>st</sup> h of the morning. In general, the lowest levels of plasma cortisol are detected by midnight, with an abrupt increase in cortisol levels on awakening<sup>12</sup>. This diurnal increase in cortisol levels is associated with the sleep-wake cycle and consists of an increase in plasma cortisol within the 1<sup>st</sup> h after awakening, surpassing the previous level at midnight by 50% and lasting for at least 1 h<sup>13</sup>. This diurnal increase is independent of most daily habits<sup>12</sup> and considered an adaptive vestige<sup>14</sup> that prepares the individual for everyday contingencies. By the time of the present study (8:00 AM), the cortisol measurements may have still reflected this circadian activity of cortisol levels and thus a preparatory response to stress. The stretcher-bearers had the lowest cortisol levels, which may be related to the burden of stress to which they would be subjected. The stretcher-bearer group is presumably less stressed than patients and surgeons. Cortisol has been considered a marker of stress<sup>15</sup>, considering other markers that are

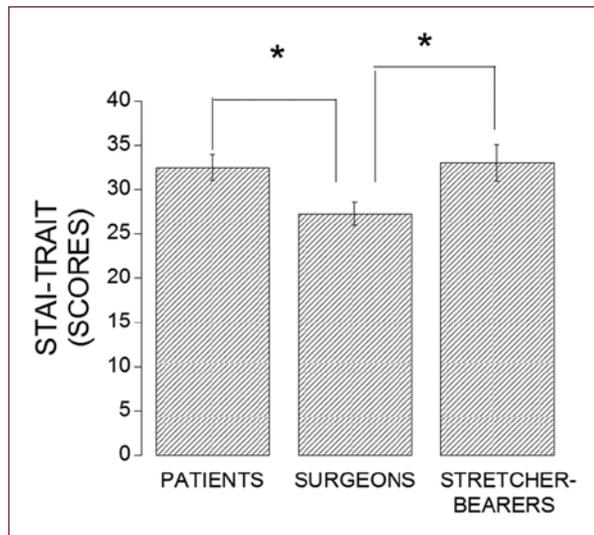


**Figure 1.** Urinary cortisol. Significant differences were found between surgeons and stretcher-bearers ( $*p < 0.007$ , Wilcoxon test). The highest levels of urinary cortisol were found in the group of surgeons.



**Figure 2.** State-trait anxiety inventory-S scores. The nonparametric analysis of variance indicated no significant differences among groups. The Wilcoxon *post hoc* test detected higher scores in patients than in surgeons ( $*p < 0.008$ ), with no significant difference between patients and stretcher-bearers or between surgeons and stretcher-bearers.

related to the activity of the autonomic nervous system, mainly catecholamines and their derivatives. In the present study, we did not evaluate activity of the autonomic nervous system. Although there was a significant difference among groups, the levels of urinary cortisol



**Figure 3.** State-trait anxiety inventory-T. Significant differences were found among groups. The surgeons had lower scores than patients ( $*p < 0.01$ , Wilcoxon test) and stretcher-bearers ( $*p < 0.02$ , Wilcoxon test).

that was found in the present study were within normal limits in the three groups. The highest concentration of cortisol was found in the group of surgeons.

When confronting a threatening situation, the first components that the individual faces are anxiety and fear. To successfully cope with the situation, a fundamental aspect is learning, which gives rise to an emotional process that ultimately leads to the choice of the best coping response. Emotional memory allows an individual to recognize signs of the environment and compare them with previous experiences to select the most appropriate response to resolve the threatening situation<sup>16,17</sup>. Both processes, learning, and selection of the best response, appear to be regulated by portions of the temporal and frontal lobes and deeper structures, such as the hippocampus and amygdala and their connections to the prefrontal and orbitofrontal cortices<sup>18-21</sup>, among other connections<sup>22</sup>. Cortisol can regulate interconnections between the amygdala and medial prefrontal cortex, in which high levels of cortisol exert a strong negative action on these connections<sup>23</sup>. In the present study, cortisol levels fell within the physiological range, and these levels may be related to a healthy response of the organism. The actions of cortisol mediate suppressive actions in some cases and preparatory actions in others<sup>24,25</sup>.

Natural stress improves immune function, but prolonged stress is associated with a deregulatory action of the immune system and promotes the inflammatory

process<sup>26</sup>. Despite some beneficial actions of cortisol, a prolonged increase above certain levels can produce negative effects on the body. Some negative effects include high plasma glucose concentrations, high blood pressure, high fluid retention, muscle weakness, obesity, and extreme fatigue.

The activation of regulatory structures of the emotional response and response to threatening situations depend on such factors as the nature of the stressor, the gender of the subject, and particularly prior experience<sup>27</sup>. In medical students, low levels of cortisol are detected during the day, and high levels occur during the afternoon on the day of scholastic tests and remain elevated even after the test, indicating some adaptive capacity<sup>28</sup>.

The STAI has been successfully applied among surgeons, demonstrating its sensitivity to the detection of anxiety and showing that stress can produce problems with surgical execution even in a surgical simulator<sup>29</sup> and even after “mental” training that is used to reduce stress in young surgeons<sup>30</sup>. In another study that explored changes in autonomic activity, a strong correlation was found between high levels of autonomic activity and high anxiety scores on the STAI<sup>11</sup>. In the present study, the scores on the STAI-S and STAI-T indicated that all three groups had very low anxiety to low anxiety, although the group of surgeons had the lowest scores on the STAI-T. Notably, STAI-T measures anxiety as a personality trait. Surgeons seemingly become adapted to the stressful stimulus that is represented by the surgical procedure.

One notable paradox was observed in the present study. The surgeons had the highest levels of cortisol while also having the lowest levels of anxiety on the STAI-T. This indicates that a process of adaptation to the stressful stimulus likely occurred, but cortisol levels remained high. In certain situations and depending on prior experience, a subject can develop resistance to threatening situations and is able to adequately manage such situations, which is known as resilience<sup>5</sup>. In the long term, these adaptive changes are beneficial for the organism and allow for proper responses to threatening situations<sup>31</sup>. A clear example is an individual who is at constant risk<sup>32</sup>, which indicates that in a prolonged stressful situation, the individual is able to adapt to stressful situations and maintain his activity within reasonably acceptable limits.

Surgery is stressful. Although strategies to cope with stress are scarce, establishing structured training for stress management is suggested among surgical students<sup>33</sup>. A study by the American College of Surgeons

found a positive correlation between the number of hours worked and the presence of burnout, particularly for those who worked more than 80 h/week<sup>34</sup>. The greatest impact of stress depends on the time of exposure and not necessarily on the stressor itself. Therefore, the inclusion of short periods of rest has been recommended<sup>35,36</sup>. Surgical stress is inevitable, and certain strategies can be developed that minimize perceived stress and maintain work activity within acceptable limits.

## Conclusion

Surgeons experience a considerable degree of stress, reflected by biochemical markers of stress (i.e., cortisol), but they appear to develop resilience and the proper management of anxiety. Nonetheless, this does not exclude the possibility that there can be some degree of damage from high cortisol levels in the long term.

## Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

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## Practical considerations for integral approach of people with intellectual disabilities

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### Abstract

People with some disability have worse health prognosis due to biological complications, inadequate access to health services, higher economic expenses, and difficulties in the communication of sensations and perceptions. Therefore, therapeutic strategies and the knowledge generated through scientific research are useful to improve their quality of life. This review addresses the most relevant issues for professionals who are interested in this field, offering the most accepted definition with its implications up to the description of the conditions that should be considered when giving a treatment, conducting research, raising public policies, modifying the health schemes, and availability of supports, among others. For this, the different domains of intellectual capacity, as well as the affected biological systems, are presented to carry out practical actions and generate objective knowledge that enhances the quality of life of people with intellectual disabilities.

**Key words:** Intellectual disability. Health. Therapeutic. Approach.

### Consideraciones prácticas para el abordaje integral de personas con discapacidad intelectual

#### Resumen

Las personas con discapacidad intelectual tienen un mal pronóstico de salud por las complicaciones biológicas, el acceso limitado a servicios de salud, mayores gastos económicos y dificultades en la comunicación de sensaciones y percepciones. Por ello, las estrategias terapéuticas, así como el conocimiento generado a través de investigaciones científicas, son determinantes para mejorar su calidad. La presente revisión aborda los temas más relevantes para profesionales que se interesan en este campo, ofreciendo la definición más aceptada con sus implicaciones hasta la descripción de las condiciones que deben considerarse al momento de dar un tratamiento, realizar investigaciones, plantear políticas públicas, modificar los esquemas de salud y disponibilidad de apoyos, entre otros. Para ello se presentan los diferentes dominios de la capacidad intelectual, así como los sistemas biológicos afectados, a fin de realizar acciones prácticas y generar conocimiento objetivo que mejore la calidad de las personas con discapacidad intelectual.

**Palabras clave:** Discapacidad intelectual. Salud. Tratamiento. Abordaje.

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## Introduction

Disability is a condition that impacts both individually and collectively, in areas as diverse as health, economy, administration, and politics, due to the implications for both the individual and the family and society that surround it<sup>1</sup>. People with disabilities tend to have the worst health scenarios and insufficient access to health-care services, with respect to the general population. They present high rates of health risks including physical inactivity, obesity, smoking, and inadequate emotional support. They also have a high prevalence of chronic conditions such as diabetes, high blood pressure, arthritis, chronic pain, and heart disease. The combination of these conditions makes persons with disabilities vulnerable to a continuous detriment in their functioning and quality of life, making this issue a matter of social interest<sup>2</sup>.

The concept of disability is difficult to define since it has not been used consistently throughout history and can be approached from multiple perspectives, from strictly medical and rehabilitation to other social, educational, work, public health, or even moral. Thus, many concepts can fit in “disability”, such as those problems caused by the loss or abnormality of any body part, or limitations in their function, rehabilitation needs, and difficulties in carrying out usual activities in a specific social and temporal context. Other causes could be included, such as the restrictions on social participation, barriers in mobility or social integration, and problems in the development of social roles for physical or mental causes and in the assumption of responsibilities or in the self-management<sup>3</sup>.

At present, the most accepted definition of disability is from the American Association of Intellectual and Developmental Disabilities (AAIDD), termed as the expression of limitations in the functioning of the individual in a social context, which represents a substantial disadvantage and often has their origin in a health condition (disorder or disease). It can be stated that disability is a generic term that encompasses deficiencies, limitations in activity, and restrictions on participation. Furthermore, it expresses the negative aspects of the interaction between an individual with health problems and their physical and social environment<sup>4</sup>. In Mexico, according to the NOM-015-SSA3-2012 for comprehensive care for people with disabilities, it is defined as hearing, intellectual, neuromotor, or visual impairment, whether permanent or temporary, which limits the ability to perform one or more daily life activities (Fig. 1). For the present review, the one of interest is the intellectual

disability characterized by limitations in mental functioning and the adaptive behavior of the environment<sup>5</sup>.

## Intellectual disability

During the past 200 years, the concept of intellectual disability has evolved from being imbecility to mental weakness, mental disability, and subnormality. At present, it is identified with the widespread use of the concept of “mental retardation” although it is being replaced by intellectual disability<sup>6</sup>. Over the years, numerous definitions of intellectual disability have been proposed, reviewed, and analyzed, due to it is a condition approached by professionals from diverse disciplines and, therefore, with very different perspectives. Medicine was one of the first professional areas that dealt with intellectual disability; consequently, the earlier definitions accentuated the biological or medical criteria. However, for other disciplines such as education or different therapies, these were not particularly useful. Besides, the culture also affected the way of interpreting disability. These observations led to the need to identify the universal aspects of disability considering the cultural and linguistic differences, integrating them in the development of a definition and classification of disability<sup>7</sup>.

Having a unified and international definition and classification of intellectual disability are useful for sharing and comparing information through epidemiological, sociological, or statistical studies. At present, it is a classification of health and health-related domains to describe changes in body function and structure, what a person with a health condition can do in a standard environment (their level of capacity), as well as what they do in their usual environment (their level of performance). Finally, health is the element that relates to the previous two.

Changes in the terminology used to define intellectual disability have a differential influence on society. The oldest definitions were based primarily on the concept of the degree of inherited intelligence, establishing criteria about how to measure intelligence and how to utilize the results to classify individuals with intellectual disabilities. Nowadays, the definitions try to change the way people think about intellectual disability. For this, it does not emphasize the disabilities of the individual, but the environment and the necessary support for their learning and for the person to improve the level of quality of life. The accepted definition of intellectual disability from the AADID states that “Intellectual disability is a disability characterized by significant limitations in both intellectual functioning and in adaptive behavior, which covers many everyday social and practical skills. This disability



**Figure 1.** Definition and classification of disability according to NOM-015-SSA3-2012.

originates before the age of 18<sup>8</sup>”. For the application of this definition, some assumptions must be considered:

1. Limitations on current functioning should be taken into account in the context of typical community environments of peers in age and culture.
2. A valid assessment considers cultural and linguistic diversity, as well as differences in communication and sensory, motor, and behavioral factors.
3. Within an individual, limitations often go hand in hand with strengths.
4. An essential purpose of describing the limitations is to develop a profile of the indispensable supports.
5. With appropriate personalized supports over a sustained period, the life functioning of the person with an intellectual disability generally will improve.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines it in total agreement with the AADID, eliminating the use of the Mental retardation concept, providing the definition of the following domains to be considered for evaluation and above all to determine the levels of severity, and also decreasing reliance on the intelligence quotient (IQ) scores for the categories, as was done in the DSM-IV<sup>9</sup>:

1. Conceptual domain (academic): it includes the competence in memory, language, reading, writing, mathematical reasoning, and the acquisition of practical knowledge, among others.
2. Social domain: it implies the recognition of the thoughts, feelings and experience of others, empathy, interpersonal communication skills for friendship, and social criteria, among others.
3. Practical domain: it includes learning and autonomy in different areas of daily life, such as personal care, responsibility, and organization in school or work tasks, money management, leisure time and recreation, and self-control of their behaviors, among others.

The term intellectual disability, on others such as mental retardation, is better aligned with current professional practices that focus on functional behaviors and

contextual factors, provides a logical basis for the provision of individualized supports based on a social framework. It is less offensive to people with disabilities and is more consistent with international terminology. Some authors, under the influence of DSM-IV, still consider as part of the definition of intellectual disability a value equal to or < 70 referring to the intellectual coefficient, as a criterion for diagnosis, which indicates some limitations in intellectual functioning and adaptive behavior. Although intellectual disability exists independently in certain conditions, there are some that frequently present it, such as Down syndrome, Rett syndrome, X-fragile syndrome, autism spectrum disorder, Prader–Willi syndrome, Angelman, Williams syndrome, and inborn errors of metabolism. However, rather than causes of the condition, these conditions do not have a necessary link with the classification criteria and are present in the minority of people diagnosed<sup>10</sup>.

### Epidemiology of disability

The United Nations Organization estimated that there are around 600 million people in the world with different types of disabilities, of which 400 million are in low-income countries and approximately 60 million in Latin America and the Caribbean. On the other hand, the World Health Organization and the Pan American Health Organization (WHO/PAHO) estimates that 6-10% of the general population is people with disabilities. However, the disability affects not only the person but also the family and the community, involving approximately 25% of the total population<sup>11</sup>. Regarding intellectual disability, in particular, it is considered frequent, with an approximate prevalence of 1-4% and a high impact on individual functioning. In Latin America, the prevalence can be 4 times higher due to its association with factors such as malnutrition, obstetric and perinatal complications, prematurity, lead poisoning, and infections of the central nervous system<sup>12</sup>.

The official reports on disability in Mexico come exclusively from the Population and Housing Census, which does not represent a diagnostic measurement but provide data. The 2010 census included an expanded questionnaire that reports to the population that presents some disability, seen this from the focus of limitations in the activity<sup>13</sup>. That is, people with some restriction to attend to personal care, walk and move, listen, talk or communicate, pay attention, see, or with some mental limitation, were counted. Depending on this report, disability reached 5.1% of the total population, that is, around 5,739,270 Mexicans. However, this registry includes many other conditions, which do not allow observing a specific figure of intellectual disability. However, as a public health issue, the underestimation of intellectual disability in Mexico is emphasized. Epidemiological research and not only general census data would confirm the existence of up to 4 million people with intellectual disabilities in Mexico, assuming a prevalence similar to the universal one of 1-4%.

### **Classification of intellectual disability**

Intellectual disability is a heterogeneous condition, so it is essential to evaluate the difficulties and strengths of functioning in each to propose an appropriate therapeutic plan. For this reason, it is important to diagnose it, considering an integral evaluation of the intellectual coefficient and the adaptive level, as well as the evaluation of the functioning of the people who suffer it. For this, it is necessary taking into account not only their health condition (disorder or illness) but also their functions and body structures, their activities and participation in the community, without forgetting their context.

The classification of intellectual disability is a difficult task, which may vary according to the aspect evaluated and the interests of the classification (Table 1). Educators use different terms to designate to the various levels of intellectual disability. For many years, students with intellectual disabilities were classified as educable mentally retarded (EMR) or trainable mentally retarded (TMR), referring to the levels of mild and moderate intellectual disability, respectively. This system did not consider children with severe and profound intellectual disabilities because they were often excluded from public education. Even though at present it is still possible to find the EMR and TMR classifications, most educators consider them inappropriate due to suggest the existence of predetermined limits of intellectual functioning.

Conventionally, IQ scores have been the primary criterion for classifying people with intellectual disabilities as mild, moderate, severe, and profound severity rating.

However, the score of upper and lower limits of each level is set according to the test used, which indicates the lack of accuracy of the intelligence assessments and the importance of the clinical judgment to determine the level of severity. Overtime, the weight of IQ scores has been reduced thanks to the development of other dimensions that show importance in the interaction of people and their environments such as adaptive behaviors and the context of social roles. The classification according to the need for support focuses on the needs of people, with the aim of providing strategies for intervention. The aspects that must be taken into account to classify an individual according to their need for support are the intellectual capacity, adaptive behavior, participation, health, interaction, and social roles. At present, disability, in general, is classified according to the framework given by the International Classification of Functioning, Disability and Health, commonly known as ICF, developed by the WHO to measure the health and disability of the individual. It classifies human functioning considering some components: (1) body functions, referring to the physiological functions of body systems, (2) body structures, anatomical parts of the body such as organs, limbs, and their components, (3) activities and participation, where activity is the execution of a task or action by an individual and participation is involvement in a life situation, and (4) environmental factors that make up the physical, social, and attitudinal environment in which people live and conduct their lives<sup>14</sup>.

### **Problems in health and health care**

People with intellectual disabilities form a heterogeneous population, with different functional levels and needs. Most experiment a stressing time when visiting the health service, due to the difficulties in communicating and correctly processing large amounts of information and technical vocabulary from the health personnel. They may have trouble giving temporary referrals, such as when they feel unwell or when was their last medical visit. They also have problems in expressing “correctly” when they go through states of discomfort or pain and could show it in the form of less adapted behaviors such as screaming, aggression, self-aggression, and hyperactivity, among others. Some people have difficulty processing sound, visual, and even tactile stimuli, being a challenge for them to tolerate situations in which the environment presents a large number of stimuli. For these reasons, it is necessary for health professionals to facilitate collaboration during the therapeutic visit, considering the difficulties that may arise and generate negative behavior<sup>16</sup>.

**Table 1.** Categories used for the classification of intellectual disability

Categories of classification	Description
By etiology	Prenatal causes: <ul style="list-style-type: none"> <li>– Chromosomal alterations</li> <li>– Inborn errors of metabolism</li> <li>– Alterations of brain development</li> </ul> Perinatal causes: <ul style="list-style-type: none"> <li>– Intrauterine disorders</li> <li>– Neonatal disorders</li> </ul> Postnatal causes: <ul style="list-style-type: none"> <li>– Cranial trauma</li> <li>– Infections</li> <li>– Degenerative disorders</li> <li>– Seizure disorders</li> <li>– Toxic-metabolic disorders</li> <li>– Malnutrition</li> <li>– Lack of social environment</li> </ul>
By intellectual capacity	Interpretation according to the IQ score obtained in the Wechsler tests: <ul style="list-style-type: none"> <li>&gt; 130: very superior</li> <li>120-129: superior</li> <li>110-119: high average</li> <li>90-109: average</li> <li>80-89: low average</li> <li>70-79: borderline</li> <li>&lt; 69: extremely low</li> </ul>
According to the need for educational support	<ul style="list-style-type: none"> <li>– Borderline intellectual disability: they show a delay in learning or some concrete learning difficulties. Many children from a disadvantaged socio-cultural environment could be included</li> <li>– Mild intellectual disability: it is the majority group, not clearly deficient. They have greater difficulty with subjects such as reading, writing, and mathematics. Minimal delay in areas in perceptual and motor areas but can develop social and communication skills</li> <li>– Moderate intellectual disability: most show a significant developmental delay during preschool age. When they grow up, the differences in intellectual, social, and general motor development that separates these children from those without disabilities often increase. They present an acceptable motor development and can acquire basic pre-technological skills to perform some work</li> <li>– Severe intellectual disability: in this category, people generally need protection or help, since their level of autonomy, both social and personal, is very poor. They usually present a significant psychomotor impairment. They can learn some communication system, but their oral language will always be very poor and their comprehension very limited. Autonomy in displacement, cleanliness, feeding, and other personal care activities is hardly achieved</li> <li>– Profound intellectual disability: they present a serious deterioration in the sensory-motor and communication aspects. Personal autonomy is seriously affected to the degree of not being able to take care of their physical needs, partially or totally lacking independent mobility, or requiring specialized care 24 h a day</li> </ul>
For support needs	<ul style="list-style-type: none"> <li>– Intermittent: support in “the occasions that are necessary,” characterized by its episodic short-term nature (for example, supports necessary in lifetime transitions such as loss of work or acute medical crises)</li> <li>– Limited: characterized by consistency overtime, time constraint, but not of an intermittent nature, requires fewer support members and less costs than more intense levels of support (e.g., support for transport)</li> <li>– Extended: characterized by performing in some environments (school, work, and home) and has no time limit (long-term support and life in the home)</li> <li>– Total: high intensity characterized by its permanence and nature of life support, usually requires more support members</li> </ul>

IQ: intelligence quotient.  
 (Adapted from Muñoz-Quesada, et al., 2017)<sup>15</sup>.

People with intellectual disabilities have a different profile of health need and higher rates of mortality and morbidity, as well as an increase in the use of health services. Higher rates of prevalence and risk have been found for important diseases such as epilepsy, diabetes, chronic constipation, human immunodeficiency virus, sexually transmitted diseases, gastrointestinal reflux, dementia, gastrointestinal cancer, thyroid disease, osteoporosis, allergies, cerebral palsy,

different genetic syndromes, and genitourinary system diseases, among others<sup>17</sup>. The mental health problems and challenging behaviors that these people show, make them one of the most medicated groups in society<sup>18</sup>.

People with intellectual disabilities have, for various reasons, more risk of presenting medical pathologies compared to people without disabilities (Table 2). This fact is related to different factors such as styles and

**Table 2.** Principal health problems in people with intellectual disabilities and general recommendations

Affected system	Principal problems	Recommendation for health area staff
Respiratory diseases	Pneumonia aspirative	Attention in textures and food consistency in people with severe and profound intellectual disabilities
Cardiovascular diseases	Aortic insufficiency Mitral insufficiency	Prevention of risk factors such as obesity, sedentary lifestyle, high blood pressure, and dyslipidemias
Digestive diseases	Constipation	Promotion of mobility and right hydration with a complete and high-fiber diet
Infectious diseases	Pneumonia Endocarditis Urinary tract infection	Correct washing of hands Consider immune deficits
Genitourinary diseases	Testicular neoplasia in men with severe intellectual disability	General examination of genitalia periodically
Obstetric and gynecological diseases	Dysmenorrhea, menorrhagia, and amenorrhea	Pay special attention to hygiene problems associated with menstruation
Neurological diseases	Epilepsia	Need to use more than one drug for the control of the crisis considering side effects (constipation, gingival hypertrophy, and excessive sedation) and drug interactions with other treatments
Sensory problems	Vision and hearing problems	Revision of auditory ducts
Endocrine diseases	Diabetes <i>mellitus</i> Hypothyroidism	Modify lifestyles such as avoiding inappropriate diets, to prevent obesity and consider the influence of certain psychotropic drugs such as some atypical antipsychotics Have control over the treatment of lithium salts
Oncological diseases	Gastrointestinal neoplasia (esophagus, stomach, and bile ducts)	Avoid high-fat diets and decrease other risk factors such as gastroesophageal reflux and constipation with correct eating habits
Bucodental diseases	Loss of teeth Gingival pathology Malocclusion problems	Correct dental hygiene Dental treatments with fluoride regularly

living conditions (obesity, restricted diets, smoking, and sedentary lifestyle) that predispose them to suffer specific pathologies. Due to abnormalities in brain structure and functioning, people with intellectual disabilities suffer epilepsy more frequently. Finally, certain genetic disorders involve anomalies in the functioning of some organs or systems, either congenitally or over the years.

### **Respiratory diseases**

They represent one of the leading causes of death in people with intellectual disabilities, although many of them can be prevented with primary care. One of the primary respiratory pathologies is pneumonia, very prevalent in the segment of people with severe intellectual disability and those with associated physical problems. In all these cases are frequent feeding problems mainly dysphagia, which leads to a risk of aspiration pneumonia, secondary to choking.

### **Cardiovascular diseases**

Most people with intellectual disabilities suffer from congenital heart diseases (coarctation of the aorta, ventricular, or atrial septal defects) that can be diagnosed at birth or remain asymptomatic until adulthood. Many of these congenital diseases are usually associated with genetic syndromes, the most common being Down syndrome, Turner syndrome or Williams syndrome, and Di George syndrome. However, they can also present non-congenital heart diseases attributable to the presence of other risk factors such as obesity, high blood pressure, and a sedentary lifestyle, prevalent in people with intellectual disabilities.

### **Digestive diseases**

Gastroesophageal reflux affects approximately half of the population with intellectual disability, mainly the

severe type, frail X syndrome, and those who suffer severe scoliosis. Although gastroesophageal reflux is easily treated, the main problem is the difficulty of diagnosis due to the difficulties for explaining the symptoms. Gastroesophageal reflux should be suspected in those who have negative attitudes about food intake, discomfort after eating, self-injurious behavior, cough at bedtime, tooth erosion, iron deficiency anemia, or weight loss. Constipation is also a very prevalent pathology in people with intellectual disabilities (especially for those with severe disabilities), attributable to immobility, hydration deficits, a restricted or low-fiber diet, and anticonvulsant medications<sup>16</sup>.

### **Overweight and obesity**

One of the foremost public health concerns of the 21<sup>st</sup> century is the obesity. 70% of obese adolescents remain obese adults with physiological, psychological, and social consequences<sup>19</sup>. Obesity is associated with a higher incidence of health problems in people with intellectual disabilities, including decreased social, physical, and quality functioning of life, difficulty in establishing relationships and stigma and discrimination between young people with and without disabilities<sup>20</sup>. Obesity in people with intellectual disabilities is one of the many characteristics used to measure inequality in health compared to the general population. It is likely that obesity contributes to increasing disparities, that is, high rates of mortality and undetected health need<sup>19</sup>. In addition to this, people with intellectual disabilities who are obese have an increased risk of diabetes, a situation that it can be exacerbated by the consumption of certain psychotropic drugs, especially some atypical antipsychotics.

### **Infectious diseases**

Infectious diseases in people with intellectual disabilities are more prevalent mainly due to behaviors that may be frequent such as incorrect hand washing or taking things to the mouth, as well as some residential environments and immune deficits characteristic of certain hereditary diseases. Communication difficulties impact whether the diagnosis of infections is delayed or not diagnosed, worsening the prognosis, and increasing the risk of mortality. Examples of frequently underdiagnosed infections in people with intellectual disabilities are pneumonia and endocarditis. In hospital and residential contexts, it is advisable to pay attention to the prevention of infectious pathology through hygienic norms and vaccination, as well as the establishment of

protocols for rapid action against possible contagious outbreaks.

### **Genitourinary diseases**

A higher incidence of prostate and urinary tract cancer has been reported in men with intellectual disability compared to those who do not possess this condition. Furthermore, higher rates of testicular neoplasms have been observed in men with severe intellectual disability, probably due to the more significant presence of genetic alterations in germ cells. For women with intellectual disability problems of dysmenorrhea, menorrhagia, and amenorrhea should be considered, as well as pay particular attention to the hygiene problems associated with menstruation. When it comes to behavior problems in menstruating women, it should always be kept in mind that in the premenstrual stage or during the days of menstruation, discomfort or pain can be associated with self-aggressive or heteroaggressive behaviors (mainly in people with communication difficulties or severe intellectual disabilities). The incidence of cervical cancer in women with intellectual disabilities is very low (mostly in institutionalized settings). However, given that women with intellectual disabilities are increasingly likely to be active on a sexual level, the relevance of screening for cervical cancer in those considered necessary according to their sexual habits should be considered<sup>16</sup>.

### **Neurological diseases**

Epilepsy is a neurological condition, particularly common in people with intellectual disabilities. For this population, prevalence rates range between 20 and 30%, increasing with the severity of the intellectual disability<sup>21</sup>. Studies suggest that approximately one in five people with intellectual disabilities will have epilepsy except for people with Down syndrome in whom the rate is lower with about one in 10 people in adulthood<sup>22</sup>.

### **Sensory problems**

The hearing and vision problems in people with intellectual disabilities are often underdiagnosed, mainly due to the difficulties to realize and express them and the problems of making a careful assessment. These deficits will mean for people with intellectual disabilities a decrease in communication skills and a significant worsening in their quality of life. Ear problems are poorly diagnosed and poorly treated. It must be remembered that a frequent cause of hearing loss is impaction of earplugs in the ear canals<sup>16</sup>.

## Oral problems

The dental treatment is contraindicated in conditions of little cooperation of the patient or parents because it is difficult to obtain a positive result; besides, iatrogenesis in the event of caries and gingival inflammation is likely. Therefore, oral hygiene is the crucial factor that determines whether or not to perform the treatment because the minimal manual ability, accompanied by poor muscle activity, can be very harmful to the patient. Other common obstacles are typical behavior, excessive limb movement, low level of cooperation, and altered nausea reflex. All these affect negatively, from the taking of X-rays and impressions for appliances to the treatment itself. Reports on the oral health of people with intellectual disabilities have identified problems such as poor oral hygiene, untreated caries, and a high prevalence of periodontal disease. In addition to worse overall health, people with intellectual disabilities experience more difficulties in obtaining dental care than people in the general population, with a significant proportion of teeth extracted and a higher prevalence of traumatic dental injuries. A good promotion of oral health can reduce the burden of diseases such as dental caries, gingivitis, and periodontal disease that is among the highest secondary conditions in people with intellectual disabilities that cause limitations in their daily activities. The oral health of these people in many cases depends on a large extent on the knowledge, attitudes, and practices of their family members or care providers. Motor impairments are a limiting factor for access to treatments<sup>23</sup>.

## Conclusions

The approach to intellectual disability, whether to define a therapeutic strategy or design a research protocol, is a multifaceted process. This complexity can be observed in the moment of determining operationally the intellectual disability, as well as the variability of concomitant conditions that can affect the outcome of an intervention. The health area staff should consider the possible involvement of numerous systems; the therapist, the diversity of behavior; and the researcher, the potential variables that may influence their object of study. However, with adequate strategies and designs, the health professionals involved in the approach of people with intellectual disabilities will be able to generate knowledge, in such a way that substantial improvements in the quality of life of this group will be achieved shortly.

## Conflicts of interest

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

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# Neuroscientific evidence support that chess improves academic performance in school

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## Abstract

*In this work, we report the cognitive benefits of playing chess for school-aged children. The most benefitted areas appear to be math and reading. To validate these results, a diversity of scientific studies are described, in which brain activation is demonstrated through magnetic resonance imaging when novice, intermediate, and advance chess players play the game. Given this evidence, it is suggested that chess be used as a tool to improve academic performance in boys and girls. In addition, it is concluded that studying the use of chess could lead to new lines of research that could validate the neural mechanisms that occur when boys and girls play chess.*

**Key words:** Chess. School. Boys. Girls. Academic performance.

## Evidencia neurocientífica apoya que el ajedrez mejora el rendimiento académico en la escuela

### Resumen

*En este trabajo se reportan los beneficios cognitivos que produce la práctica del ajedrez en niños en edad escolar. Las áreas más beneficiadas parecen ser las matemáticas y la lectura. Para validar lo anterior se describen diversos trabajos científicos que muestran la activación cerebral a través de imágenes de resonancia magnética cuando los jugadores de ajedrez novatos, intermedios o avanzados practican este juego. Con base en ello se sugiere usar el ajedrez como una herramienta que permita la mejora del rendimiento escolar en niños y niñas. Se concluye además que a partir de la utilización de este juego se pueden generar líneas de investigación que busquen validar mecanismos neurales que ocurren cuando niños y niñas juegan ajedrez.*

**Palabras clave:** Ajedrez. Escuela. Niños. Niñas. Rendimiento escolar.

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## Introduction

Chess is a game that allows the transfer of cognitive abilities<sup>1</sup>. This is due to the fact that it involves high-level cognitive aspects, requires sophisticated problem-solving abilities<sup>2-5</sup>, has a positive impact on academic achievements of those who play it<sup>6</sup> and positive effects on mental development. This may be because, during the game of chess, cognitive abilities<sup>7</sup> such as creativity, anticipation, perception, and memory<sup>5</sup> are used. Chess, in addition, offers an opportunity to study individual differences in cognitive processes<sup>3</sup>.

Regardless of grade level, chess can be used as a learning tool in boys and girls, since this game allows them to self-regulate their learning and reach specific objectives<sup>8</sup>. In addition, through diverse chess problems, the level of knowledge of boys and girls in similar activities can be determined<sup>9</sup>. This is because chess has a complex rule system, and knowledge depends on each student's individual level<sup>5</sup>. Similarly, regardless of the level of the game performance of each individual, neuroimaging studies have shown brain activation during game play<sup>10</sup>.

The objective of this work is to present scientifically validated information demonstrating that chess is a useful tool for improving boys' and girls' academic performance in school. To do so, diversity of studies is described in which chess players are evaluated using functional magnetic resonance imaging (fMRI). After analyzing these studies, we suggest that chess can be used as a tool to improve learning in school-aged boys and girls.

## Chess in schools

Playing chess, both in and outside of school, has a large potential for developing academic knowledge in children<sup>11,12</sup>. In Mexico, the level of academic performance by each child can be quantified, since their performance is evaluated and they receive a grade score for their performance in mathematics and Spanish. However, chess playing is not graded. Even so, a variety of benefits, apparently indicating a positive impact of playing chess on mathematics and reading scores have been reported.

In recent studies, it has been reported that teaching chess yields benefits in school<sup>7,9,11,13,14</sup>. These benefits have been detected, particularly in children's math<sup>12,15-21</sup> (Table 1) and reading comprehension scores<sup>22-25</sup> (Table 2), though the effect is not the same between the two subjects. According to a recent meta-analysis

evaluating which of the two subject areas (math or reading) is most benefitted, the area most positively impacted was math<sup>26</sup>. This may be because the game cultivates a high level of non-specific skills (for example, persistence, self-control, objectivity, memory, and problem-solving) which are relevant to academic performance overall<sup>27</sup>.

Playing and training for chess have been considered an important learning tool in education<sup>12</sup>, leading to some institutions to incorporate it into their school curricula<sup>1</sup> or as an afterschool extracurricular activity. Notwithstanding, increased dissemination of the benefits of this game among education officials at the federal, state, and municipal levels is needed so that they will support initiatives in favor of educational spaces in the schools, and as such, bring the benefits of chess to schools.

Chess allows boys and girls to obtain benefits in diverse cognitive areas<sup>4,11,16,22,28</sup>; it has been shown that subjects that play chess improves their spatial reasoning, long-term planning, decision-making, memory<sup>11</sup>, cognitive development, academic performance<sup>4,5</sup>, and strategic, creative, and critical thinking<sup>5</sup>. At the same time, chess can be used to evaluate cognitive processes, for example, by asking children to place the game pieces on the board in random order or standard positions<sup>29</sup>. However, further investigation is needed to describe the effects of this science game.

In this work, we describe some of the research reporting a positive effect of chess on academic performance, spatial concepts, executive functions, and basic cognitive, and social skills.

## Studies evaluating the effects of chess

The results presented here showed a positive effect on the educational process of boys and girls who received training in chess.

In a study in Seoul, South Korea, it was found that presenting students with a heuristic chess problem were helpful for evaluating students' intellectual levels and using that knowledge, choose adequate methodologies for improving each student's level of academic performance<sup>1</sup>. The study was carried out among 38 students aged 8-12, divided into two categories: (1) those with high intellectual level and (2) those at risk of failing the school year, from three different primary schools<sup>1</sup>.

Another study showed that a group that trained in chess improved basic skills (i.e., attention and

**Table 1.** Some of the research in which chess has been found to impact mathematics performance in school

Author(s)	Country	N	Study objective	Tests	Results
Fernández-Amigo et al. <sup>15</sup>	Spain	N = 141 experimental group (79 boys, 62 girls)	Analyze, qualitatively and quantitatively, the utility of instructional materials using chess for teaching mathematics during the second grade of primary school	EFAI (“Evaluación factorial de las aptitudes intelectuales”, in English, Factorial Evaluation of Intellectual Aptitudes) <sup>29</sup> Numerical score, reasoning score, ethnographic interview, surveys	Satisfaction was achieved in the utility of the chess - based learning materials for teaching mathematics
Achig <sup>17</sup>	Ecuador	N = 35 experimental group (20 boys, 15 girls)	Test the impact of chess on logical-mathematical reasoning in sixth-grade primary school students	Theoretical chess test before and after, Mathematics class score	The average math class score increased
Guerrero et al. <sup>18</sup>	Mexico	N = 32 The number of boys versus girls is not given	Describe the effect of chess on basic mathematical operations in fifth-grade primary school students	Pre-test and post-test on fractions and operations based on ENLACE 2011 and 2012 test questions, surveys and interviews	Better concentration, and memory and higher math class score
Gumede and Rosholm <sup>19</sup>	Denmark	N = 264 The number of boys versus girls is not given	Characterize the impact of chess in the subject of mathematics in first-and third-grade primary school students	Pre-intervention tests, characteristics of the child and the child’s mother and father	Positive effects in both immigrant and non-immigrant Danish children
Sala et al. <sup>20</sup>	Italy	N = 309 experimental group (169 boys, 140 girls). N = 251 control group (116 boys, 135 girls).	Investigate the potential of online chess lessons on problem-solving abilities in second, fourth, and fifth-grade primary school students	Programme for International Student Assessment and chess survey following Trinchero <sup>28</sup> Item 12	Highly positive correlation between math score and chess in the experimental group
Sala et al. <sup>21</sup>	Italy	N = 309 experimental group (169 boys, 140 girls) N = 251 control group (116 boys, 135 girls)	Experimental study of chess in fourth grade primary school students using a placebo group	Six tests evaluating mathematics abilities, IEA – TIMSS <sup>31</sup> psychometric test	The chess group was more effective in math skills than the GO group, but not in school activities
Rosholm et al. <sup>12</sup>	Denmark	N = 323 experimental group. N = 159 control group	Analyze the effect of replacing one mathematics lesson per week with one based on chess instruction in first and third grade primary school students	Mathematics test (including calculations, geometry, pattern recognition, and basic problem solving)	Improvement in the composition of mathematical sequences in the experimental group

memory), complex cognitive skills (e.g., association, analysis, synthesis, planning, and foresight), and social-personal skills, compared to two control groups – one that did not participate in chess or any sport and another that played soccer and basketball<sup>14</sup>.

In another study, the effect of training in chess in 6-year-old children showed an increase in spatial

concept comprehension compared to a group of children that did not play chess<sup>7</sup>; and finally, a study showed that children who trained in chess had higher results on evaluations of executive function than those that did not<sup>13</sup>.

These results have caught the attention of neuroscientists, who have begun to describe brain activation when children participate in the game of chess.

**Table 2.** List of research papers investigating the impact of chess on reading comprehension in school

Author(s)	Country	Number of participants	Study objective	Tests	Results
Margulies et al. <sup>22</sup>	United States of America	N = 1118 Groups of participants N = 22	Escribe the effect on reading before and after chess instruction in primary school	Degree of reading power test (DRP)	The group of chess students improved more than the average student
Liptrap et al. <sup>23</sup>	United States of America	N = 571 total Chess group N = 67 Group that did not play chess N = 504	Determine the degree of participation by students in a chess club	Texas Assessment of Academic Skills (TAAS). Texas Learning Index (TLI)	The chess group improved more in math skills than in reading
Duccette <sup>24</sup>	United States of America	Experimental group N = 151	Analyze the effect of a chess program on behavior, math, and reading	Philadelphia's behavior grade and attendance, Pennsylvania System of school Achievement (PSSA) score in Reading and mathematics	After 1 year, the group that played chess improved in math and reading, and these values were correlated, while in the control group none of these patterns were present
Dapica-Tejada <sup>25</sup>	Spain	N = 60 Total Chess group N = 30 (21 boys, 9 girls) Control Group N = 30 (20 boys, 10 girls)	Test whether there are significant differences in reading comprehension and saccadic movements (SM*) in boys and girls that play chess	Chess participation survey, PROLEC-SE battery of tests of reading processes and the King Devick SM test	The chess group improved on the different tests by which they were evaluated, which did not occur in the no-chess group. In addition, there was a correlation between SM and reading comprehension and between chess and SM

\*SM are produced in the eyes when we read, look, or search for information, refers to movement speeds of 500°/S. During these MS, the eyes can remain still for intervals of around 200-300 ms.

## Brain activation while playing chess

fMRI is one of the most important scientific advances since it allows the development of the cognitive sciences in ways never seen before. This is because fMRI allows a detailed study of brain cartography, and therefore, characterization of brain functions. fMRI is a technique that can measure hemodynamic changes after neuronal activity<sup>32</sup>. fMRI detects brain activity by directly measuring tissue perfusion, changes in blood volume, and changes in oxygen concentration<sup>33</sup>.

We see four main studies that can be used to describe how fMRI is used to investigate cognitive processes in chess players. These studies have demonstrated differential activation of the brain<sup>2,34-36</sup> during games of novices and experts<sup>37</sup>.

One of these studies was carried out using novice chess players. fMRI results showed brain region associations that are activated during the analysis of game positions. These regions are the premotor areas, frontal lobes, parietal cortices, occipital lobe, and the left hemisphere of the cerebellum<sup>2</sup>.

Another study showed that among expert chess players, there is no difference in the areas of brain activity; however, when their patterns of brain activity were compared to those of novice players, there were differences, since the novices produced activation among the posterior areas of both hemispheres, which did not occur among the expert players<sup>34</sup>.

The third scientific study was carried out using both novice and expert chess players. This study aimed to determine whether the subjects recognize general and specific patterns in chess. The experiment consisted of putting the game pieces on the board at random and instructing the subjects to recognize and analyze the patterns of the pieces using their eye movements. The results showed that while novice players examine irrelevant aspects, the expert chess players focused immediately on relevant aspects of the task. To corroborate this difference, the experiment was done using fMRI, which allowed the description of differences in patterns of general and specific recognition. In the novice players, there was activation in the temporal-occipital area, while in experts, who were able to recognize specific objects

during the test, there was bilateral activation in the middle part of the collateral sulci. This experiment showed evidence suggesting that subjects are able to identify general and specific patterns in chess; in addition, it describes the cognitive process they used. As such, this work could help describe essential perceptive mechanisms in humans<sup>35</sup>.

The last study we will comment on was carried out with novice players who had been training for only a short time and expert players with years of intensive training. fMRI was used to characterize their neuronal activity. The results suggest that specific training activated or inhibited specific brain structures, such as the bilateral caudate nucleus. At the same time, the volume of brain activity in that area was significantly smaller in experts than in novices<sup>36</sup>.

Despite the costliness of fMRI testing, the effects of playing chess have been investigated for many years<sup>38</sup>. As a consequence, the recent discoveries in neurosciences using neuroimaging techniques could allow the description of the underlying neural mechanisms of chess playing<sup>2,34-36</sup>, establish a correlation in the theory of the mind<sup>39</sup> and identify common high level areas in cognitive processes, which could result in new theories of cognitive process<sup>2</sup> or exploration of higher functions of the human brain<sup>40</sup>. In any case, we believe that there is a link between playing chess, increased academic performance in school, and the fMRI results.

Finally, we believe that the studies described above could lay the neuroscientific foundation for new scientific research on chess and other board games.

## Brain activation in games other than chess

It is possible that the academic improvement in boys and girls could be achieved not only through playing chess but also through other similar games. It is, therefore, important to consider what is known about the effects of other games on activation of different brain areas.

For example, one study analyzed the brain activity of 28 professional and amateur players of the board game Shogi. The average age of the subjects was 30.6 years. In the professional players, there was activation in specific brain areas, particularly in the precuneus of the parietal lobule during the perception of patterns on the board, and in the caudate nucleus of the basal ganglia when the players were carrying out their "best move." Considering these results, the researchers suggest that the precuneus-caudate circuit

is involved in the automatic patterns of the process of pattern perception on the board and the perception of the next move<sup>37</sup>.

Another study was carried out among university students (not professionals) with the aim of describing which brain areas are activated when subjects participate in the game GO. The fMRI results showed that the activated areas were the cortical, prefrontal, parietal, occipital posterior temporal, primary somatosensory system, and motor areas. It is thought that this type of activation may be due to the fact that the game emphasizes an overall strategy rather than a specific strategy, as occurs in chess<sup>41</sup>.

Although analyzing the rules and other characteristics of Shogi, Go, and chess, reveal clear differences among them, it is important to emphasize that the studies described used fMRI and have helped to describe which brain areas are most active while these games are being played. In the near future, it is possible that a cognitive model of learning could be described for games other than chess from the perspective of neuroscience or other cognitive models.

## Conclusions

In this review, we have described the benefits and favorable academic effects in boys and girls in the school setting, as well as the neuronal activation that occurs when playing chess. As such, we consider that playing this game could be a viable strategy for improving expected learning and relevant knowledge in boys and girls<sup>42</sup>, as long as the educator that works with them keeps them motivated in a fun, collaborative environment<sup>14</sup>.

In several countries, this strategy has been used to improve academic performance, for example, in Mexico, where ENLACE academic evaluations<sup>43</sup> during primary school and Programme for International Student Assessment evaluations in the secondary school show that girls and boys are below the worldwide average<sup>44</sup>. In addition, we believe that using the foundations described here, new lines of research could be generated, considering the game of chess as a potential catalyst for academic improvement in boys and girls.

## Conflicts of interest

There are no conflicts of interest for the authors of this work.

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# Pharmacogenetics of adverse cutaneous reactions to lamotrigine

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## Abstract

Cutaneous adverse drug reactions include maculopapular exanthema, Stevens-Johnson syndrome, and toxic epidermal necrolysis and are a global public health problem associated with the use of antiepileptic drugs (AEDs). Lamotrigine (LTG) stands out among AEDs because it does not cause sedation and does not affect cognition. Cutaneous adverse reactions (cADRs) to LTG occur in patients carrying certain allele variants of the human leukocyte antigen (HLA) system; although infrequent, they are alarming because they put the life at risk and force discontinuation of the treatment. The fear of neurologists to cADRs to LTG decreases its prescription despite its therapeutic advantages. Here, we review the allele variants of the HLA system that have been associated with cADRs to LTG in Mexican mestizos and other ethnic groups; identification of these variants would serve to select the patients that may be treated with LTG.

**Key words:** Pharmacogenetics. Antiepileptic drugs. Lamotrigine. Cutaneous adverse drug reactions. Human leukocyte antigen system.

## Farmacogenética de las reacciones cutáneas adversas a la lamotrigina

### Resumen

Las reacciones cutáneas adversas a medicamentos incluyen el exantema maculopapular, el síndrome de Stevens-Johnson y la necrólisis epidérmica tóxica y son un problema de salud pública global asociado al uso de fármacos antiepilépticos. La lamotrigina destaca entre los fármacos antiepilépticos porque no causa sedación ni afecta la cognición. Las reacciones cutáneas adversas a lamotrigina ocurren en pacientes que portan ciertas variantes alélicas del sistema HLA; aunque infrecuentes, son alarmantes porque ponen en riesgo la vida y obligan a abandonar el tratamiento. El temor de los neurólogos a las reacciones cutáneas adversas a lamotrigina limita la prescripción del medicamento a pesar de sus ventajas terapéuticas. Aquí revisamos las variantes alélicas del sistema HLA que han sido asociadas a las reacciones cutáneas adversas a lamotrigina en mestizos mexicanos y otros grupos étnicos; la identificación de estas variantes permitiría seleccionar a los pacientes que podrían ser tratados con lamotrigina.

**Palabras clave:** Farmacogenética. Fármacos antiepilépticos. Lamotrigina. Reacciones cutáneas adversas a medicamentos. Sistema HLA.

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## Introduction

Antiepileptic drugs (AEDs) are among the most common drugs known to induce cutaneous adverse reactions (cADRs) such as maculopapular exanthema (MPE), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), with significant morbidity and mortality. The incidence of SJS/TEN is estimated to vary from 1 in 1,000 to 10,000 drug exposures, and its mortality is as high as 35%. The highest rates of adverse drug reactions (ADRs) related to AEDs are caused by lamotrigine (LTG), one of the newer AEDs<sup>1</sup>.

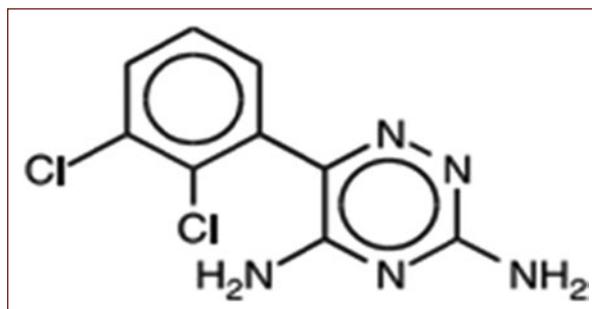
Pharmacogenetics aims to identify the genetic polymorphisms associated with the efficacy and safety of medicines. In this paper, we review the allele variants of the human leukocyte antigen (HLA) system that have been associated with cADRs induced by LTG. Genotyping of the HLA allele variants would, therefore, serve to select the patients that might tolerate and benefit from LTG treatment.

## Epilepsy

Epilepsy is a chronic brain disease caused by an imbalance in the electrical activity of neurons that affects 70 million people in the world and at least five million in Latin America. It is characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure<sup>2</sup>.

Epileptic seizures are considered focal if the electrical activity originates within networks limited to a cerebral hemisphere and affect a limb or a hemibody, generally contralateral. Seizures are generalized if they originate at some point of the cortical and subcortical networks distributed bilaterally; they may affect awareness and sometimes are accompanied by loss of sphincter control with frequencies ranging from less than once a year to several times a day<sup>3</sup>.

Epilepsy has diverse etiologies. The most frequent type is primary or idiopathic epilepsy, in which a genetic or structural cause has not been identified, that affects six out of every 10 patients. Epilepsy from known causes is called secondary or symptomatic epilepsy. It may be due to brain damage from prenatal or perinatal injuries (e.g., asphyxia or trauma during birth, and low birth weight), congenital malformations or genetic alterations with associated brain malformations, severe head trauma, stroke limiting the arrival of oxygen to the



**Figure 1.** Chemical structure of lamotrigine. PubChem CID: 3878. Chemical name: 3, 5-diamino-6-(2, 3-dichlorophenyl)-1, 2, 4-triazine. Molecular formula: C<sub>9</sub>H<sub>7</sub>Cl<sub>2</sub>N<sub>5</sub>. Molecular weight: 256.09.

brain, brain infections (such as meningitis, encephalitis, or neurocysticercosis), some genetic syndromes, and brain tumors<sup>4</sup>.

The treatment of epilepsy is not always easy but accessible with AEDs, whose purpose is to free patients from seizures without side effects and return them to the life of quality without seizures. However, despite numerous attempts to develop safe and innocuous drugs, AEDs have different mechanisms of action, and all can cause adverse or undesirable effects. The appearance of ADRs during the therapy of epilepsy makes it difficult to control seizures, hinders adherence and promotes the suspension of treatment in 25% of cases with the consequent increase in the cost of therapy and the impact on the life quality of patients<sup>5</sup>.

## Lamotrigine

LTG stands out among the more than 17 AEDs approved for the treatment of focal and generalized epilepsy<sup>6,7</sup>. It was approved by the FDA in 1994 for the treatment of partial seizures and generalized secondary seizures in adults and in 1998 as a complementary treatment for generalized seizures associated with the Lennox-Gastaut syndrome<sup>8</sup>.

LTG is a phenyltriazine (Figure 1) from a group that includes carbamazepine, phenytoin, and valproic acid that potentiate the inhibition mediated by sodium channels<sup>9</sup>. When a neuron is depolarized, sodium channels become inactive. When a neuron is repolarized, its sodium channels are inactivated by a short period (refractory period) during which massive sodium entrance is blocked; this inactivation constitutes a crucial point for the prevention of recurrent discharges into an epileptic potential focus<sup>10</sup>.

**Table 1.** Classification of adverse drug reactions and examples of those induced by antiepileptic drugs (adapted from Fricke-Galindo et al. 2018)<sup>5</sup>

Class	Features	Examples of adverse drug reactions
A	Dosage-dependent; excessive pharmacological response; predictable; reversible; frequent low severity	Dizziness, headache, tremor, drowsiness, insomnia, vertigo, ataxia, diplopia, depression, hyponatremia, paresthesias, gastrointestinal disorders
B	Not related to the dose or the mechanism of pharmacological action; related to individual vulnerability; unpredictable; infrequent; high morbidity and mortality; reversible	Skin and hypersensitivity reactions (mild maculopapular exanthema, Stevens-Johnson syndrome, toxic epidermal necrolysis, etc.), hepatotoxicity, aplastic anemia, agranulocytosis
C	Related to dose and time (dose accumulation); infrequent; chronicles; most are reversible	Weight gain or loss, gingival hyperplasia, visual loss
D	Related to time, usually with prenatal dose and exposure; infrequent; irreversible	Teratogenicity
E	Related to the suspension of the medication	Insomnia, anxiety, and disorders after sudden withdrawal of benzodiazepines
F	Unexpected therapeutic failure; frequent related to the dose and interaction of drugs	Decrease in plasma drug concentration by enzymatic induction of concomitant therapy



**Figure 2.** Clinical presentations of adverse drug reactions to medications. **A:** Maculopapular exanthema. **B:** Toxic epidermal necrolysis. Photos of these patients were taken and provided to us by Dr. Ildefonso Rodríguez-Leyva.

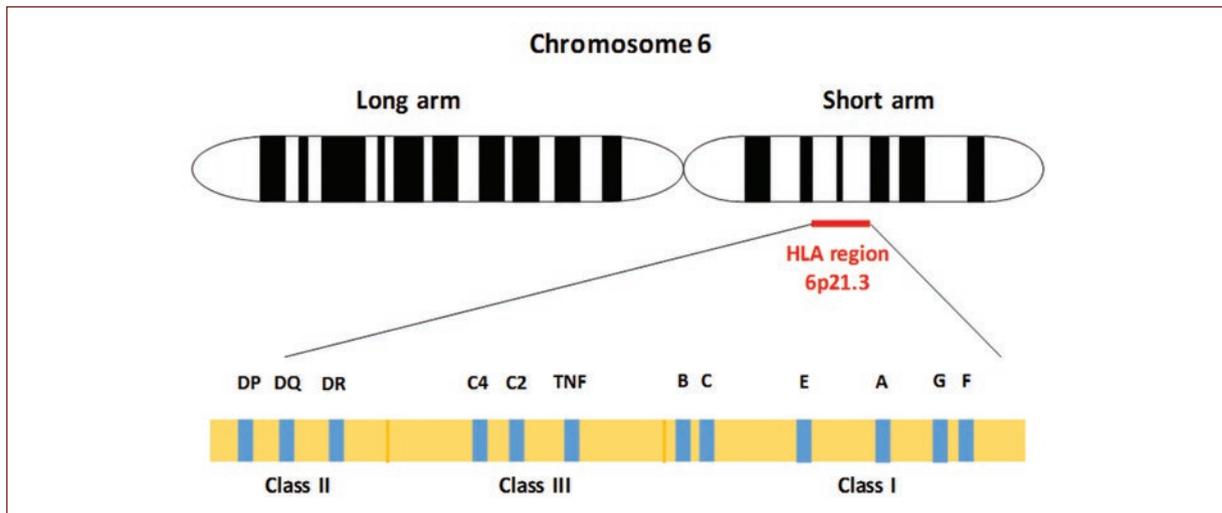
### cADRs to AEDs

cADRs are defined as “the unintended, harmful response to a drug that occurs with the standard dose used in humans for the prophylaxis, diagnosis, or treatment of a disease or the modification of some function”<sup>11</sup>.

The cADRs to AEDs represent a serious problem for public health and the individuals who suffer them because their prevalence ranges from 0.7% to 35% and they occur in 15% of hospitalized patients<sup>12</sup>. They are classified according to their mechanisms of

pathogenesis (Table 1), the most common being types A and B<sup>5</sup>.

Type B reactions are idiosyncratic in nature, less frequent, but more severe than type A reactions; their control requires immediate suspension of the drug or even additional treatment. Type B reactions include severe cADRs whose clinical manifestations range from MPE of varying severity, to life-threatening cutaneous reactions that include the SJS and TEN (Figure 2), with mortalities of up to 5% for SJS and 30% for NET. One of their most important sequels is ocular



**Figure 3.** Genetic region of the human major histocompatibility complex. The MHC region is located on the short arm of chromosome 6 (6p21.3) and occupies a DNA segment that extends around 3600 kbp. It is a region of highly polymorphic genes that form two separate groups: those of Class I (telomeric) and those of Class II (centromeric). Another group of unrelated genes, called Class III genes, separates the two regions.

because up to 75% of patients with NET can have complications as severe as blindness<sup>5</sup>.

The highest rates of cADRs related to AEDs are due to LTG, carbamazepine, and phenytoin, drugs structurally related by an aromatic ring<sup>12</sup>.

### Pharmacogenetics of the cADRs by LTG

Pharmacogenetics emerged from various observations of heritable enzyme deficiencies associated with the toxicity of certain drugs in specific groups of individuals. Pharmacogenetic studies consider the association of allele variants of the genes that encode transporters, receptors, and drug metabolizing enzymes with variations in the requirements of dose, efficiency, and development of ADRs<sup>15</sup>. Knowledge of individual genetics can improve the choice of pharmacotherapy to avoid undesirable effects and adverse reactions in patients<sup>13</sup>.

### The HLA system

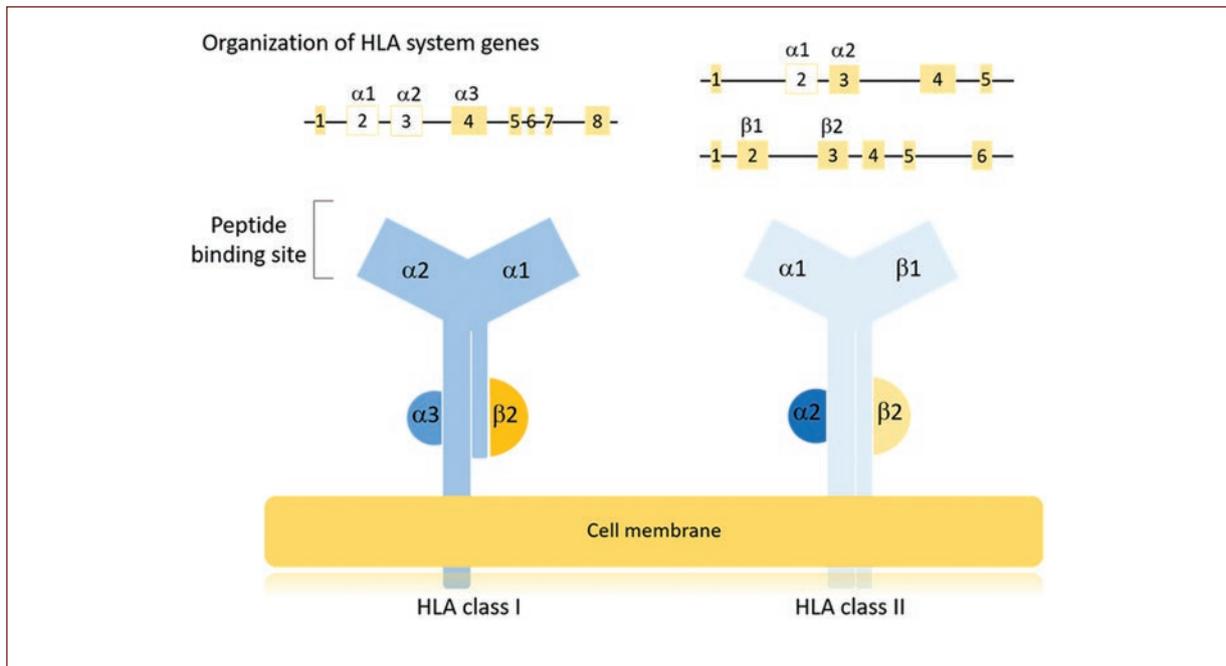
The genes of the human major histocompatibility complex (MHC), also called the HLA system, are located in the short arm of chromosome 6. They encode cell surface molecules specialized in the presentation of antigenic peptides to lymphocytes T that activate critical processes in the generation of the immune response<sup>14</sup>.

Antigen-presenting MHC molecules are of two main Classes I and II. Class I molecules are encoded in the telomere region, and Class II molecules in the centromere region. Between them is the Class III gene region, or central MHC, of approximately one million base pairs (Figure 3).

The Class I region encodes classical (HLA-A, -B, -C) and non-classical (HLA-E, -F, -G) HLA proteins, whereas the relatively homogeneous Class II region contains the genes encoding HLA-DP, DQ and DR proteins, heterodimers of an alpha and a beta chain that are present in B lymphocytes and monocytes. MHC Class I and Class II regions are so named because they mainly contain HLA genes, whereas the Class III region does not have that defining characteristic because it contains a large number of genes with diverse functions either participating or not in the immune system. MHC gene families have resulted from multiple gene duplication events, so some individual gene pairs such as HLA-B and HLA-C are almost identical<sup>15</sup>.

Some of the risks associated with the HLA system are autoimmune diseases such as rheumatoid arthritis, type 1 diabetes, Graves' disease, multiple sclerosis<sup>16</sup>, and ADRs, among which the cADRs are mediated by dose-independent immune mechanisms associated with allele variants of this system<sup>5</sup>.

The main function of the immune system is to recognize and initiate rapid and specific responses against non-self-antigens. Further reactions occur



**Figure 4.** Genes and human leukocyte antigen (HLA) molecules of Class I and Class II. In the scheme of the upper part of the figure, the squares represent the exons, and the lines represent the introns of the HLA system genes. The domains of the HLA molecules encoded by the exons are indicated on the squares; blank squares highlight the exons that contain most of the polymorphisms.

when the system responds inadequately to an adequate stimulus; inadequate responses on cADRs are associated with certain allelic variants of the HLA system.

Although the mechanism of cADRs is not fully defined, two theories have been proposed to explain them: hapten/prohapten and drug/receptor (p-i) immunological interaction<sup>5</sup>. In the first case, it is assumed that, as the drug molecule is too small to induce an immunological response, it acts as a hapten or prohapten that becomes immunogenic by its covalent bond with endogenous proteins to form a hapten-carrier complex. This complex is processed by MHC antigen-presenting cells located in the lymph nodes and other tissues, which stimulate the production of T cells and the consequent clinical manifestations. The p-i theory (pharmacological interactions of drugs with immunological receptors) proposes that some drugs bind directly and reversibly (non-covalently linked) to MHC receptors or to the T cell receptor to stimulate T cells specific for the inducer drug<sup>17</sup>.

Since in the classic HLA system genes the more polymorphic exons encode Class I and Class II molecules (Figure 4), pharmacogenetic studies associated with cADRs by AED have focused on the

identification of HLA Class I alleles and to a lesser extent on Class II alleles<sup>5</sup>.

### Allele variants of the HLA system associated with cADRs by LTG

In the decades following isolation of the first HLA gene by molecular cloning (HLA-B7 cDNA), thousands of alleles have been identified whose names and sequences are included in the IMGT/HLA database (<http://www.ebi.ac.uk/imgt/hla/index.html>), an invaluable tool for all HLA typing systems.

The first attempt at HLA DNA typing involved analysis of restriction fragment length polymorphism, which has many limitations. Development of the polymerase chain reaction (PCR) led to amplification of the polymorphic second and third exons of the HLA Class I and Class II genes and the analysis of polymorphic sequence segments with hybridization sequence-specific oligonucleotide probes. Immobilization of these probes first on membranes and later on spherical particles, together with the first sets of sequence-specific primers (SSP), gave rise to the current set of HLA typing reagents<sup>18</sup>.

SSP-PCR is a fast, efficient, and relatively low-cost method. It has the advantage of distinguishing

**Table 2.** Class I HLA alleles and haplotypes associated with cutaneous adverse reactions to lamotrigine in various ethnic groups

Alleles/haplotypes	cADRs	Ethnic group	HLA+/total	Year of publication	Reference
HLA-A*24:02	cADRs	Norwegians	10/28	2015	20
	MPE	Korean	15/21	2015	21
HLA-A*30:01	MPE	Chinese-Han	6/86	2013	22
HLA-A*33:03	MPE	Thai	3/86	2013	22
HLA-A*68:01	cADRs	Europeans	4/44	2009	23
HLA-B*44:03	SJS/TEN	Korean	3/5	2015	24
HLA-B*58:01	cADR	Mixed population	3/44	2009	23
HLA-B*35:01:01	MPE	Mexican mestizos	6/10	2014	12
HLA-B*38:01:01	SJS/TEN	White people	3/3	2017	25
HLA-B*57:01:01	SJS	Mexican mestizos	1/2	2014	12
HLA-B*58:01:01	SJS	Mexican mestizos	1/2	2014	12
HLA-A*24:02/C*01:02	MPE	Korean	10/21	2015	21
HLA-B*40:02:01	SJS	Mexican mestizos	2/4	2014	12
HLA-A*02:07:01	MPE/SJS	Asians	5/15	2017	26
HLA-B*44:03:01	MPE	Asians	3/10	2017	26
HLA-A*02:01:01/B*35:01:01/C*04:01:01	MPE	Mexican mestizos	5/10	2014	12
HLA-B*13:02	MPE	Chinese-Han	6/86	2013	22
HLA-B*15:02:01	MPE/SJS	Asians	6/15	2017	26
HLA-A*23:01:01	SJS	Mexican mestizos	1/4	2014	12

cADRs: cutaneous adverse reactions, HLA+/total: number of HLA allele positive subjects in the total number of subjects included, MPE: maculopapular exanthema, SJS: Stevens-Johnson syndrome, TEN: toxic epidermal necrolysis.

several alleles because it detects differences of a single base in the DNA sequence of two alleles, although it cannot detect a new undefined allele unless the change occurs in a location detectable by the primer<sup>19</sup>.

The prevention of cADRs has focused on the HLA locus. Association studies in different populations have described that HLA alleles associated with cADRs are drug-specific and that ethnicity is important. The clinically relevant HLA alleles that have been associated with cADRs induced by LTG are presented in Table 2.

Due to their incidence in cADRs by LTG, the five HLA alleles and the one HLA haplotype most clinically relevant in Mexican mestizos are the following: HLA-A\*23:01:01, -B\*35:01:01, -B\*40:02:01, -B\*57:01:01, B\*58:01:01, and

HLA-A\*02:01:01/B\*35:01:01/C\*04:01:01<sup>12-20</sup>. The use of SSP-PCR to identify them would allow to predict the individual risk of cADR and to select the epileptic patients that may be treated with LTG and benefit from it.

## Conclusion

LTG is a valuable AED that does not produce sedation and does not affect cognition. However, its use is limited by the fear of severe cADRs that could compromise the health and lives of the patients. Five alleles and one haplotype of the HLA system have been associated with cADRs by LTG in Mexican mestizos and other ethnic groups. Sequencing of the HLA-A and HLA-B SSP-PCR products would identify the epileptic patients that could tolerate and benefit from LTG treatment.

## Funding

None.

## Conflicts of interest

None.

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## The increasing Parkinson's disease incidence rates: A call for collaboration

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To the Editor,

It was with great interest that we read Rodríguez-Violante et al's. article on the last issue of *Rev Mex Neuroci*, regarding the incidence rates of Parkinson's disease (PD) in Mexico in the 2014-2017 period<sup>1</sup>; the authors report an increase of 26.7% in the average annual percent change from 2014 to 2017. We believe this to be an extremely valuable contribution, being the first nation-wide study on the subject; notwithstanding the limitations, the authors draw our attention to an ever-growing menace: the burden of PD.

PD is the second most common neurodegenerative disease, only second in frequency to Alzheimer's disease. In 2017, the Global Burden of Neurological Disease reported that PD was the only one with increasing rates of prevalence, disability and death<sup>2</sup>. Last year, the Global Burden of PD study published in *The Lancet Neurology*<sup>3</sup> reported that worldwide 6.1 million individuals were living with PD, a dramatic increase from the 2.5 million in 1990; emphasizing PD as the fastest-growing neurodegenerative disorder and the need for further epidemiological and clinical studies.

As the number is projected to dramatically increase up to even 17 million worldwide in 2040<sup>4</sup>, some authors have advocated taking action on the oncoming PD pandemic<sup>5</sup>. This call of action requires an interdisciplinary and multicenter collaboration between clinicians and

other allied healthcare professionals across the country. May this article serve as our own national call for collaboration on the PD pandemic. As Professor Baastian Bloem from the Netherlands declared on the 5<sup>th</sup> World Parkinson Congress (June 4-7, Kyoto, Japan): "Collaboration is the new competition. Don't do it alone."

### Conflicts of interest

The authors declare that there are no conflicts of interest.

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