TRABAJO LIBRE - BDM00016

Prevalencia de anemia en un grupo de estudiantes de la Universidad Juárez Autónoma de Tabasco.

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UNIVERSIDAD JUÁREZ AUTÓNOMA DE TABASCO

Introducción: En estado de anemia, los eritrocitos o glóbulos rojos resultan insuficientes para satisfacer las necesidades fisiológicas del organismo. Estas células transportan O2 y CO2 hacia los diferentes tejidos del cuerpo. La anemia se origina por la pérdida de sangre, la falta de producción de glóbulos rojos, las deficiencias nutricionales (hierro, ácido fólico, vitaminas B12, A, C), problemas hormonales, el embarazo, o bien, al aumento en la velocidad de destrucción de los glóbulos rojos. Estos antecedentes apoyan la idea de que la prevalencia de anemia podría ser considerada un indicador del estado de salud de una población.

Objetivo: Determinar la prevalencia de anemia en un grupo de estudiantes de la Universidad Juárez Autónoma de Tabasco (UJAT).

Metodología: Se realizó un estudio transversal retrospectivo que incluyo la revisión y compilación de 391 análisis clínicos de estudiantes de la División Académica de Ciencias Básicas de la UJAT realizados durante Febrero-Agosto del 2015. El análisis de los datos antropométricos (genero, edad, peso, talla, IMC) y de las Biometrías Hemáticas (hemoglobina, eritrocitos, HCT, VCM, HCM, CHCM) se realizaron en el programa IBM SPSS® 19.

Resultados: Dentro de la DACB, los estudiantes de las Licenciaturas de QFB y Geofísica fueron los grupos más representativos con el 48 y 42% del total de la población, mientras que Química y Física solo constituyeron el 7.4 y 2.6% respectivamente. El 53% de la población fueron mujeres, mientras que cerca del 47% fueron hombres, la edad promedio para ambos grupos fue de 19 años. El diagnóstico de anemia se realizó de acuerdo a los estándares establecidos por la OMS para hombres y mujeres no embarazadas. De acuerdo con este análisis, solo el 0.25% de la población estudiantil de la UJAT, presento Anemia de tipo Microcítica Hipocrómica. En este estudio no se identificó la presencia de Anemia Macrocítica.

Conclusiones: De acuerdo con la OMS, una prevalencia menor al 5% de anemia en las poblaciones es un indicativo de un estado de salud favorable, sin embargo resulta imperativo desarrollar estudios epidemiológicos de mayor alcance para incrementar nuestra calidad y certeza en el diagnóstico.

TRABAJO LIBRE - BDM00017

Factores de riesgo cardiovascular y metabólico asociados a prediabetes en niños en edad escolar

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Introducción: En 2003, la Asociación Americana de Diabetes reconoció la existencia de un grupo de sujetos cuyos niveles de glucosa resultan elevados para ser considerados normales pero no cumplen con los criterios para establecer el diagnóstico de diabetes, esta condición fue categorizada como Prediabetes. En población adulta, la presencia de prediabetes representa un factor de riesgo para el desarrollo de Diabetes y enfermedades cardiovasculares; sin embargo, poco se ha caracterizado esta problemática en niños.

Objetivo: Identificar los principales factores de riesgo cardiovascular y metabólico asociados al desarrollo de prediabetes en niños en edad escolar

Metodología: Estudio transversal analítico. Se estudiaron niños en edad escolar de instituciones públicas de educación básica de la ciudad de Durango. A todos los participantes se les realizaron las siguientes mediciones somatométricas: Peso, talla, índice de masa corporal, porcentaje de grasa corporal y tensión arterial. Se realizó toma de muestra sanguínea venosa para la cuantificación de los niveles de glucosa, perfil de lípidos, resistencia a la insulina y biometría hemática.

Resultados: Se incluyeron 489 niños, 249 hombres y 240 mujeres. Se identificaron 23 casos de niños con prediabetes (4.7%). La prevalencia de sobrepeso en el total de la muestra fue 17.2% (84 sujetos) mientras que la de obesidad fue de 12.5% (61 sujetos). El 23.7% (112 sujetos) presentaron hipertrigliceridemia y un 8.2% (40 sujetos) presentaron hipercolesterolemia. En el análisis de regresión logística la presencia de prediabetes se asoció significativamente con el porcentaje de grasa corporal (OR 1.056, IC95% 1.008-1.106), el nivel de triglicéridos (OR 1.013, IC95% 1.006-1.019) y colesterol (OR 1.015, IC95% 1.004-1.019). De igual forma, la presencia de hipertrigliceridemia (OR 4.297, IC95% 1.698-10.872) y resistencia a la insulina (OR 9.902, IC95% 4.094-23.952) se observaron fuertemente asociadas al desarrollo de prediabetes.

Conclusiones: La prevalencia de factores de riesgo cardiovascular y metabólico en la población escolar estudiada fue elevada. Las principales variables asociadas al desarrollo de prediabetes en niños fueron la presencia de hipertrigliceridemia y resistencia a la insulina, así como el porcentaje de grasa corporal y el nivel de colesterol.

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En los últimos diez lustros han existido grande cambios que han revolucionado el mundo farmacéutico, ante los cuales es necesario una constante adaptación y reinvención. Así, es como la Asociación Farmacéutica Mexicana AC ha logrado trascender en el tiempo y cumplir medio siglo de ser la Asociación por Excelencia de los profesionales Farmacéuticos.

Ha sido una ardua labor cumplir con los altos estándares que se exigen en este sector, por lo que se ha requerido de un gran compromiso y competitividad para cumplir "50 años de Innovación, Experiencia y Excelencia".

Este año al celebrar la cuadragésima novena edición del Congreso Nacional de Ciencias Farmacéuticas y Séptima Edición Internacional, la AFMAC reafirma su contribución en la formación de profesionistas de calidad mundial, con un programa científico de alto nivel con prestigiados ponentes extranjeros y nacionales, expertos en sus respectivos campos de estudio, buscando que los contenidos sean de utilidad para acrecentar el conocimiento requerido en el ejercicio diario de las diferentes áreas que conforman el gremio farmacéutico. Por otra parte, con la presentación de los trabajos libres, una de las actividades fundamentales del congreso, se presentarán los esfuerzos de diferentes grupos de investigación; esto se logra con el intercambio de experiencias y opiniones de manera cordial y sencilla, sin perder objetividad y visualizar la actualidad de las Ciencias Farmacéuticas en México.
Finalmente, quiero aprovechar este espacio para hacer un afectuoso reconocimiento al trabajo realizado por el Comité Científico, el Consejo Directivo y el Personal de Apoyo de la Asociación Farmacéutica Mexicana AC, sin cuya participación no sería posible realizar esta reunión que nos permite trascender como gremio competitivo.

Dra. Elizabeth Sánchez-González
Directora de Ciencia y Tecnología
AFM AC

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Por la presentación del trabajo:

Polimorfismos en genes codificantes de transportadores de urato asociados con deterioro cognitivo en adulto mayor.

durante XLIX Congreso Nacional de Ciencias Farmacéuticas
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TRABAJO LIBRE - BDM00008

Valores de referencia de hemoglobina glucosilada de una población entre 20 y 30 años

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Introducción: La diabetes mellitus tipo 2 (DM2) es una alteración metabólica, que se caracteriza por niveles elevados de glucosa, debido a una deficiencia en la producción o en la acción de la insulina; afecta a más de 11.5 millones de mexicanos en una edad entre 20 a 79 años. Es un padecimiento que favorece el desarrollo de complicaciones como retinopatías, nefropatías y enfermedades cardiovasculares. Existen criterios diagnósticos para la DM2, en donde a partir del 2010 la American Society of Diabetes (ADA) incorpora la hemoglobina glucosilada (HbA1c) como criterio de diagnóstico. La HbA1c es una proteína que sirve para estimar el promedio de glucosa de un paciente durante los últimos tres meses. Los valores de referencia, son magnitudes importantes que se utilizan para la interpretación médica de resultados clínicos y es fundamental que cada laboratorio de diagnóstico cuente con valores de referencia propios debido a que dependen de la etnia, la edad y el sexo.

Objetivo: Establecer valores de referencia de HbA1c en estudiantes de la Universidad Autónoma del Estado de Morelos (UAEM).

Metodología: Se realizó un estudio transversal con una muestra aleatoria de estudiantes de la UAEM. Los estudiantes interesados en participar firmaron una carta de consentimiento informado y contestaron un cuestionario socio-demográfico. Se realizarón mediciones antropométricas de peso, talla, circunferencia de cintura y presión arterial. Se tomó una muestra sanguínea para cuantificar los niveles de glucosa y de HbA1c. La determinación de HbA1c y glucosa se realizaron con técnicas inmunoenzimáticas con un equipo COBAS 111-Roche USA.

Resultados: Participaron 92 estudiantes entre 20 y 30 años de edad de las diferentes facultades la UAEM, obteniendo los siguientes resultados: 33% hombres y 59% mujeres, el valor promedio de glucosa en ayuno fue de 70.78 (±16.12) mg/dl, la media de la población de HbA1c fue de 5.41% (±0.232), y los intervalos de referencia obtenidos fueron: límite inferior de 4.94% y un límite superior de 5.88%

Conclusiones: Se obtuvo un intervalo de referencia para esta población de 4.94% a 5.88%, intervalo con una diferencia de 0.19%, pero cerca del valor reportado por la ADA y la OMS (< 5.7%) en personas sanas.

TRABAJO LIBRE - BDM00009

Genotipificación del polimorfismo rs2228001 del gen XPC en mujeres con preeclampsia y embarazo normoevolutivo

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Introducción: La preeclampsia es un síndrome clínico caracterizado por hipertensión con disfunción orgánica múltiple, proteinuria y edema. Las bases moleculares de los factores causales implicados en la patogenia de la preeclampsia no son muy claras. Genes asociados con la prevención o reparación del ADN se han propuesto como candidatos potenciales para ser estudiados y determinar su posible rol en el desarrollo de la preeclampsia. El gen *XPC* codifica para una proteína indispensable del sistema de reparación por escisión de nucleótidos. El polimorfismo rs2228001 (T/G) ha sido asociado a distintos tipos de cáncer incluyendo el de pulmón y vejiga, sin embargo, no hay estudios que evalúen su posible asociación con la preeclampsia.

Objetivo: Determinar si existe asociación entre el polimorfismo rs2228001 del gen *XPC* y la preeclampsia.

Metodología: Estudio prospectivo de casos (diagnóstico de preeclampsia) y controles (embarazo normoevolutivo). De sangre periférica se extrajo ADN utilizando el sistema QIAamp DNA Blood Mini Kit. La genotipificación se realizó utilizando sondas Taqman. Se usaron medidas de tendencia central y de dispersión para los datos descriptivos, para las diferencias entre grupos se usaron las pruebas T de Student y Chi cuadrada. Para la estimación del riesgo (Odds Ratio, OR) se utilizó el software SNPstats.

Resultados: Al comparar los grupos (100 casos y 194 controles) se encontraron diferencias estadísticamente significativas en la TA sistólica y diastólica, semanas de gestación e IMC. En la edad y antecedente de preeclampsia no hubo diferencias entre los grupos. Las frecuencias alélicas fueron T=0.65, G=0.35 (controles), T=0.72 y G=0.28 (casos). Las frecuencias genotípicas fueron T/T=0.42, T/G=0.47, G/G=0.11 (controles), T/T=0.53, T/G=0.39, G/G=0.08 (casos). Aunque estadísticamente no se encontró asociación entre el polimorfismo rs2228001 y la preeclampsia al estimar la OR en los modelos de herencia codomiante, dominante y recesivo, el modelo dominante muestra una tendencia hacia la probabilidad de que este polimorfismo sea un factor protector (OR=0.64, IC95=0.39-1.04).

Conclusiones: Aunque las evidencias sugieren que el polimorfismo rs2228001 del gen *XPC* no se relaciona con la preeclampsia, es necesario realizar nuevos estudios con tamaño de muestra mayores en población mexicana para confirmar nuestros resultados.

TRABAJO LIBRE - BDM00012

Frecuencia de SNPs del gen MDR1 en pacientes de cardiología del HRAEB tratados con digoxina

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Introducción: La glicoproteína P es producto del gen de resistencia a multi- fármacos (MDR1 o ABCB1) y sus variantes genéticas pueden influenciar la biodisponibilidad y farmacocinética de varios fármacos. Tres polimorfismos (SNPs), C3435T, G2677T/A y C1236T, se han asociado al desequilibrio en la función de PGP y su genotipificación podría resultar de gran importancia para el tratamiento farmacológico personalizado de ciertos pacientes. La frecuencia genotípica ayudaría a catalogar la importancia del diagnóstico molecular.

Objetivo: Evaluar la frecuencia y genotipificación de los SNPs C3435T, C1236T y G2677 A/T del gen MDR1 en pacientes de cardiología del Hospital Regional de Alta Especialidad Bajío tratados con digoxina.

Metodología: Se obtuvo DNA genómico de 28 muestras de sangre completa de pacientes del área de cardiología del HRAEB tratados con digoxina, previa firma del consentimiento informado. Las muestras de sangre fueron obtenidas con EDTA como anticoagulante y el DNA fue purificado con el sistema Wizard Genomic DNA Purification kit. Los SNPs (C3435T, C1236T y G2677T/A) fueron identificados por MS-PCR, empleando cebadores específicos (M3435T/C/Rev; M1236T/C/Rev; M2677T/C/rev). Una vez obtenido el genotipo se calculó la frecuencia genotípica de la población incluida.

Resultados: De los 28 individuos incluidos en la población se observaron solo dos de los tres posibles genotipos para el SNP C1236T, con una frecuencia de CC(0.32) y CT(0.68). Para el SNP G2677T/A fueron cuatro de los seis genotipos posibles con una frecuencia de GA(0.04), TT(0.11), GG(0.21), GT(0.64). Para C3435T, se observaron los tres genotipos posibles con una frecuencia de CC (0.11), CT(0.86) y TT(0.03).

Conclusiones: Los genotipos más frecuentes fueron los heterocigotos CT, CT y GT para el SNP 3435, 1236 y 2677 respectivamente. Reportes sugieren que los homocigotos AA y TT para el SNP 2677 y TT para 3435 presentan menor expresión de PGP intestinal y un incremento en niveles plasmáticos de digoxina administrada vía oral, lo cual sugiere que al menos tres individuos con estos genotipos en la población estudiada pudieran tener un riesgo de intoxicación. Sin embargo es necesario realizar estudios de farmacovigilancia con el objetivo de demostrar la susceptibilidad que pudieran tener los pacientes con este genotipo.

TRABAJO LIBRE - BDM00013

Polimorfismos en IL6 e IL10 como factor de riesgo para la infección por *Toxoplasma gondii*

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Introducción: La toxoplasmosis es una de las zoonosis parasitarias más comunes ocasionada por el protozoario *Toxoplasma gondii*, el cual infecta a todas las especies animales de sangre caliente incluyendo al humano. La respuesta inmune desempeña un papel en la determinación de la evolución de la enfermedad y, posiblemente, en la respuesta a la terapia convencional. Evidencias recientes demuestran que los polimorfismos -819 T/C del gen *IL-10* y -174 G/C del gen *IL-6* se asocian con bajos niveles de expresión. En virtud del papel que las interleucinas juegan en el proceso de respuesta inmune en contra de *Toxoplasma gondii* , diversos grupos de investigación han evaluado el efecto de estos y otros polimorfismos en los genes que las codifican.

Objetivo: Determinar si los polimorfismos -819 T/C del gen *IL-10* y -174 G/C del gen *IL-6* son un factor de riesgo para la toxoplasmosis.

Metodología: Estudio transversal integrado por 252 individuos del municipio de San Dimas en el estado de Durango. Se tomaron muestras de sangre periférica a partir de las cuales se extrajo ADN utilizando el sistema QIAamp DNA Blood. La genotipificación se realizó utilizando sondas Taqman. La infección por toxoplasma se evaluó determinando la presencia de anticuerpos IgG e IgM anti-*Toxoplasma gondii* mediante un inmunoensayo enzimático.

Resultados: Tomando en consideración la positividad (casos, n=169) o negatividad (controles, n=83) se conformaron los grupos de análisis. El 50% de la población fueron mujeres (n=126). De la población estudiada el 97.64% manifestó tener contacto con animales (gatos, perros, aves domésticas y/o animales de granja). Al analizar las frecuencias alélicas y genotípicas de ambos polimorfismos encontramos diferencias estadísticamente significativas en las frecuencias alélicas del polimorfismo -819 T/C (p=0.041) al comparar los grupos. Al estimar el riesgo que confieren estos polimorfismos en un modelo de herencia dominante, encontramos los siguientes resultados: una OR=1.06 (IC_{95}=0.59-1.92) para C/G-C/C en el polimorfismo -174 G/C y una OR=1.95 (IC_{95}=1.13-3.36) para T/C-C/C en el polimorfismo -819 T/C.

Conclusiones: El polimorfismo -819 T/C del gen *IL-10* puede ser un factor de riesgo para la toxoplasmosis en la población estudiada.

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JN-CAR-IC-45.

NIVELES DE ÁCIDO ÚRICO EN SUJETOS DE DURANGO CON ENFERMEDAD DE PARKINSON

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INTRODUCCIÓN.

La función del ácido úrico (AU) y su efecto fisiopatológico en casos de EP en México han sido poco descritos. El AU ejerce un efecto antioxidante en neuronas y se conoce como un quelador de hierro. Previos reportes en otras poblaciones han asociado niveles bajos de AU con la EP.

OBJETIVO.

Determinar si existen diferencias en los niveles séricos de AU entre casos de EP y controles en población Duranguense.

MATERIAL Y MÉTODO.

Estudio de 61 casos de EP y 69 controles en sujetos que acudieron al Hospital General 450, el Hospital Santiago Ramón y Cajal del ISSSTE y Ciudad del Anciano en Durango.

RESULTADOS.

Encontramos niveles de AU de 5.35 $\pm$ 2.30 mg/dL para los casos y 6.03 $\pm$ 1.31 mg/dL para los controles (p = 0.010). Al estratificar por género, los niéveles de AU en mujeres con EP fue de 5.35 $\pm$ 1.46 mg/dL y de 5.62 $\pm$ 1.24 mg/dL para el grupo control (p = 0.442). En el grupo de hombres los niveles de AU fueron de 5.52 $\pm$ 6.45 mg/dL para los casos con EP y 6.46 $\pm$ 1.26 mg/dL para los controles (p = 0.008).

CONCLUSIONES.

Existen diferencias estadísticamente significativas en los niveles de AU, siendo menores en los individuos con EP. Al estratificar por género, observamos que esta diferencia solamente se mantiene en los hombres. Nuestros resultados concuerdan con lo previamente reportado en otras poblaciones.

PALABRAS CLAVE.

Enfermedad de Parkinson, ácido úrico, antioxidante.

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JN-CAR-IC-46.

CARACTERIZACIÓN DE LAS VARIANTES H1/H2 DE MAPT Y RS1801133 DE MTHFR EN SUJETOS MEXICANOS CON ENFERMEDAD DE PARKINSON

Miranda Morales Ernesto Gerardo[1], Castellanos Juárez Francisco Xavier[1], La Llave León Osmel[1], Méndez Hernández Edna Madai[1], Sandoval Carrillo Ada[1], Quiñones Canales Gerardo[2], Ruano Calderón Luis Ángel[3], Arias Carrión Oscar[4], Salas Pacheco José Manuel[1].

1. Instituto de Investigación Científica, UJED-Durango
2. Hospital General Santiago Ramón y Cajal-ISSSTE, Durango
3. Hospital General 450, Durango
4. Hospital General Dr. Manuel Gea González, Ciudad de México

INTRODUCCIÓN.

Se han identificado mutaciones y polimorfismos en genes relacionados con la Enfermedad de Parkinson (EP). No obstante, las bases genéticas, y bioquímicas asociadas a la EP han sido poco estudiadas en nuestro país.

OBJETIVO.

Genotipificar los haplotipos H1/H2 de MAPT y rs1801133 del gen MTHFR en sujetos con EP e individuos sanos. Posteriormente, se determinará si estos polimorfismos están asociados a cambios epigenéticos.

MATERIAL Y MÉTODO.

Estudio de 108 casos y 91 controles en sujetos que acudieron al Hospital General Dr. Manuel Gea González en la Ciudad de México, el Hospital General 450, el Hospital Santiago Ramón y Cajal del ISSSTE y Ciudad del Anciano en Durango.

RESULTADOS.

Las frecuencias para los genotipos H1/H2 de MAPT fueron H1/H1: 0.80, H1/H2: 0.18 y H2/H2: 0.02, con respecto a los casos y H1/H1: 0.85, H1/H2: 0.14, y H2/H2: 0.01, con respecto a los controles. Las frecuencias genotípicas para el SNP rs1801133 de MTHFR fueron C/C: 0.19, C/T: 0.47, y T/T: 0.34, con respecto a los casos y C/C: 0.23, C/T: 0.53, y T/T: 0.24, para los controles. No se observaron diferencias estadísticamente significativas al comparar las frecuencias alélicas y genotípicas entre los casos y los controles (p = 0.3600 para H1/H2 de MAPT y p = 0.1450 para rs1801133 de MTHFR). Al estratificar por región (centro y norte del país) tampoco se observaron diferencias.

CONCLUSIONES.

Nuestros resultados sugieren que las variantes estudiadas no se asocian con la EP en la población estudiada.

PALABRAS CLAVE.

Enfermedad de Parkinson, MAPT, MTHFR.

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JN-CAR-IC-44.

PARAMETROS HEMATOLÓGICOS EN SUJETOS DURANGUENSES CON ENFERMEDAD DE PARKINSON

Miranda Morales Ernesto Gerardo[1], Castellanos Juárez Francisco Xavier[1], La Llave León Osmel[1], Méndez Hernández Edna Madai[1], Sandoval Carrillo Ada[1], Quiñones Canales Gerardo[2], Ruano Calderón Luis Ángel[3], Arias Carrión Oscar4 y Salas Pacheco José Manuel[1].

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3. Hospital General 450, Durango
4. Hospital General Dr. Manuel Gea González, Ciudad de México

INTRODUCCIÓN.

Los parámetros hematológicos y su asociación con la Enfermedad de Parkinson (EP) han sido poco descritos. En particular, el incremento en los niveles de Hemoglobina (Hb) se ha asociado con una mayor incidencia de EP.

OBJETIVO.

Determinar si existen diferencias en los parámetros hematológicos entre sujetos con EP y un grupo control.

MATERIALES Y MÉTODOS.

Estudio de 35 casos de EP y 35 controles en sujetos que acudieron al Hospital General 450, el Hospital Santiago Ramón y Cajal del ISSSTE y Ciudad del Anciano en Durango.

RESULTADOS.

Los niveles de Hb fueron de 14.71±2.02 dL y 14.21±2.02 dL, en casos y controles, respectivamente (p = 0.315). El recuento de glóbulos rojos (RBC) de casos fue de 4.72±0.51 y de los controles de 4.74±0.63 (p = 0.939). El volumen corpuscular medio (VCM) de 90.72±7.73 en casos y 91.62±4.98 en controles (p = 0.264). El Hematocrito (HCT) se encontró en 42.87±5.75 en casos y 43.35±5.54 en controles (p = 0.485). La Hemoglobina corpuscular media (HCM) fue de 31.08±2.11 en casos y 30.05±2.20 en controles (p = 0.049). Finalmente, la concentración de la hemoglobina corpuscular media (CHCM) se encontró en 34.35±2.04 en casos y 32.79±1.81 en controles (p < 0.001).

CONCLUSIÓN.

Aunque los niveles de Hb fueron ligeramente mayores en los casos, no se encontraron diferencias significativas. Sin embargo, si se observaron diferencias significativas en los niveles de HCM y CHCM. Futuros estudios con tamaños muestrales mayores son necesarios para corroborar estos hallazgos en nuestra población.

PALABRAS CLAVE.

Enfermedad de Parkinson, parámetros hematológicos, hemoglobina.

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XLII Congreso Nacional de Genética Humana

MÉRIDA, YUCATÁN, Noviembre 29 a Diciembre 2 de 2017

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CENTRO DE INVESTIGACIONES REGIONALES "DR. HIDEYO NOGUCHI"
UNIVERSIDAD AUTÓNOMA DE YUCATÁN
MÉXICO

Alma Cristina Salas Leal, Francisco Xavier Castellanos Juárez, Osmel La Llave León, Edna Madai Méndez Hernández, Gerardo Quiñones Canales, Luis Ángel Ruano Calderón, Oscar Arias Carrión, José Manuel Salas Pacheco y Ada Sandoval Carrillo

Por la presentación del trabajo libre en modalidad Cartel:

CARACTERIZACIÓN DE LOS PERFILES DE EXPRESIÓN DEL GEN *SNCA* Y SU VARIANTE rs356219 EN PACIENTES CON ENFERMEDAD DE PARKINSON

Mérida, Yucatán, diciembre 1 de 2017

DR. JORGE E. ZAVALA CASTRO
Director CIR Dr. Hideyo Noguchi UADY

DRA. DORIS PINTO ESCALANTE
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DR. RODRIGO RUBI CASTELLANOS
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XLII Congreso Nacional de Genética Humana

MÉRIDA, YUCATÁN, Noviembre 29 a Diciembre 2 de 2017

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MÉRIDA

Edith Maldonado-Soto, Sergio M. Salas-Pacheco, Ernesto G. Miranda-Morales, Edna M. Méndez-Hernández, Francisco X. Castellanos-Juárez, Osmel La Llave-León, Oscar Arias-Carrión, José M. Salas-Pacheco y Ada Sandoval-Carrillo

Por la presentación del trabajo libre en modalidad Cartel:

POLIMORFISMOS EN GENES DE REPARACION DE ADN Y SU ASOCIACIÓN CON LA ENFERMEDAD DE PARKINSON

Mérida, Yucatán, noviembre 30 de 2017

DR. JORGE E. ZAVALA CASTRO
Director CIR Dr. Hideyo Noguchi UADY

DRA. DORIS PINTO ESCALANTE
Presidente AMGH

DR. RODRIGO RUBI CASTELLANOS
Secretario AMGH

JN-CAR-IC-47.

CARACTERIZACIÓN DE POLIMORFISMOS EN LOS GENES SNCA, UBE2K, ALDH1A1, HSPA8, SKP1A Y PSMC4 EN SUJETOS CON ENFERMEDAD DE PARKINSON

Salas Leal Alma Cristina[1], Castellanos Juárez Francisco Xavier[1], La Llave León Osmel[1], Méndez Hernández Edna Madai[1], Quiñones Canales Gerardo[2], Ruano Calderón Luis Ángel[3], Arias Carrión Oscar[4], Salas Pacheco José Manuel[1], Sandoval Carrillo Ada[1].

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3. Hospital General 450, Durango
4. Hospital General Dr. Manuel Gea González, Ciudad de México

INTRODUCCIÓN.

La enfermedad de Parkinson (EP) es una enfermedad neurodegenerativa que se manifiesta como una desregulación en el control del movimiento. La EP está caracterizada por la pérdida de dopamina y la presencia de cuerpos de Lewy, formados por ubiquitina y a-sinucleína. A la fecha se han realizado diversos estudios que han asociado variantes génicas con la EP en diversas poblaciones; sin embargo, este tipo de estudios son muy escasos en población mexicana.

OBJETIVO.

Determinar las frecuencias alélicas y genotípicas de los polimorfismos rs3764435 de ALDH1A1, rs234365 de PSMC4, rs2110585 de SKP1, rs305124 de UBE2K, rs2236659 de HSPA8 y rs356219 de SNCA y su asociación con la EP.

MATERIALES Y MÉTODOS.

Se reclutaron 45 casos y 70 controles. La genotipificación se realizó por PCR tiempo real. Los análisis se realizaron con el programa SNPStats.

RESULTADOS.

El análisis de las frecuencias alélicas y genotípicas evidenció que solo el polimorfismo rs356219 del gen SNCA es un factor de riesgo para la EP (OR=2.8, IC951.277-6.163, p=0.009). Las frecuencias alélicas para este polimorfismo fueron A=0.46, G=0.54 en controles y A=0.30, G=0.70, en casos. Las genotípicas fueron A/A=0.19, G/A=0.54, G/G=0.27 en controles y A/A=0.11, G/A=0.38, G/G=0.51 en casos.

CONCLUSIONES.

El alelo G del polimorfismo rs356219 del gen SNCA es más frecuente en los pacientes con EP. Nuestros resultados confirman lo reportado previamente en otras poblaciones en los que se ha observado que el alelo G incrementa el riesgo de la EP. No se observó asociación con ninguna de las otras variantes y la EP.

PALABRAS CLAVE.

Enfermedad de Parkinson, SNCA, rs356219.

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Por la presentación del trabajo libre en modalidad Cartel:

VARIANTES DEL GEN *TNF-α* Y SU ASOCIACIÓN CON DEPRESIÓN EN MUJERES EMBARAZADAS

Mérida, Yucatán, diciembre 1 de 2017

DR. JORGE E. ZAVALA CASTRO
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Por la presentación del trabajo ***"VARIANTES DEL GEN TNF-α Y SU ASOCIACIÓN CON DEPRESIÓN EN MUJERES EMBARAZADAS"****, realizado en las Jornadas Académicas "La Investigación Científica, Compromiso y Pertinencia Social", en el marco conmemorativo del XLVIII Aniversario del IIC y II Encuentro de Investigación de la DES - Ciencias de la Salud de la UJED.*

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Por la presentación del trabajo ***"ANÁLISIS POSTMORTEM DE POLIMORFISMOS Y PERFILES DE EXPRESIÓN DE LOS GENES HMGCR, SREBP2, SOAT1 Y CYP46A1 Y SU ASOCIACIÓN CON SUICIDIO"****, realizado en las Jornadas Académicas "La Investigación Científica, Compromiso y Pertinencia Social", en el marco conmemorativo del XLVIII Aniversario del IIC y II Encuentro de Investigación de la DES - Ciencias de la Salud de la UJED.*

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Por la presentación del trabajo ***"ASOCIACIÓN ENTRE LOS NIVELES DE PLOMO EN SANGRE Y LA ACTIVIDAD DE LA ENZIMA ÁCIDO DELTA-AMINOLEVULÍNICO DESHIDRATASA"****, realizado en las Jornadas Académicas "La Investigación Científica, Compromiso y Pertinencia Social", en el marco conmemorativo del XLVIII Aniversario del IIC y II Encuentro de Investigación de la DES - Ciencias de la Salud de la UJED.*

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Por la presentación del trabajo ***"RELACIÓN ENTRE LOS NIVELES DE PLOMO EN SANGRE Y LA EXPOSICIÓN OCUPACIONAL EN MUJERES EMBARAZADAS DE DURANGO"****, realizado en las Jornadas Académicas "La Investigación Científica, Compromiso y Pertinencia Social", en el marco conmemorativo del XLVIII Aniversario del IIC y II Encuentro de Investigación de la DES - Ciencias de la Salud de la UJED.*

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Por la presentación del trabajo ***"POLIMORFISMOS EN GENES DE REPARACION DE ADN Y SU ASOCIACIÓN CON LA ENFERMEDAD DE PARKINSON"****, realizado en las Jornadas Académicas "La Investigación Científica, Compromiso y Pertinencia Social", en el marco conmemorativo del XLVIII Aniversario del IIC y II Encuentro de Investigación de la DES - Ciencias de la Salud de la UJED.*

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A ***Alfredo Martínez Juárez, José M. Salas Pacheco, Francisco X. Castellanos Juárez, Alma Rosa Pérez Álamos, Osmel La Llave León***

Por la presentación del trabajo ***"NIVELES DE PLOMO EN SANGRE Y MUERTE FETAL EN MUJERES EMBARAZADAS DE DURANGO"****, realizado en las Jornadas Académicas "La Investigación Científica, Compromiso y Pertinencia Social", en el marco conmemorativo del XLVIII Aniversario del IIC y II Encuentro de Investigación de la DES - Ciencias de la Salud de la UJED.*

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Por la presentación del trabajo ***"PARÁMETROS HEMATOLÓGICOS EN SUJETOS DE DURANGO CON ENFERMEDAD DE PARKINSON"****, realizado en las Jornadas Académicas "La Investigación Científica, Compromiso y Pertinencia Social", en el marco conmemorativo del XLVIII Aniversario del IIC y II Encuentro de Investigación de la DES - Ciencias de la Salud de la UJED.*

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Por la presentación del trabajo ***"CARACTERIZACIÓN DE LAS VARIANTES H1/H2 DE MAPT y rs1801133 DE MTHFR EN SUJETOS MEXICANOS CON ENFERMEDAD DE PARKINSON"****, realizado en las Jornadas Académicas "La Investigación Científica, Compromiso y Pertinencia Social", en el marco conmemorativo del XLVIII Aniversario del IIC y II Encuentro de Investigación de la DES - Ciencias de la Salud de la UJED.*

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Por la presentación del trabajo ***"NIVELES DE ÁCIDO ÚRICO EN SUJETOS DE DURANGO CON ENFERMEDAD DE PARKINSON"****, realizado en las Jornadas Académicas "La Investigación Científica, Compromiso y Pertinencia Social", en el marco conmemorativo del XLVIII Aniversario del IIC y II Encuentro de Investigación de la DES - Ciencias de la Salud de la UJED.*

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A ***Salas-Leal A C, Pérez-Gavilán Ceniceros J A, Salas-Pacheco J M, Arias-Carrión O, Quiñones-Canales G, Ruano-Calderón L A, Castellanos-Juárez F X, Méndez-Hernández E M, La Llave-León O, Sandoval-Carrillo A A.***

Por la presentación del trabajo ***"ASOCIACIÓN DEL SNP rs3764435 DEL GEN ALDH1A1 CON ENFERMEDAD DE PARKINSON EN POBLACIÓN MEXICANA"****, realizado en las Jornadas Académicas "La Investigación Científica, Compromiso y Pertinencia Social", en el marco conmemorativo del XLVIII Aniversario del IIC y II Encuentro de Investigación de la DES - Ciencias de la Salud de la UJED.*

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Victoria de Durango, Dgo. a 05 de Octubre de 2018

Dr. Luis Francisco Sánchez Anguiano
Director del IIC

Dra. Laura Ernestina Barragán Ledesma
Representante de la DES
Ciencias de la Salud

UNIVERSIDAD JUÁREZ DEL ESTADO DE DURANGO

INSTITUTO DE INVESTIGACIÓN CIENTÍFICA

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Constancia

A ***Salas-Leal A C, Salas-Pacheco J M, Arias-Carrión O, Quiñones-Canales G, Ruano-Calderón L A, Castellanos-Juárez F X, Méndez-Hernández E M, La Llave-León O, Sandoval-Carrillo A A***

Por la presentación del trabajo ***"α-SINUCLEINA Y ENFERMEDAD DE PARKINSON EN POBLACION MEXICANA",*** *realizado en las Jornadas Académicas "La Investigación Científica, Compromiso y Pertinencia Social", en el marco conmemorativo del XLVIII Aniversario del IIC y II Encuentro de Investigación de la DES - Ciencias de la Salud de la UJED.*

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A ***Ana Karem Sosa Hernández, Edna Madaí Méndez Hernández, Oscar Árias Carrión, José Manuel Salas Pacheco, Ada Agustina Sandoval Carrillo, Francisco Xavier Castellanos Juárez, Marcelo Barraza Salas***

Por la presentación del trabajo ***"CARACTERIZACIÓN DE LOS PATRONES DE EXPRESIÓN DE LOS GENES CLOCK Y VARIABLES POLISOMNOGRÁFICAS EN PACIENTES CON ENFERMEDAD DE PARKINSON"****, realizado en las Jornadas Académicas "La Investigación Científica, Compromiso y Pertinencia Social", en el marco conmemorativo del XLVIII Aniversario del IIC y II Encuentro de Investigación de la DES - Ciencias de la Salud de la UJED.*

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Trabajo 41

Variantes génicas y perfiles de expresión de genes reguladores de la síntesis de colesterol cerebral (HMGCR, SREBP2 y CYP46A1) y su asociación con la presencia de Trastorno Depresivo Mayor

Ponente: MENDEZ HERNANDEZ EDNA MADAI

(1)Méndez Hernández Edna Madai; (2) Marcela Araceli Segoviano Mendoza; (2) Manuel de Jesús Cárdenas de la Cruz; (3) Oscar Arias Carrión; (2) Marcelo Barraza Salas; (2) Francisco Xavier Castellanos Juarez; (2) José Manuel Salas Pacheco

(1)Hospital Regional De Alta Especialidad Ixtapaluca; (2) Universidad Juárez del Estado de Durango; (3) Hospital General "Dr. Manuel Gea González

Área: BIOMEDICA

Antecedentes. Evidencia reciente sugiere que las alteraciones en la biosíntesis del colesterol representan un mecanismo asociado con el desarrollo del trastorno depresivo mayor (TDM) al afectar las vías de señalización serotoninérgicas centrales. La enzima de unión al elemento regulador de esteroles 2 (SREBP-2), la enzima 3-hidroxi-3-metilglutaril-CoA reductasa (HMGCR) y la enzima colesterol 24-hidroxilasa (CYP46A1) participan en la síntesis del colesterol cerebral. Los polimorfismos en los genes SREBP-2, HMGCR y CYP46A1 y sus perfiles de expresión podrían estar asociados con TDM. Por lo tanto, investigamos este vínculo entre los polimorfismos y los perfiles de expresión de los genes HMGCR, SREBP-2 y CYP46A1 y MDD en 424 sujetos adultos de la población mexicana mestiza.

Objetivo. Establecer si existe asociación entre los polimorfismos y perfiles de expresión de los principales genes reguladores de la síntesis de colesterol cerebral (HMGCR, SREBP2 y CYP46A1) con la presencia de Trastorno Depresivo Mayor

Material y Métodos. Estudio de casos y controles que incluyó 212 sujetos deprimidos y 212 controles sanos. Los polimorfismos rs2228314, rs376174, rs3846662 y rs754203 y los perfiles de expresión se analizaron usando rtPCR. Se determinaron los niveles plasmáticos de 24 S-hidroxicolesterol, colesterol, triglicéridos y colesterol de lipoproteínas de alta densidad (HDL-c) y colesterol de lipoproteínas de baja densidad (LDL-c).

Resultados. La frecuencia de hipocolesterolemia fue significativamente mayor en sujetos con TDM (31.13% vs 13.68%, p <0.001). El genotipo heterocigoto de rs3846662 se asoció con MDD (OR 1.72 IC95% 1.076-2.761, p 0.02). Los niveles de expresión del gen SREBP-2 fueron significativamente más bajos (p <0.002), mientras que los niveles de expresión del gen HMGCR fueron significativamente más altos (p <0.023) en el grupo con TDM en comparación con el grupo control. Una correlación inversa entre los niveles de lípidos en suero y los niveles de expresión del gen HMGCR (r -0.331, p 0.005).

Conclusión. Nuestros resultados muestran por primera vez una asociación entre los polimorfismos HMGCR rs3846662 y MDD así como entre los perfiles de expresión del perfil de los genes SREBP-2 y HMGCR con MDD en la población mexicana mestiza

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POLIMORFISMOS NULOS DE LOS GENES *GSTT1* Y *GSTM1* Y ENFERMEDAD DE PARKINSON

Alvarado-Retana KM, Salas-Pacheco SM, Antuna-Salcido EI, Sandoval-Carrillo AA, Castellanos-Juárez FX, Méndez-Hernández EM, La Llave-León O, Salas-Pacheco JM*

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La enfermedad de Parkinson (EP) es una patología neurodegenerativa que afecta aproximadamente al 3% de la población mundial, es multifactorial. Diversos estudios han asociado factores genéticos y ambientales con el desarrollo de la EP. Las Glutation S Transferasa (GST) son una familia de enzimas que intervienen tanto en el metabolismo de toxinas como en la desintoxicación celular lo que hipotéticamente implica una función neuroprotectora. Las GST más ampliamente estudiadas en relación a la EP son la GSTM1 y la GSTT1. Aunque se ha sugerido una asociación entre mutaciones nulas en estos genes y la EP, también hay estudios que sugieren que no existe, por lo que se ha propuesto que dicha asociación dependería de la población analizada. Por tal motivo, el objetivo de este trabajo fue determinar si existe una asociación entre las mutaciones nulas en *GSTT1* y *GSTM1* y la EP en población mexicana. Se llevó a cabo un estudio de casos (75 pacientes con diagnóstico de EP) y testigos (75 individuos sin enfermedad neurodegenerativa) los cuales fueron pareados por edad y género. Se obtuvo DNA de sangre periférica y se realizó la genotipificación por PCR de punto final. Se realizaron las pruebas UPDRS, minimental y Hamilton para evaluar la severidad de la EP, estado cognitivo y depresión, respectivamente. La media de edad tanto para casos como para testigos fue de 70 años. Al comparar los resultados de las pruebas de minimental y Hamilton entre casos y testigos, solo la escala de Hamilton presentó diferencias estadísticamente significativas ($p<0.001$), siendo mayor en los casos que en los testigos. La media para los casos del UPDRS fue de 66.63. La mutación nula *GSTT1* se presentó en 7 de los casos y 11 de los testigos y la mutación nula en *GSTM1* en 27 de los casos y 26 de los testigos. Al comparar ambos grupos no encontramos diferencias estadísticamente significativas ni para la mutación nula en *GSTT1* ni para *GSTM1* ($p=0.314$ y $p=0.864$, respectivamente). En conclusión, los resultados sugieren que no existe asociación entre las mutaciones nulas en *GSTT1* y *GSTM1* y la EP.

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CARACTERIZACION DE LAS VARIANTES rs1805386 del gen *LIG4* y rs1805377 del gen *XRCC4* y SU ASOCIACIÓN CON LA PREECLAMPSIA

Gaytán-Esparza A[1], Sandoval-Carrillo A[1], Antuna-Salcido EI[1], Castellanos-Juárez FX[1], La Llave-León O[1], Méndez-Hernández EM[1], Guijarro-Bustillos J[2], Salas-Pacheco JM[1*]

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La preeclampsia (PE), enfermedad exclusiva del embarazo, es una de las principales causas de mortalidad materna en el mundo. Se caracteriza por presión arterial mayor de 140/90 mm/Hg y proteinuria mayor de 0,3 g/l después de las 20 semanas de gestación. Hoy en día se reconoce a la preeclampsia como un desorden placentario que tiene un origen genético multifactorial, es decir, es resultado de la interacción de genes y factores ambientales. A la fecha existen diversos estudios que demuestran que el daño al ADN es más elevado en pacientes con PE. Debido a esto, se ha propuesto que variantes en genes que participan en los procesos de reparación del ADN pueden asociarse a la PE. Por lo antes mencionado, el objetivo principal del presente trabajo fue determinar la asociación entre las variantes rs1805386 del gen *LIG4* y rs1805377 del gen *XRCC4* y la PE en mujeres de Durango. Se llevó a cabo un estudio transversal, observacional de casos y controles. Se incluyeron 155 mujeres con PE y 160 con embarazo normotenso. La genotipificación se realizó mediante PCR en tiempo real. Los controles presentaron una media de edad de 24.52±7.32 años y los casos de 23.53±6.8 años (p=0.083). Las medias de semanas de gestación fueron 37.95±3.54 y 35.38±5.30 para los controles y casos, respectivamente (p<0.001). El 30% de los controles y el 43.2% de los casos tuvo antecedentes de PE (p=0.015). Las frecuencias alélicas y genotípicas para la variante rs1805386 fueron T=0.90, C=0.10, T/T=0.84, T/C=0.11 y C/C=0.05 para los controles y T=0.93, C=0.07, T/T=0.85, T/C=0.14 y C/C=0.01 para los casos. Para la variante rs1805377 fueron G=0.62, A=0.38, G/G=0.37, G/A=0.49 y A/A=0.14 para los controles y G=0.6, A=0.4, G/G=0.4, G/A=0.4 y A/A=0.2 para los casos. No encontramos diferencias estadísticamente significativas para ninguna de las variantes al, comparar los grupos. Finalmente, se estimó la OR ajustando por edad y semanas de gestación; no encontramos asociación entre las variantes y la PE. En conclusión, nuestros resultados sugieren que en nuestra población, las variantes rs1805386 del gen *LIG4* y rs1805377 del gen *XRCC4* no se asocian con la PE.

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EL POLIMORFISMO *rs1800435* (*G177C)* DEL GEN *ALAD* COMO FACTOR DE RIESGO PARA INTOXICACIÓN POR PLOMO Y PREECLAMPSIA

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La exposición a tóxicos ambientales, como el plomo, se ha asociado con algunas complicaciones del embarazo como abortos y preeclampsia. Existe evidencia sobre la influencia de ciertos genes en la absorción y distribución del plomo en el organismo. Un gen implicado en la susceptibilidad a la toxicidad del plomo es *ALAD*, el cual codifica la ácido δ-aminolevulínico deshidratasa, una enzima que cataliza el segundo paso en la síntesis del grupo hemo en los eritrocitos. En algunas poblaciones se ha encontrado asociación entre el polimorfismo *rs1800435* (G177C) del gen *ALAD* y los niveles de plomo en sangre (NPS). Por su participación en mecanismos que desencadenan estrés oxidante, este polimorfismo podría estar involucrado también en los mecanismos explicativos de la fisiopatología de la preeclampsia; un síndrome que causa entre 70,000 y 80,000 muertes maternas cada año en el mundo. Para la posible asociación de este polimorfismo con los NPS y con la preeclampsia se realizó un estudio de casos y controles anidado en una cohorte de 462 mujeres embarazadas del estado de Durango. Durante el seguimiento, 63 mujeres sufrieron preeclampsia (casos) y fueron seleccionadas al azar 252 controles (cuatro por cada caso). Se determinó NPS por espectrofotometría de absorción atómica con horno de grafito y se realizó la genotipificación por PCR en tiempo real con sondas TaqMan. Las frecuencias genotípicas en la cohorte fueron de 0.92 para el homocigoto silvestre GG (ALAD1-1); 0.07 para el heterocigoto GC (ALAD1-2) y 0.01 para el homocigoto mutado CC (ALAD2-2). La prueba *t* de Student mostró NPS más altos en las portadoras del alelo polimórfico en comparación con el genotipo homocigoto silvestre (3.07 ± 5.20 µg/mL vs 1.94 ± 2.38 µg/mL; p = 0.037). Aunque el porcentaje de preeclampsia fue mayor entre las portadoras del alelo polimórfico (12.7% vs 6.3%), el análisis de regresión logística no mostró asociación entre el polimorfismo y la preeclampsia [OR = 2.15, IC 95% (0.87 – 5.27); p = 0.096)]. Los resultados sugieren la necesidad de realizar más investigación sobre la posible asociación entre este polimorfismo y el riesgo de sufrir preeclampsia.

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ASOCIACIÓN DEL SNP RS3764435 DEL GEN ALDH1A1 CON ENFERMEDAD DE PARKINSON EN POBLACIÓN MEXICANA

Salas-Leal AC[1], Pérez-Gavilán Ceniceros JA[1], Salas-Pacheco JM[1], Arias-Carrión O[2], Quiñones-Canales G[3], Ruano-Calderón LA[4], Castellanos-Juárez FX[1], Mendez-Hernández EM[1], La Llave-León O[1], Sandoval-Carrillo AA[1]*

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La Enfermedad de Parkinson (EP) es el segundo desorden neurodegenerativo más frecuente. Recientemente se han reportado nuevos descubrimientos acerca de factores genéticos implicados en esta enfermedad. El gen ALDH1A1 codifica para la enzima aldehído deshidrogenasa, involucrada en la degradación de productos neurotóxicos resultado del metabolismo de la dopamina. Se ha demostrado que los niveles de ALDH1A1 y su actividad, se encuentran disminuidos en pacientes con EP. Entre los polimorfismos de un solo nucleótido (SNP) que podrían modular los niveles de expresión, se encuentra el SNP rs3764435 (A/C). El objetivo principal de este estudio fue establecer si existe asociación entre el SNP rs3764435 del gen ALDH1A1y la EP. Se trata de un estudio de casos (119 pacientes con diagnóstico de EP) y controles (177 individuos sin enfermedad neurodegenerativa). Se obtuvo ADN de sangre periférica y se realizó la genotipificaión por PCR tiempo real. El grupo control presentó una frecuencia para el alelo A=0.47 y para el alelo C=0.53; las frecuencias genotípicas fueron A/A=0.24, A/C=0.47 y C/C=0.29. Con respecto a los casos, las frecuencias alélicas fueron A=0.57 y C=0.43 y las genotípicas A/A=0.27, A/C=0.60 y C/C=0.13. Encontramos diferencias estadísticamente significativas entre los grupos tanto en las frecuencias alélicas como en las genotípicas (p=0.022 y p=0.006, respectivamente). El análisis de la estimación de riesgo evidenció que el genotipo C/C del SNP rs356219 del gen ALDH1A1 es un factor protector tanto en un modelo de herencia codominante como en el recesivo (OR=0.38, IC95%=0.20-0.71 y OR=0.42, IC95%=0.20-0.86, respectivamente). Nuestros resultados sugieren que el genotipo C/C del SNP rs3764435 del gen ALDH1A1 es un factor de protección para la EP en población mexicana y debido a su posición intrónica, se sugiere que el SNP puede tener un efecto positivo en la actividad enzimática como resultado del splicing alternativo o incluso influir en el incremento de la expresión génica.

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PERFILES DE EXPRESIÓN DE LOS GENES *HMGCR* Y *SREBP2* Y SU ASOCIACIÓN CON LA PRESENCIA DE TRASTORNO DEPRESIVO MAYOR

Segoviano Mendoza MA[1], Barraza Salas M[2], Castellanos Juárez FX[3], Salas Pacheco JM[3], Arias Carrión O[4], Méndez Hernández EM*[5]

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Se ha sugerido que la presencia de niveles reducidos de colesterol se asocia al desarrollo de Trastorno Depresivo (TD). En la síntesis de colesterol a nivel periférico y central, la proteína de unión a elementos reguladores de esteroles (SREBP2) y la enzima 3-hidroxi-3metil glutaril CoA reductasa (HMGCR) representan importantes blancos reguladores, por lo que sus niveles de expresión podrían estar asociados a la presencia de TD. Se incluyeron 35 casos de TD y 35 controles sanos. Se cuantificaron los niveles de colesterol en sangre venosa utilizando el método colorimétrico. Para el análisis de expresión génica, se utilizaron los kits *MagMax ambion* y *High Capacity cDNA reverse transcription* para la extracción y retrotranscripción. La cuantificación de la expresión relativa se realizó por qPCR. El análisis comparativo de los niveles de expresión del gen *SREBP2* reporta una expresión significativamente menor (p 0.025) en el grupo TD; la expresión de *HMGCR* tiene un incremento significativo en los casos comparada con los controles (p 0.0005). Se observó una correlación inversa entre los niveles de colesterol sérico y los niveles de expresión del gen *HMGCR (r -0.296, p 0.013)*. Se observó un patrón diferencial en los perfiles de expresión génica de *HMGCR* y *SREBP2* entre los grupos de estudio. Así mismo, la correlación inversa entre los niveles de colesterol y la expresión de *HMGCR* puede ser resultado de una adecuada respuesta del mecanismo de regulación transcripcional.

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Toxoplasma gondii exposure and Parkinson's disease: a case-control study.

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Abstract

OBJECTIVES: To determine the association between *Toxoplasma gondii* infection and Parkinson's disease and to investigate whether *T. gondii* seropositivity is associated with the general characteristics of patients with Parkinson's disease.

DESIGN: Case-control study.

SETTING: Cases and controls were enrolled in Durango City, Mexico.

PARTICIPANTS: 65 patients with Parkinson's disease and 195 age- and gender-matched control subjects without Parkinson's disease.

PRIMARY AND SECONDARY OUTCOME MEASURES: Serum samples of participants were analysed for anti-*T. gondii* IgG and IgM antibodies by commercially available enzyme-linked immunoassays. Prevalence of *T. gondii* DNA was determined in seropositive subjects using PCR. The association between clinical data and infection was examined by bivariate analysis.

RESULTS: Anti-*T. gondii* IgG antibodies were found in 6/65 cases (9.2%) and in 21/195 controls (10.8%) (OR 0.84; 95% CI 0.32 to 2.18; p=0.81). The frequency of high (>150 IU/mL) antibody levels was similar among cases and controls (p=0.34). None of the anti-*T. gondii* IgG positive cases and four of the anti-*T. gondii* IgG positive controls had anti-*T. gondii* IgM antibodies (p=0.54). The prevalence of *T. gondii* DNA was comparable in seropositive cases and controls (16.7% and 25%, respectively; p=1.0). Seroprevalence of *T. gondii* infection was associated with a young age onset of disease (p=0.03), high Unified Parkinson Disease Rating Scale scores (p=0.04) and depression (p=0.02). Seropositivity to *T. gondii* infection was lower in patients treated with pramipexole than in patients without this treatment (p=0.01). However, none of the associations remained significant after Bonferroni correction.

CONCLUSIONS: The results do not support an association between *T. gondii* infection and Parkinson's disease. However, *T. gondii* infection might have an influence on certain symptoms of Parkinson's disease. Further research to elucidate the role of *T. gondii* exposure on Parkinson's disease is warranted.

KEYWORDS: Parkinson's disease; Toxoplasma gondii; case-control study; infecti

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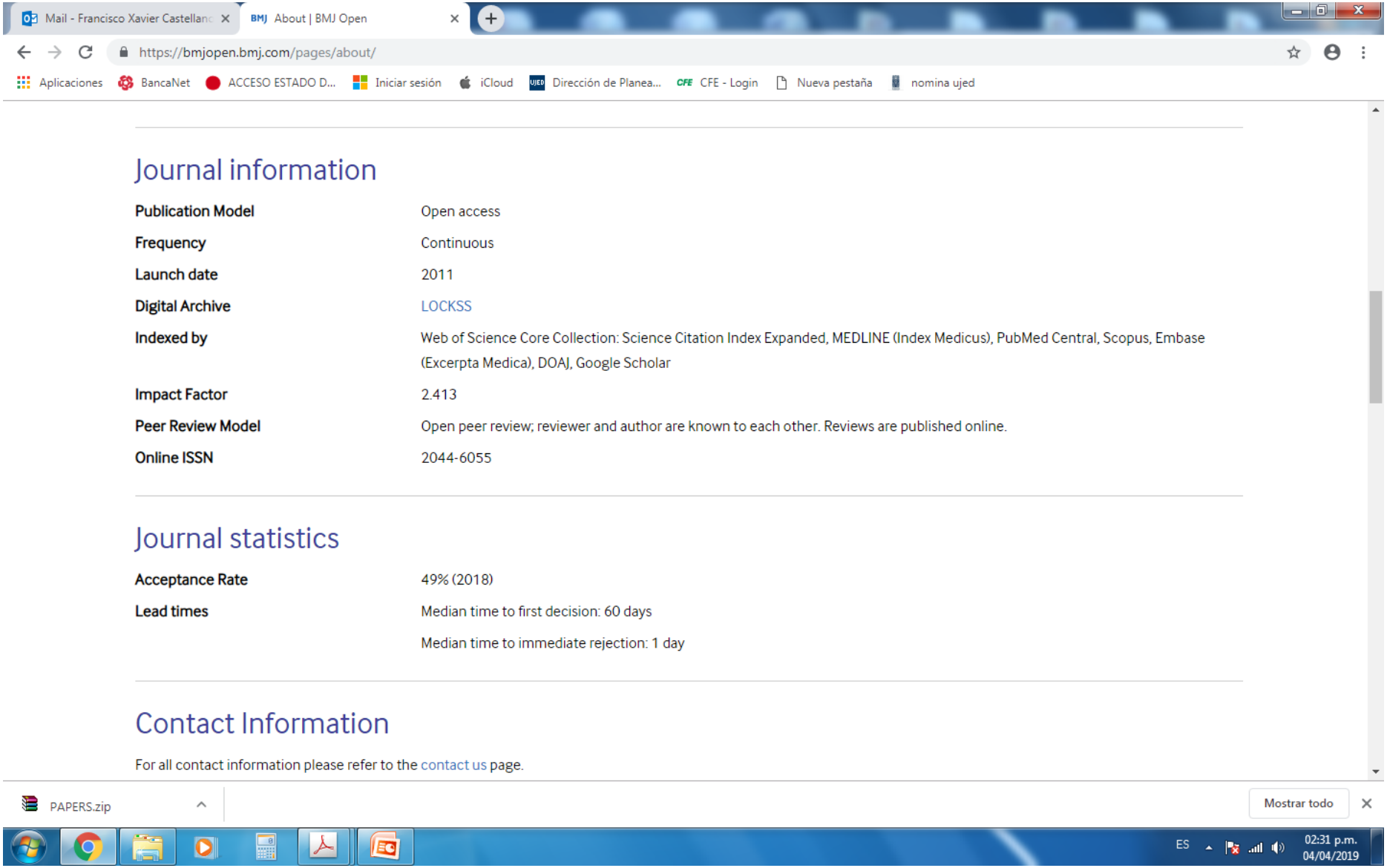
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Toxoplasma gondii exposure and Parkinson's disease: a case–control study

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ABSTRACT

Objectives: To determine the association between *Toxoplasma gondii* infection and Parkinson's disease and to investigate whether *T. gondii* seropositivity is associated with the general characteristics of patients with Parkinson's disease.

Design: Case–control study.

Setting: Cases and controls were enrolled in Durango City, Mexico.

Participants: 65 patients with Parkinson's disease and 195 age- and gender-matched control subjects without Parkinson's disease.

Primary and secondary outcome measures: Serum samples of participants were analysed for anti-*T. gondii* IgG and IgM antibodies by commercially available enzyme-linked immunoassays. Prevalence of *T. gondii* DNA was determined in seropositive subjects using PCR. The association between clinical data and infection was examined by bivariate analysis.

Results: Anti-*T. gondii* IgG antibodies were found in 6/65 cases (9.2%) and in 21/195 controls (10.8%) (OR 0.84; 95% CI 0.32 to 2.18; p=0.81). The frequency of high (>150 IU/mL) antibody levels was similar among cases and controls (p=0.34). None of the anti-*T. gondii* IgG positive cases and four of the anti-*T. gondii* IgG positive controls had anti-*T. gondii* IgM antibodies (p=0.54). The prevalence of *T. gondii* DNA was comparable in seropositive cases and controls (16.7% and 25%, respectively; p=1.0). Seroprevalence of *T. gondii* infection was associated with a young age onset of disease (p=0.03), high Unified Parkinson Disease Rating Scale scores (p=0.04) and depression (p=0.02). Seropositivity to *T. gondii* infection was lower in patients treated with pramipexole than in patients without this treatment (p=0.01). However, none of the associations remained significant after Bonferroni correction.

Conclusions: The results do not support an association between *T. gondii* infection and Parkinson's disease. However, *T. gondii* infection might have an influence on certain symptoms of Parkinson's disease. Further research to elucidate the role of *T. gondii* exposure on Parkinson's disease is warranted.

Strengths and limitations of this study

- This study provides evidence for a better understanding on the association of *Toxoplasma gondii* infection and Parkinson's disease.
- This is the first study that adds molecular detection of *T. gondii* to assess its link with Parkinson's disease.
- Matching by age and sex was performed.
- This study provides clinical characteristics of Parkinson's disease associated with *T. gondii* infection.
- The seroprevalence of *T. gondii* infection was low.

INTRODUCTION

Toxoplasma gondii (*T. gondii*) is an Apicomplexan parasite of medical importance.[1] Infections with *T. gondii* are common and occur worldwide.[2] The main routes of human infection with *T. gondii* include ingestion of water or food contaminated with parasite oocysts shed by cats and consumption of raw or undercooked meat containing parasite tissue cysts.[3] In rare cases, transmission of *T. gondii* may occur by blood transfusion or transplantation.[4] *T. gondii* spreads to a number of organs of the infected host and is able to cross biological barriers and enter into the brain, eye and placenta.[5] Primary infection with *T. gondii* during pregnancy may lead to infection of the fetus.[6] The clinical spectrum of *T. gondii* infection varies from asymptomatic to severe disease with lymphadenopathy, chorioretinitis and meningoencephalitis.[3 6 7]

Infection with *T. gondii* has been linked to a number of neuropsychiatric diseases including schizophrenia, Parkinson's disease and Alzheimer's disease, and the

neurobiological data of this link have recently been reviewed.[8] The aetiology of Parkinson's disease is largely unknown; however, progressive impairment of voluntary motor control—which is a clinical feature of this disease—is caused by a loss of midbrain substantia nigra dopamine neurons.[9] Tissue cysts of *T. gondii* may be found in all brain areas,[10] and *T. gondii* may lead to neurological damage.[11] It therefore raises the question whether infection with *T. gondii* may lead to Parkinson's disease. On the other hand, infection with *T. gondii* may increase the production of dopamine in the brain.[12] Therefore, it also raises the question whether Parkinson's disease could be negatively associated with infection with *T. gondii*. However, the potential link of *T. gondii* infection and Parkinson's disease has been poorly investigated, and conflicting results about the association of *T. gondii* exposure and Parkinson's disease have been reported. Miman *et al*[13] found a significantly higher rate of anti-*T. gondii* IgG antibodies in patients with Parkinson's disease than in controls. In contrast, Celik *et al*[14 15] found similar seropositivity rates to *T. gondii* in 50 patients with idiopathic Parkinson's disease and 50 healthy volunteers. In addition, Oskouei *et al*[16] found similar prevalences of anti-*T. gondii* IgG antibodies in 75 patients with Parkinson's disease and 75 controls. Given these conflicting results, we assessed the association of *T. gondii* infection and Parkinson's disease in a cohort of patients attending public hospitals in Durango City, Mexico. In addition, we investigated the association of *T. gondii* seropositivity and the sociodemographic and clinical characteristics of patients with Parkinson's disease.

MATERIALS AND METHODS

Patients with Parkinson's disease and controls

We performed a case–control study of 65 patients with Parkinson's disease (cases) and 195 control subjects. Diagnosis of Parkinson's disease was made using the UK Parkinson's Disease Society brain bank clinical diagnostic criteria.[17] Patients were enrolled in the departments of neurology at two public hospitals: the Hospital 'Santiago Ramón y Cajal' of the Institute of Security and Social Services for the State Workers, and the Hospital '450' of the Secretary of Health in Durango City, Mexico. Serum samples were obtained from January to December 2014. Inclusion criteria for the cases were patients with Parkinson's disease of either sex who voluntarily accepted to participate in the study. Exclusion criteria for the cases were presence of renal or liver diseases, gout, alcoholism, history of cerebrovascular disease or other neurological diseases, and use of acetylsalicylic acid or allopurinol. Cases were aged 39–95 years (mean 69.08±11.39 years) and included 30 men and 35 women. We used a convenience sampling to enrol cases. Inclusion criteria for controls were subjects from the general population of the same city without neurological disease, matched with cases by age and sex. We included three controls per case. Controls were aged 38–91 years (mean 68.56±10.08 years) and included 90 men and 105 women. There was no difference in age between cases and controls (p=0.85).

Sociodemographic and clinical data of cases

We obtained the sociodemographic and clinical data of the patients with Parkinson's disease through face-to-face neurological consultations and with the aid of a questionnaire. Since the correlation of *T. gondii* infection with clinical features of Parkinson's disease is largely unknown, we explored the association between *T. gondii* seropositivity and a number of clinical characteristics directly or indirectly associated with Parkinson's disease. Sociodemographic data obtained included age and sex. Clinical data included Hoehn and Yahr stages,[18] Unified Parkinson Disease Rating Scale scores, age at onset of Parkinson's disease, duration of disease, presence of tremor or rigidity at disease onset, most affected body side, familial history of Parkinson's disease, presence of hyposmia, syncope, paraesthesias, dementia, impairments of memory and vision, depression, anxiety, sialorrhoea, constipation, weight loss, sleep disorders, erectile dysfunction and orthostatic hypotension. In addition, information about the presence of obesity, dyslipidaemia, diabetes mellitus, arterial hypertension, smoking, diarrhoea, nausea and/or vomiting was obtained from each patient. Antiparkinsonian medication was also registered and included the use of levodopa, carbidopa, pramipexole, trihexyphenidyl, biperiden, amantadine, rasagiline, selegiline, azilect, rotigotine and bromocriptine. The occurrence of dyskinesia, urinary incontinence and motor fluctuations (ie, end-of-dose wearing-off, unpredictable off, delay on and no on) related to treatment was also recorded.

Detection of anti-*T. gondii* antibodies

Anti-*T. gondii* IgG antibodies were detected in the serum of participants using the commercially available enzyme immunoassay *Toxoplasma* IgG kit (Diagnostic Automation, Woodland Hills, California, USA). This test determines the presence and also the levels of IgG antibodies. A cut-off of 8 IU/mL of specific anti-*T. gondii* IgG antibody was used. All serum samples positive for anti-*T. gondii* IgG antibodies were further analysed for anti-*T. gondii* IgM antibodies by the commercially available enzyme immunoassay *Toxoplasma* IgM kit (Diagnostic Automation). All tests were performed following the manufacturer's instructions.

Detection of *T. gondii* DNA by PCR

Whole blood samples of cases and controls with anti-*T. gondii* IgG antibodies were further examined to detect *T. gondii* DNA by nested PCR. Whole blood extraction of DNA followed the protocol described by Iranpour and Esmailizadeh (http://www.protocol-online.org/prot/Protocols/Rapid-Extraction-of-High-Quality-DNA-from-Whole-Blood-Stored-at-4-C-for-Long-Period-4175.html). A PCR protocol with two pairs of primers directed

against the B1 gene of *T. gondii* was used, as previously described.[19] The amplified PCR products were detected using gel electrophoresis, stained with ethidium bromide and visualised under ultraviolet light.

Statistical analysis

We used the software Microsoft Excel 2010, Epi Info V.7 (Centers for Disease Control and Prevention: http://wwwn.cdc.gov/epiinfo/) and SPSS V.15.0 (SPSS, Chicago, Illinois, USA) to analyse the results. For calculation of the sample size we used a 95% confidence level, power of 80%, 1:3 proportion of cases and controls and a reference seroprevalence of 12.0%[20] as the expected frequency of exposure in controls. The result of the sample size calculation was 60 cases and 179 controls. To avoid bias, we excluded subjects with missing clinical data. Age values among the groups were compared with the paired Student's t-test. The Fisher exact test was used to evaluate the association between seropositivity to *T. gondii* and the characteristics of the patients. ORs and 95% CIs were calculated and a p value <0.05 was considered statistically significant. Bonferroni correction was applied for adjustment of multiple testing.

RESULTS

Anti-*T. gondii* IgG antibodies were found in 6/65 cases (9.2%) and in 21/195 controls (10.8%) (OR 0.84; 95% CI 0.32 to 2.18; p=0.81). Of the six anti-*T. gondii* IgG positive cases, five (83.3%) had anti-*T. gondii* IgG antibody levels >150 IU/mL and one (16.7%) 12 IU/mL. In contrast, of the 21 anti-*T. gondii* IgG positive controls, 11 (52.4%) had anti-*T. gondii* IgG antibody levels >150 IU/mL, one (4.8%) between 100 to 150 IU/mL and 9 (42.8%) between 8 and 99 IU/mL. The frequency of high (>150 IU/mL) antibody levels was similar among cases and controls (p=0.34). None of the six anti-*T. gondii* IgG positive cases had anti-*T. gondii* IgM antibodies whereas four (19.0%) of the 21 anti-*T. gondii* IgG positive controls had anti-*T. gondii* IgM antibodies. There was no difference in the rate of IgM seropositivity among cases and controls (p=0.54). Anti-*T. gondii* IgG antibodies were detected in four (11.4%) of 35 female cases and in seven (6.7%) of 105 female controls (OR 1.80; 95% CI 0.49 to 6.58; p=0.46), whereas anti-*T. gondii* IgG antibodies were detected in two (6.7%) of 30 male cases and in 14 (15.6%) of 90 male controls (OR 0.38; 95% CI 0.08 to 1.81; p=0.35). The frequency of high (>150 IU/mL) anti-*T. gondii* IgG antibody levels was similar in male and female cases (2/30 (6.7%) and 3/35 (8.6%), respectively, p=1.00). Seroprevalence of *T. gondii* infection was similar among cases and controls of several age groups (table 1). One (16.7%) of the six cases seropositive to *T. gondii* IgG antibodies was positive for *T. gondii* DNA by PCR. We were able to test 20 of 21 controls seropositive to *T. gondii* IgG antibodies. Five (25%) of these 20 controls were positive for *T. gondii* DNA by PCR. The prevalence of *T. gondii* DNA was similar in cases and controls (p=1.0).

With respect to clinical characteristics of patients, seroprevalence of *T. gondii* infection was higher in patients with an onset of Parkinson's disease at a young age (≤40 years) than in those with a disease onset at older ages (p=0.03). Table 2 shows a selection of clinical characteristics of patients with Parkinson's disease and their correlation with *T. gondii* seropositivity. Seroprevalence of infection with *T. gondii* was also higher in patients with higher Unified Parkinson Disease Rating Scale scores (88–136) than in those with lower scores (p=0.04). Seropositivity to *T. gondii* was observed in six (17.1%) of 35 patients suffering from depression but in none of 30 patients without depression (p=0.02). Other clinical characteristics of patients including Hoehn and Yahr stages, duration of disease, presence of tremor or rigidity at disease onset, most affected body side, familial history of Parkinson's disease, presence of hyposmia, syncope, paraesthesias, dementia, impairments of memory and vision, anxiety, sialorrhoea, constipation, weight loss, sleep disorders, erectile dysfunction, and orthostatic hypotension did not show an association with *T. gondii* seropositivity. In addition, *T. gondii* exposure was not associated with the presence of obesity, dyslipidaemia, diabetes mellitus, arterial hypertension, smoking, diarrhoea, nausea and/or vomiting in the patients. Seropositivity to *T. gondii* infection was significantly (p=0.01) lower in patients receiving pramipexole than in patients not treated with this drug (table 2). Seroprevalence of infection was similar in patients regardless of the use of other antiparkinsonian medications including levodopa, carbidopa, trihexyphenidyl, biperiden, amantadine, rasagiline, selegiline, azilect, rotigotine and bromocriptine. The presence of

Table 1 Comparison of IgG seropositivity rates in cases and controls according to age groups

	Cases			Controls			
	Subjects tested	Seropositive		Subjects tested	Seropositive		
	N	N	%	N	N	%	p Value
Age groups							
≤40 years	2	1	50	6	0	0	0.25
41–60 years	12	1	8.3	22	1	4.5	1.00
61–80 years	41	4	9.8	144	17	11.8	1.00
>80 years	10	0	0	23	3	13	0.53

Table 2 Bivariate analysis of clinical data and infection with *Toxoplasma gondii* in patients with Parkinson's disease

Characteristic	Subjects tested N	Prevalence of *T. gondii* infection N	%	p Value
Age at Parkinson onset				
≤40 years	4	2	50	0.03
>40 years	61	4	6.6	
Duration of disease				
≤10 years	57	5	8.8	0.56
>10 years	8	1	12.5	
Tremorigenic type				
Yes	49	5	10.2	1.00
No	16	1	6.3	
Rigid type				
Yes	25	3	12	0.66
No	40	3	7.5	
Hoehn and Yahr stages				
0	5	0	0	0.59
1	17	3	17.6	
2	14	1	7.1	
3	20	1	5	
4	5	1	20	
5	4	0	0	
Unified Parkinson disease rating scores				
0–87	55	3	5.5	0.04
88–136	10	3	30	
Constipation				
Yes	29	4	13.8	0.39
No	36	2	5.6	
Syncope				
Yes	6	1	16.7	0.45
No	59	5	8.5	
Paraesthesias				
Yes	12	3	25	0.07
No	53	3	5.7	
Weight loss				
Yes	27	4	14.8	0.22
No	38	2	5.3	
Dementia				
Yes	23	3	13	0.65
No	42	3	7.1	
Depression				
Yes	35	6	17.1	0.02
No	30	0	0	
Anxiety				
Yes	30	4	13.3	0.40
No	35	2	5.7	
Vision impairment				
Yes	22	3	13.6	0.39
No	43	3	7	
Dyskinesia				
Yes	21	3	14.3	0.37
No	44	3	6.8	
Use of pramipexole				
Yes	43	1	2.3	0.01
No	22	5	22.7	

dyskinesia, urinary incontinence and motor fluctuations (end-of-dose wearing-off, unpredictable off, delay on and no on) did not correlate with *T. gondii* infection. None of the associations between clinical data and *T. gondii* seropositivity remained significant after Bonferroni correction.

DISCUSSION

T. gondii is an intracellular parasite and can persist in neurons, modifying their function and structure.[21] Cysts of *T. gondii* can be found throughout the brain,[10] and this parasite alters dopamine metabolism.[21] Thus, it raises the question whether infection with *T. gondii* has any link with a dopamine-related neurological disease. There is controversy concerning the association of *T. gondii* infection and Parkinson's disease. The number of reports about this association is very small. We therefore sought to determine the association between *T. gondii* seropositivity and patients with Parkinson's disease in the northern Mexican city of Durango. This age- and gender-matched case–control seroprevalence study showed similar frequencies of *T. gondii* infection in cases and controls. Similarly, we did not find differences in the frequency of high levels of anti-*T. gondii* IgG antibodies, IgM seropositivity rates and prevalence of *T. gondii* DNA among cases and controls. The 9.2% seroprevalence found in patients with Parkinson's disease is comparable to the 12% seroprevalence of *T. gondii* infection reported in elderly people[20] and 13.3% in patients with liver disease[22] in the same Durango City. In contrast, the seroprevalence found in patients with Parkinson's disease is lower than seroprevalences reported in other population groups in Durango City including 15.4% in female sex workers,[23] 20% in schizophrenic patients[24] and 21.1% in inmates[25] and waste pickers.[26] Therefore, the results of our study do not support an association between *T. gondii* infection and Parkinson's disease. The lack of association between *T. gondii* infection and the presence of Parkinson's disease is consistent with similar results reported by Celik *et al*[14 15] and Oskouei *et al*.[16]

In contrast, our results conflict with those reported by Miman *et al*[13] who found a significantly higher seroprevalence of anti-*T. gondii* IgG antibodies in patients with Parkinson's disease than in controls. Other studies have also linked toxoplasmosis with Parkinson's disease. For instance, in 1992 Noël *et al*[27] reported hemichorea and parkinsonism in two AIDS patients with cerebral toxoplasmosis. Basal ganglia, which are involved in the control of voluntary motor movements, can be affected in cerebral toxoplasmosis, as reported in patients with AIDS,[28–30] a patient with acute myeloid leukaemia undergoing two allogenic stem cell transplantations,[31] an immunocompromised female renal transplant recipient[32] and a non-immunocompromised pregnant woman.[33] Improvement of parkinsonism in an AIDS patient with cerebral toxoplasmosis was achieved after anti-*T. gondii* and antiretroviral therapies.[34] Infection with *T. gondii* has been associated with elevated levels of dopamine within dopaminergic cells,[12] whereas an important feature of Parkinson's disease is the loss of dopamine-producing neurons.[35] However, the interaction of *T. gondii* and neurons in patients with Parkinson's disease is largely unknown. It raises the question whether dopamine production during infection with *T. gondii* is too low to compensate for the deficit of dopamine and to induce a clinical improvement in patients with Parkinson's disease. Further research to elucidate the role of dopamine produced during *T. gondii* infection on neurons of patients with Parkinson's disease is needed.

Interestingly, the frequency of *T. gondii* infection was higher in patients with onset of Parkinson's disease at a young age than in those with a disease onset at older ages. It is not clear why *T. gondii* infection was associated with a young onset of Parkinson's disease. This young onset of disease is less common than middle and late onsets, and patients with young onset have a long survival and suffer from depression more frequently than patients with older onset of disease.[36] Remarkably, we found that seropositivity to *T. gondii* was associated with depression in the patients with Parkinson's disease studied. To the best of our knowledge, this is the first report of an association between *T. gondii* exposure and depression in patients with Parkinson's disease. Infection with *T. gondii* has been linked to depression in other population groups, such as women veterans[37] and pregnant women.[38] However, other studies including a meta-analysis of 50 studies of psychiatric patients and healthy controls,[39] a cross-sectional internet study on a non-clinical population of 5535 subjects[40] and the third National Health and Nutrition Survey in the USA[41] have not found a correlation between *T. gondii* infection and depression

Of note, seroprevalence of *T. gondii* infection correlated with high Unified Parkinson Disease Rating Scale scores. In a search for this association in the medical literature, no reports were found. This association suggests that *T. gondii* infection might have an influence on clinical characteristics of patients with Parkinson's disease. It is possible that *T. gondii* does not associate per se with the presence of Parkinson's disease because of the opposite relations with dopamine production—that is, *T. gondii* infection induces an increase in dopamine production whereas Parkinson's disease is related to a decrease in dopamine production. However, infection with *T. gondii* might be involved in the appearance of symptoms found in patients with Parkinson's disease such as depression. Further research on the influence of *T. gondii* infection on signs and symptoms of Parkinson's disease should be conducted.

We also observed that seropositivity to *T. gondii* infection was significantly lower in patients treated with pramipexole than in those not receiving this treatment. This finding suggests a protective effect of pramipexole for *T. gondii* infection. It is not clear why pramipexole users had a low frequency of *T. gondii* infection. No anti-*T. gondii* activity of pramipexole has been reported. Further research to elucidate the negative association of pramipexole with *T. gondii* infection is needed.

This study has limitations. The sample size was small. Further studies with larger sample sizes should be conducted. The low number of cases seropositive for

T. gondii did not allow us to perform multivariate analysis to determine the association between patient characteristics and seropositivity to *T. gondii*. In addition, the associations between clinical data and *T. gondii* seropositivity found in this study should be interpreted with care, since the statistical power of comparisons was low (<0.80) and no associations remained statistically significant after Bonferroni correction.

CONCLUSIONS

The results obtained in a cohort of patients in Durango, Mexico do not support an association between *T. gondii* infection and Parkinson's disease. However, the results suggest that *T. gondii* infection might influence the symptoms of Parkinson's disease. Further research to elucidate the role of *T. gondii* exposure on the clinical characteristics of Parkinson's disease is therefore needed.

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Contributors CA-E designed the study protocol, performed the laboratory tests and data analysis and wrote the manuscript. EMM-H, JMS-P, LAR-C and AAS-C obtained the blood samples and clinical dat, and performed the data analysis. JH-T, OA-C, LFS-A, FXC-J and OL performed the data analysis and wrote the manuscript. All authors read and approved the final version of the manuscript.

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The relationship between blood lead levels and occupational exposure in a pregnant population.

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Abstract

BACKGROUND: Pregnant women exposed to lead are at risk of suffering reproductive damages, such as miscarriage, preeclampsia, premature delivery and low birth weight. Despite that the workplace offers the greatest potential for lead exposure, there is relatively little information about occupational exposure to lead during pregnancy. This study aims to assess the association between blood lead levels and occupational exposure in pregnant women from Durango, Mexico.

METHODS: A cross-sectional study was carried out in a population of 299 pregnant women. Blood lead was measured in 31 women who worked in jobs where lead is used (exposed group) and 268 who did not work in those places (control group). Chi-square test was applied to compare exposed and control groups with regard to blood lead levels. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. Multivariable regression analysis was applied to determine significant predictors of blood lead concentrations in the exposed group.

RESULTS: Exposed women had higher blood lead levels than those in the control group (4.00 ± 4.08 ug/dL vs 2.65 ± 1.75 ug/dL, p = 0.002). Furthermore, women in the exposed group had 3.82 times higher probability of having blood lead le
group. Wearing of special workwear, changing clothes after work, living near a painting store, printi
washing the workwear together with other clothes resulted as significant predictors of elevated bloc

CONCLUSIONS: Pregnant working women may be at risk of lead poisoning because of occupation
increases if they do not improve the use of protective equipment and their personal hygiene.

KEYWORDS: Blood lead; Occupational exposure; Pregnant women; Risk factors

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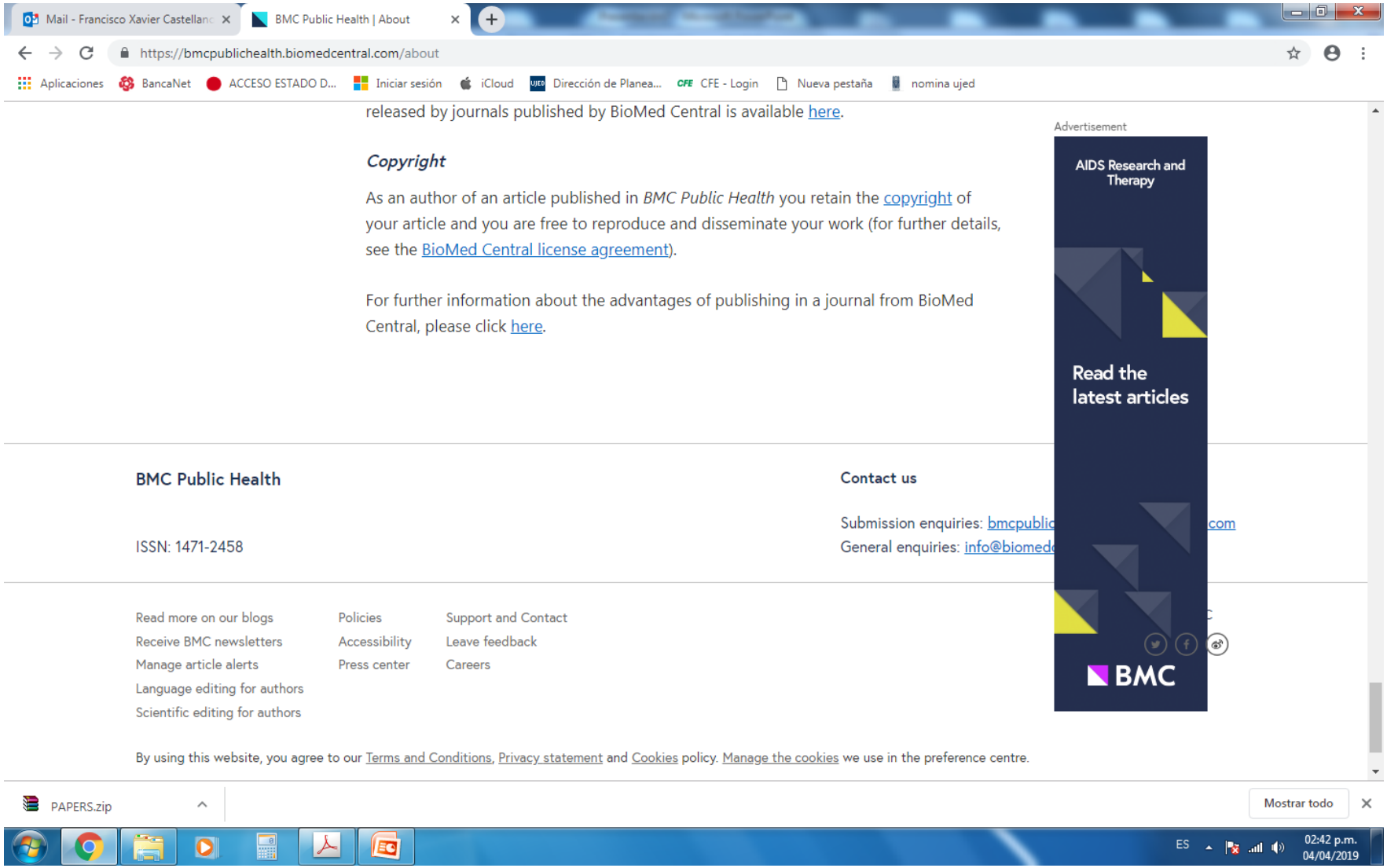
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The relationship between blood lead levels and occupational exposure in a pregnant population

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Abstract

Background: Pregnant women exposed to lead are at risk of suffering reproductive damages, such as miscarriage, preeclampsia, premature delivery and low birth weight. Despite that the workplace offers the greatest potential for lead exposure, there is relatively little information about occupational exposure to lead during pregnancy. This study aims to assess the association between blood lead levels and occupational exposure in pregnant women from Durango, Mexico.

Methods: A cross-sectional study was carried out in a population of 299 pregnant women. Blood lead was measured in 31 women who worked in jobs where lead is used (exposed group) and 268 who did not work in those places (control group). Chi-square test was applied to compare exposed and control groups with regard to blood lead levels. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. Multivariable regression analysis was applied to determine significant predictors of blood lead concentrations in the exposed group.

Results: Exposed women had higher blood lead levels than those in the control group (4.00 ± 4.08 μg/dL vs 2.65 ± 1.75 μg/dL, $p = 0.002$). Furthermore, women in the exposed group had 3.82 times higher probability of having blood lead levels ≥ 5 μg/dL than those in the control group. Wearing of special workwear, changing clothes after work, living near a painting store, printing office, junkyard or rubbish dump, and washing the workwear together with other clothes resulted as significant predictors of elevated blood lead levels in the exposed group.

Conclusions: Pregnant working women may be at risk of lead poisoning because of occupational and environmental exposure. The risk increases if they do not improve the use of protective equipment and their personal hygiene.

Keywords: Blood lead, Occupational exposure, Pregnant women, Risk factors

Background

Lead has been clearly shown to be a neurotoxic agent widely distributed in the environment [1]. Excessive lead exposure may occur in the workplace. Some jobs that expose people to lead include: mining, smelting, foundry work, construction, plumbing, radiator manufacturing, lead-acid battery recycling, manufacturing of rubber products, and the chemical industry. Years ago, lead was also used regularly in paint, ceramics, and pipe solder among other things. Because of its potential health problems, the amount of lead used in these products today has lessened or has been removed. However, lead is still common in many industries, including construction, mining, and manufacturing [2].

Lead can harm many of the body's organ systems. Human exposure to lead can result in a wide range of biological effects [3]. It is well known that childhood and

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pregnancy are the most sensitive population to lead exposure. A pregnant woman with an elevated blood lead concentration may expose her fetus to the toxic effect of lead. Elevated blood lead levels (BLLs) in children cause learning and behavioral deficits [4, 5]. Low-level lead exposure, including prenatal exposure, has been linked to decreased performance on IQ tests for school children [6–9]. Several studies have suggested that any level of exposure is potentially detrimental and no threshold for these effects has been identified [10, 11].

Lead concentrations have declined in the last decades due to the increase in health interventions [12]. In spite of this, lead exposure remains a risk factor for female reproductive health, even at low levels of lead in blood [13]. Once absorbed from the gastrointestinal tract or the respiratory system, lead is transported bound to erythrocytes and accumulates in bone [14]. During pregnancy, calcium demands increase. This leads to increased bone turnover, with a consequential release of lead from bone and increased blood lead levels [15, 16]. Lead can cross the placenta and expose the fetus to the harmful effects of this toxic, thus affecting the embryonic development of multiple organs and causing neurobehavioral impairments in infancy and early childhood [4, 5, 9, 17]. Therefore, pregnancy is considered a critical time for exposure to lead for the mother and the fetus [14, 18].

Over the past several decades there has been a remarkable reduction in environmental sources of lead and a decreasing trend in the prevalence of elevated blood lead levels [2]. However, some reproductive health damages at levels of lead in blood below 10 μg/dL have been reported. Therefore, in recent years, many studies have focused on the health effects at low levels of lead in blood. Low blood lead concentrations in pregnant women have been associated with miscarriage [19, 20], pregnancy hypertension, or preeclampsia [12, 21–24] premature delivery [13], premature rupture of the membranes [25], and low birth weight [26, 27]. On the other hand, it is considered that lead-related toxicity can occur at levels as low as 5 μg/dL [28]. Hence, maternal exposure to lead plays an important role in adverse pregnancy outcomes.

Despite that the workplace offers the greatest potential for lead exposure, there is relatively little information about the occupational exposure to lead during pregnancy. It is necessary to identify sources of lead exposure relevant to this population. Some of the jobs that commonly involve lead exposure are battery manufacture or repair; construction (welding or cutting lead-painted metal); radiator manufacture or repair; wire cable cutting and manufacture, and cable, battery, or scrap metal salvage, plating operations; manufacturing or using leaded paints, dyes or pigments, or lead soldering in the electronics industry, among others [29]. In Mexico, and in other developing countries, it is common to find pregnant women working in places with potential sources of lead exposure. The aim of this study was to assess the association between blood lead levels and occupational exposure in pregnant women from Durango, Mexico.

Methods

Study population

From June 2007 to May 2008 a cross-sectional study was conducted to evaluate the association between BLLs and some risk factors in pregnant women who received health attention in the State of Durango, Mexico [30]. The study population consisted of pregnant women who received medical attention in two sanitary jurisdictions pertaining to the Secretary of Health. The total estimated number of pregnant women seen in these two jurisdictions during a 1 year period was obtained from the Secretariat of Health databases, and the sample required was distributed equally in 12 municipalities. The participants were recruited from Obstetrics and Gynecology Departments of the municipal hospitals. All women who presented for prenatal care on the days that the study team visited, independent of their gestational age, were asked to participate in the study if they met the inclusion criteria. The inclusion criteria were: being pregnant, living in Durango, able to understand Spanish, and receiving health care paid for by the Secretary of Health. Each municipality was visited two or three times during the recruitment period, until the sample size was completed. Of the 337 pregnant women who presented for prenatal care on the days of the visits, 12 women were excluded because they did not live in Durango and 26 declined to participate in the study. A total of 299 women were included in the study (Aditional file 1). The interviewer's interaction with patients was standardized. All patients gave their informed written consent and answered a set of questions in a face-to-face interview. The research protocol was approved by the Ethical Committee of Durango General Hospital.

First, the group was treated as a cohort. After that, a regression with lead levels as outcome allowed to attribute the proportion of risk from occupational and non-occupational exposure. For assessment of the association between blood lead levels and occupational exposure, subjects were classified into two groups: women who worked in places where lead is used (exposed group) and women who did not work in those places (control group). Women who worked in automotive repair shops, mining laboratories, welding workshops, automotive harness factories, hairdressing salons, and road sweepers were included in the exposed group. Unemployed women and those women who had a job where lead-containing materials are not used, were included in the control group.

Blood lead measurement

Blood samples were collected using lead-free tubes containing EDTA. Samples were stored in the original tube at 4° C before being transferred to the Environmental Toxicology Laboratory, Faculty of Medicine, Juarez University of Durango State. The time between receipt and analysis varied from 1 to 3 weeks. During which time, the specimens were stored refrigerated at 4 °C. Lead concentration was determined by graphite furnace atomic absorption spectrometry. Bovine blood obtained from the National Institute of Standards and Technology (NIST) was used as standard reference material.

Statistical analysis

Data were analyzed to describe demographic characteristics, BLLs, and potential sources of lead exposure. The normality of the variables was tested using the Kolmogorov-Smirnov test. BLLs were log-transformed prior to analysis. Multivariable regression analysis was conducted to determine the proportion of risk from each occupational and non-occupational exposure. After that, the study population was divided into two groups according to occupation (occupationally exposed and non-occupationally exposed). Student *t*-test was applied for comparison of quantitative variables. Chi-square test was applied to compare exposed and control groups regarding blood lead levels (BLLs ≥ 5 μg/dL vs BLLs < 5 μg/dL). Odds ratio (OR) and 95% confidence intervals were calculated. To identify non-occupational sources of lead exposure for pregnant women we explored the following: the way in which workwear is washed (together with other clothes or alone), use of lead-glazed pottery, use of hair dyes, living near workplaces where lead is used (mining zones, battery workshops, junkyards, rubbish dumps and painting workshops), pica behavior and living with someone who works with lead, in both exposed and control groups. These activities have been documented to be lead-related. Chi-square test was also used to compare both groups regarding non-occupational sources of lead exposure. Student *t*-test was also used to compare blood lead levels according to some protection habits in the exposed group. Use of respiratory protective equipment, habit of wearing gloves, wearing of special workwear, handwashing before eating, changing clothes after work, and use of any protective equipment were analyzed as dichotomous variables. Finally, backward stepwise multivariable regression analysis was applied to determine significant predictors of blood lead concentrations in the exposed group. A set of variables selected on the basis of previous knowledge or because of associations with lead levels in bivariate analyses (at $p < 0.25$) were entered into the model. The full model was followed by stepwise backward elimination to determine whether each variable remained significant after non-significant covariates were excluded. All statistical analyses were performed using SPSS for Windows statistical package version 15.0. A p-value < 0.05 was considered statistically significant.

Results

The mean blood lead concentration in the study population was 2.79 μg/dL (SD 2.14), geometric mean 2.38 μg/dL, 95% CI (2.25 – 2.54). Among the 299 pregnant women enrolled in the study, 31 (10.4%) worked in places where lead is used, and 268 (89.6%) did not work where lead-containing materials are used (Table 1). Results of multiple linear regression on association between blood lead levels and risk factors are shown in Table 2. Living in a mine zone was associated with increased blood lead ($p = 0.044$). However, working in places where lead is used was the main factor associated with blood lead concentration. On the basis of this result, the study population was divided into two groups: exposed and non-exposed.

Table 3 summarizes the main characteristics of both groups. There were no significant differences between the groups regarding age, gestational age, number of pregnancies, body mass index (BMI), hemoglobin and monthly income per person. However, the blood lead concentration of the exposed group was significantly higher than that of the control group ($p = 0.002$).

Frequency of BLLs ≥ 5 μg/dL is depicted in Table 4. The proportion of women with BLLs ≥ 5 μg/dL in the exposed group was significantly higher compared to the control group (22.6% vs 7.1%; $p < 0.01$). In addition, women in the exposed group had 3.8 times more

Table 1 General information and blood lead levels of study population ($N = 299$)

Variables	Percent	Mean (SD)
Age (years)		24.32 (6.71)
Gestational age (weeks)		24.07 (8.68)
Pregnancies		2.0 (1.0)
Body mass index (kg/m^2)		27.23 (5.63)
Hemoglobin (g/dL)		12.55 (1.34)
Monthly income per person, USD		140.95 (144.73)
Working in places where lead is used		
Yes	10.4	
No	89.6	
Blood lead levels (μg/dL)		2.79 (2.14)
Geometric mean (95% CI)		2.38 (2.25 – 2.54)

Table 2 Results from the multiple linear regression analysis on the association between blood lead and risk factors

Risk factor	Coefficient β	95% CI	*p*
Washing the workwear together with other clothes	0.106	- 0.018 – 0.229	0.093
Use of lead glazed pottery	0.033	- 0.102 – 0.168	0.634
Dyeing hair	- 0.016	- 0.147 – 0.115	0.813
Living near workplaces where lead is used	- 0.021	- 0.197 – 0.156	0.818
Living near mining zone	0.237	0.006 – 0.468	0.044
Living near battery workshop	- 0.016	- 0.209 – 0.177	0.869
Living near junkyard	- 0.079	- 0.284 – 0.127	0.452
Living near rubbish dump	0.141	- 0.060 – 0.342	0.169
Living near straightening and painting workshop	0.023	- 0.172 – 0.218	0.819
Pica behavior	0.115	- 0.032 – 0.261	0.124
Living with someone who works with lead	0.056	- 0.071 – 0.183	0.387
Living near painting store	0.081	- 0.167 – 0.329	0.521
Living near printing office	- 0.120	- 0.441 – 0.201	0.461
Working in places where lead is used	0.306	0.103 – 0.509	0.003

R2 = 0.082

probability to have BLLs above 5 μg/dL than those in the control group.

Non-occupational sources of lead exposure for exposed and control groups are summarized in Table 5. The proportion of women who had the habit of dyeing their hair was significantly higher in exposed women when compared to the control group ($p = 0.010$) and the same was observed in the exposed group regarding living near workplaces where lead is used when compared with control women ($p = 0.043$). However, there were no significant differences in other variables between the compared groups.

To evaluate the influence of some work conditions on blood lead levels in the exposed group, some protection habits were explored (Table 6). Blood lead levels were significantly higher in women who did not wear special workwear ($p = 0.028$) and in those who did not have the habit of changing clothes after work ($p = 0.025$).

Table 7 displays potential sources of blood lead in the exposed group. After multivariable analysis, seven variables were retained in the final model: wearing of special workwear, changing clothes after work, living near a painting store, living near a printing office, living near a junkyard, living near a rubbish dump and washing the workwear together with other clothes. These variables accounted for 86.5% of the total variance. The model was adjusted by age, educational level and gestational age.

Discussion

In this cross-sectional study, we examined the association of blood lead levels with occupational exposure in pregnant women. The blood lead levels in our

Table 3 General information and blood lead levels of the exposed subjects and control group[a]

Variable	Exposed group ($n = 31$)	Control group ($n = 268$)	*p* value[*]
Age (years)	26.03 (6.17)	24.13 (6.76)	0.135
Gestational age (weeks)	22.71 (8.06)	24.22 (8.75)	0.358
Number of pregnancies	2.55 (1.38)	2.23 (1.47)	0.253
Body mass index (kg/m^2)	28.81 (4.79)	27.04 (5.70)	0.098
Hemoglobin (g/dL)	12.97 (1.11)	12.50 (1.36)	0.065
Monthly income per person, USD	165.62 (130.59)	138.00 (146.28)	0.316
Blood lead levels (μg/dL)	4.00 (4.08)	2.65 (1.75)	0.002[**]

[a]Values shown as mean (standard deviation)
[*] *p* value was calculated from Student *t*-test
[**] *p* value from Log BLL

Table 4 Frequencies of BLL ≥ 5 μg/dL in the study population

Subjects	BLLs ≥ 5 μg/dL n (%)	BLLs <5 μg/dL n (%)
Exposed group ($n = 31$)	7 (22.6)	24 (77.4)
Control group ($n = 268$)	19 (7.1)	249 (92.9)
Total ($n = 299$)	26 (8.7)	273 (91.3)

$X^2 = 6.56$; $p = 0.010$; OR = 3.822; 95%; IC (1.460 – 10.008)

study population (2.79 ± 2.14 μg/dL) did not exceed the accepted threshold of 10 μg/dL. They are even below the 5 μg/dL recommended by the CDC [31]. Furthermore, the mean blood lead level in our test subjects is lower compared to values reported in some populations of pregnant women. A study by Taylor et al. [14] reported mean BLL of 3.67 ± 1.47 μg/dL in a cohort of pregnant women in The United Kingdom. In China, the lead concentrations during the three pregnancy trimesters and postpartum were 5.95 ± 2.27 μg/dL, 5.51 ± 1.93 μg/dL, 5.57 ± 1.85 μg/dL, and 6.88 ± 1.90 μg/dl; respectively [32]. In addition, Gerhardsson and Lundh [33] reported median blood lead of 11.0 μg/L (range 4.2–79 μg/L) in pregnant females residing in Sweden; and Alvarez et al. [34] found a blood lead average of 11.63 ± 4.64 μg/dL in pregnant women living in the island of Tenerife, Spain. However, some researchers have reported lower blood lead concentrations in pregnant women. Mean blood lead levels of 2.551 ± 2.592 μg/dL were found in pregnant women from Saudi Arabia [35]. In a socioeconomically disadvantaged population of New York, a geometric mean of 1.58 μg/dL was reported by Schell et al. [15]. Moreover, Bakhireva et al. [36] found mean blood lead of 1.06 ± 1.55 μg/dL in a cross-sectional study designed to ascertain risk factors of lead exposure among pregnant women in New Mexico, United States.

In Mexico, the Secretary of Health is the health care institution which attends the smallest workforces. Nevertheless, we found 31 women working in places where lead is used and who represent 10.4% of the recruited subjects. In spite of this, lead in the workplace results a significant determinant of blood lead levels. Therefore, similar results may be expected in other pregnant populations with low income and low level of employment.

Our exposed group was made up of women who worked in automotive repair shops, mining laboratories, welding workshops, automotive harness factories, hairdressing salons, and as road sweepers, regardless of intensity and exposure time. At any rate, we found significantly higher blood lead concentrations in exposed women than in the control group (4.24 ± 4.60 μg/dL vs. 2.66 ± 1.73 μg/dL). Our findings are consistent with a study by Popovic et al. [37], who found mean blood lead of 2.73 ± 2.39 μg/dL in women formerly working in a smelter, and 1.25 ± 2.10 μg/dL in women with no known occupational exposure to lead.

In the present study, no difference was observed in hemoglobin level between exposed women and the control group. This is expected considering the low BLLs obtained for this population. According to previous studies, lead anemia appears at BLLs higher than 40 μg/dL [3, 38]. On the other hand, the US Environmental Protection Agency (EPA) suggests a threshold BLL of 20 – 40 μg/dL for risk of anemia [39]. However, blood lead concentrations in our compared groups are much lower.

Table 5 Comparison of non-occupational sources of lead exposure between exposed and control groups[a]

Potential source of lead exposure	Exposed group ($n = 31$)	Control group ($n = 268$)	p value*
Washing the workwear together with other clothes	12 (38.7)	123 (45.9)	0.447
Use of lead glazed pottery	10 (32.3)	81 (30.2)	0.816
Dyeing hair	27 (87.1)	172 (64.2)	0.010
Living near workplaces where lead is used	22 (71.0)	139 (51.9)	0.043
Living near mining zone	4 (12.9)	25 (9.3)	0.752
Living near battery workshop	7 (22.6)	43 (16.0)	0.356
Living near junkyard	4 (12.9)	30 (11.2)	0.777
Living near rubbish dump	3 (9.7)	39 (14.6)	0.641
Living near straightening and painting workshop	7 (22.6)	45 (16.8)	0.421
Pica behavior	10 (32.3)	62 (23.1)	0.261
Living with someone who works with lead	16 (51.6)	101 (37.7)	0.133

[a]Values shown as frequency (percentage)
*p value from Chi-square test

Table 6 Comparison of blood lead levels regarding protection habits in exposed women

Protection habits	Blood lead levels, μg/dL [a]		*p* value*
	No	Yes	
Use of respiratory protective equipment	27 (4.03 ± 4.23)	4 (3.75 ± 3.43)	0.901
Wearing gloves habit	19 (4.32 ± 4.96)	12 (3.48 ± 2.18)	0.521
Wearing of special workwear	20 (4.92 ± 4.85)	11 (2.31 ± 0.68)	0.028
Hand washing before eating	11 (3.55 ± 1.48)	20 (4.24 ± 5.00)	0.571
Changing clothes after work	24 (4.51 ± 4.52)	7 (2.24 ± 0.60)	0.025
Use of any protective equipment	9 (5.64 ± 7.03)	22 (3.32 ± 1.83)	0.356

[a] Values shown as frequency (mean ± standard deviation)
* *p* value from Student *t*-test

Recent findings concerning lead-related adverse reproductive outcomes suggested that pregnant women should avoid lead exposure that would result in blood lead concentrations higher than 5 μg/dL [3]. Among the 299 women included in our study, 26 (8.7%) had BLLs ≥ 5 μg/dL. In a cohort of 4, 285 pregnant women, Taylor et al. [14] reported 14.4% of women with BLLs of 5 μg/dL or higher; cigarette smoking, alcohol, and coffee drinking were found to be predictors of BLLs. However, in our study the frequencies of smoking, alcohol and coffee drinking among the women were very low; therefore, these variables were not included in the analysis. Regarding occupation, the 2005 – 2007 Adult Lead Epidemiology and Surveillance (ALES) by the United States of America Centers for Disease Control and Prevention reported that 32% of women of childbearing age with BLL ≥ 5 μg/dL were occupationally exposed to lead [38]. Zhu et al. [40] evaluated reasons for testing and potential sources of exposure among women, and reported that 29.2% of women with blood lead of 5–14.9 μg/dL had a job with potential lead exposure.

Our results indicated that exposed women were more than 3.8 times likely to have BLLs ≥ 5 μg/dL than non-exposed women. This finding suggests that occupation represents an important factor for elevated blood lead concentrations in our studied population. According to a study by Kosnett et al. [3], it is recommendable for pregnant women to avoid lead exposure that would result in blood lead levels above 5 μg/dL, due to the raised concerns regarding the toxicity of this blood lead concentration. Several studies have associated blood lead levels above 5 μg/dL with miscarriage [19, 20], pregnancy hypertension [12, 21–24, 41], premature delivery [13], premature rupture of the membranes [25], and low birth weight [26, 27]. According to CDC recommendations [28], pregnant women with a current or past BLL ≥5 μg/dL should be assessed for the adequacy of their diet and provided with prenatal vitamins, calcium and iron supplements.

We found a higher proportion of women living near workplaces where lead is used among exposed women compared with the control group. There was also a significant association between the BLLs and the habit of dyeing the hair. Some hair dyes may contain lead and other harmful substances. Our results agree with Marzulli [42] who reported a significant correlation between blood lead and hair lead in people who used lead contained hair dyes. Use of these products by a pregnant woman may harm the health of her unborn child. None of the cited investigations, carried out in an occupational cohort, analyzed non-occupational exposure. However, our findings suggest that the contribution of non-occupational activities must be explored for determining total lead exposure and subsequent health effects.

Table 7 Regression analysis for predictors of BLLs in exposed group (*N* = 31)

Variable	Coefficient β	95% CI	*P**
Wearing of special workwear	- 0.608	- 1.115 – -0.102	0.021
Changing clothes after work	- 0.637	- 1.261 – - 0.013	0.046
Living near painting store	3.937	1.174 – 6.699	0.008
Living near printing office	7.418	.963 – 10.873	0.001
Living near junkyard	3.661	0.691 – 6.632	0.019
Living near rubbish dump	3.469	0.036 – 6.901	0.048
Washing the workwear together with other clothes	2.372	0.267 – 4.477	0.029

$R^2 = 0.865$
* Adjusted by age, educational level and gestational age

Occupational lead exposure can occur because of the use of lead material and products. For that reason, employers should provide their employees with adequate working conditions and protection information regarding hazards at their worksites. Exposed workers should use protective equipment and practice personal hygiene, such as showering and changing into clean clothes at the end of the shift [43]. In this study, working women who did not change their clothes after work showed significantly higher blood lead concentration in comparison with those women who had this habit. There was also statistical association of BLLs related to the use of special workwear. It is well known that appropriate workwear can greatly reduce exposure to hazardous substances [44]. In addition, clothing contaminated with lead can be an important route of exposure for pregnant women.

Despite the scientific data and practical considerations regarding the prevention of lead exposure during pregnancy, routine blood lead testing for pregnant women is not established in many countries. Nevertheless, it is the main way to make sure that women have not been affected by lead. Furthermore, some researchers have demonstrated that lead exposure during pregnancy affects children's physical neonatal development, and available evidence suggests there are no BLLs without risk of health effects [41].

Relatively little is known about the current prevalence, risk factors, and sources of lead poisoning among pregnant women [45]. Our study identified some risk factors associated with blood lead in occupationally exposed women. Despite the growing evidence that relatively low levels of environmental lead exposure may be associated with adverse pregnancy outcomes, there is no specific regulation in existence regarding occupational lead exposure during pregnancy in Mexico. Therefore, it is necessary to improve engineering controls and personal hygiene to reduce the risk of lead exposure during pregnancy. Much work needs to be done to reduce environmental lead exposure. Furthermore, exposed women should undergo blood lead testing to prevent lead poisoning.

We have recognized that our study has several limitations. First, the cross-sectional design did not allow an evaluation of the length and the extent of the exposure. Consequently, all the exposed women were included in a single group, regardless of the time spent in the working place. Longitudinal studies are needed to evaluate the changes in blood lead levels during the exposure time. Second, in our study calcium supplementation, dietary iron intake and indicators of iron status were not measured. It has been documented that low calcium intake may contribute to lead mobilization from the maternal skeleton during pregnancy [46] and that calcium supplementation reduces bone resorption [47] and minimizes release of lead from bone stores with subsequent fetal lead exposure [48, 49]. On the other hand, an inverse relationship between body stores of iron and lead retention has also been observed [50, 51]. Nevertheless, to our knowledge, it is the first study on this topic conducted in occupationally exposed pregnant women in Mexico. Therefore, the results of the present research can be used for comparison with future investigations regarding occupational exposure to lead during pregnancy.

Conclusions

Our results constitute evidence that pregnant women who work in some places where lead products are used may be at risk for presenting higher blood lead levels if they do not use protective equipment and do not practice adequate personal hygiene. The risk increases if women live near some places that are considered sources of lead exposure such as a painting store, a printing office, a junkyard, or a rubbish dump. Additional studies using larger sample sizes and multiple prospective measurements are needed to verify our findings.

Additional file

Additional file 1: Database: Blood lead levels in pregnant women from Durango, Mexico. (XLS 733 kb)

Abbreviations

ALES: Adult lead epidemiology surveillance; BLLs: Blood lead levels; BMI: Body mass index; CDC: Centers for disease control and prevention; CI: Confidence interval; EDTA: Ethylenediaminetetraacetic acid; NIST: National Institute for Standard Technology; OR: Odds ratio; SD: Standard deviation

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Availability of data and material

All data analyzed during this study are included in this published article, in the Additional file 1: DatabasePb.xls.

Authors' contributions

OLLLL designed the study, participated in the elaboration of the questionnaire, prepared the background, results and discussion sections, as well as part of the methods sections, JMSP participated in the elaboration of the questionnaire, he was the field supervisor and contributed to the discussion of results, SEM collaborated in the statistical analysis and interpretation of results, EER carried out part of the literature review, participated in the process of data collection and contributed to the discussion and interpretation of results, FXCJ contributed to the discussion and interpretation of results and prepared part of the results and discussion sections, ASC participated in the elaboration of the questionnaire, in the

process of data collection and critically reviewed the manuscript, AMLQ participated in the design of the questionnaire, carried out part of the literature review and collaborated to the interpretations of results, FVA collaborated in the statistical analysis and interpretation of results, EMMH contributed to the discussion of the findings, she also contributed in drafting and writing of the manuscript, GGV supervised the procedures for blood lead measurements and contributed to the discussion of the findings. JDS contributed with blood lead measurements, interpreting the results, and providing critical comments. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
This study was approved by the Ethical Committee of Durango General Hospital. All participants gave their informed written consent before being enrolled.

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Association between Blood Lead Levels and Delta-Aminolevulinic Acid Dehydratase in Pregnant Women.

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Abstract

Blood lead levels (BLLs) and delta-aminolevulinic acid dehydratase (ALAD) activity are considered biomarkers of lead exposure and lead toxicity, respectively. The present study was designed to investigate the association between BLLs and ALAD activity in pregnant women from Durango, Mexico. A total of 633 pregnant women aged 13-43 years participated in this study. Blood lead was measured by a graphite furnace atomic absorption spectrometer. ALAD activity was measured spectrophotometrically. Mean blood lead was 2.09 ± 2.34 µg/dL; and 26 women (4.1%) crossed the Centers for Disease Control (CDC) recommended level of 5 µg/dL. ALAD activity was significantly lower in women with levels of lead ≥5 µg/dL compared to those with BLLs < 5 µg/dL ($p = 0.002$). To reduce the influence of extreme values on the statistical analysis, BLLs were analyzed by quartiles. A significant negative correlation between blood lead and ALAD activity was observed in the fourth quartile of BLLs ($r = -0.113$; $p < 0.01$). Among women with blood lead concentrations ≥2.2 µg/dL ALAD activity was negatively correlated with BLLs ($r = -0.413$; $p < 0.01$). Multiple linear regression demonstrated that inhibition of ALAD in pregnant women may occur at levels of lead in blood above 2.2 µg/dL.

KEYWORDS: blood lead levels; delta-aminolevulinic acid dehydratase (ALAD) activity

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Association between Blood Lead Levels and Delta-Aminolevulinic Acid Dehydratase in Pregnant Women

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Association between Blood Lead Levels and Delta-Aminolevulinic Acid Dehydratase in Pregnant Women

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Abstract: Blood lead levels (BLLs) and delta-aminolevulinic acid dehydratase (ALAD) activity are considered biomarkers of lead exposure and lead toxicity, respectively. The present study was designed to investigate the association between BLLs and ALAD activity in pregnant women from Durango, Mexico. A total of 633 pregnant women aged 13–43 years participated in this study. Blood lead was measured by a graphite furnace atomic absorption spectrometer. ALAD activity was measured spectrophotometrically. Mean blood lead was 2.09 ± 2.34 μg/dL; and 26 women (4.1%) crossed the Centers for Disease Control (CDC) recommended level of 5 μg/dL. ALAD activity was significantly lower in women with levels of lead ≥5 μg/dL compared to those with BLLs < 5 μg/dL ($p = 0.002$). To reduce the influence of extreme values on the statistical analysis, BLLs were analyzed by quartiles. A significant negative correlation between blood lead and ALAD activity was observed in the fourth quartile of BLLs ($r = -0.113$; $p < 0.01$). Among women with blood lead concentrations ≥2.2 μg/dL ALAD activity was negatively correlated with BLLs ($r = -0.413$; $p < 0.01$). Multiple linear regression demonstrated that inhibition of ALAD in pregnant women may occur at levels of lead in blood above 2.2 μg/dL.

Keywords: blood lead levels; delta-aminolevulinic acid dehydratase (ALAD) activity; pregnant women; lead exposure; lead toxicity

1. Introduction

Lead is known to represent a significant environmental hazard to pregnant women and their offspring. Exposure to high environmental levels of lead during pregnancy has been associated with some adverse outcomes [1]. However, recent findings indicate that lead may be toxic at levels previously considered to have no adverse effects. Research suggests that lead exposure at both low

and high concentrations adversely affects hematopoietic, vascular, nervous, renal and reproductive systems [2]. During pregnancy, adverse reproductive outcomes may occur at levels of lead in blood below 10 μg/dL. Infertility [3], spontaneous abortion [4], preeclampsia [5–7] and preterm delivery [8] have all been associated with lead exposure at levels previously considered safe.

Blood lead concentrations above 2.5 μg/dL have been associated with an increased risk of infertility [3]. A significant association between blood lead concentrations and hypertension during pregnancy has been documented [5,7]. Significantly higher blood lead levels have been reported in women with pregnancy-induced hypertension compared to normotensive patients, and significant correlations between blood lead levels and systolic and diastolic blood pressures have been found [7]. Moreover, higher levels of lead in umbilical cord blood have been found in preeclampsia cases compared to women without this condition [5].

Elevated lead levels have been also associated with abortion and duration of pregnancy [4,8]. In a prospective study in Mexico city a statistically significant relationship between low-to-moderate maternal lead levels and the risk of spontaneous abortion was demonstrated [4]. Furthermore, researchers have found significantly higher blood lead levels during the first trimester of pregnancy in mothers who delivered preterm babies when compared with those whohadfull-term pregnancies [8].

Several biological techniques and biomarkers are useful for risk assessment of lead in the field of environmental health. Blood lead is the most widely used biomarker of lead exposure. This indicator represents a measure of soft tissue lead, body burden and absorbed doses of lead, whereas the critical effects of lead in bone marrow can be used as biomarker of effect. The effects of lead in bone marrow arise mainly from lead interaction with some enzymatic processes involved in heme synthesis [9].

The main biomarkers of effect are the inhibition of delta-aminolevulinic acid dehydratase (ALAD) and the variation in some metabolite concentrations, such as zinc protoporphyrin (ZP) in blood, delta-aminolevulinic acid in urine (ALA-U), delta-aminolevulinic acid in blood (ALA-B), delta-aminolevulinic acid in plasma (ALA-P) and coproporphyrin in urine (CP). However, not all mentioned indicators equally reflect dose and internal dose/effect relationship [2].

Lead toxicity may be explained by its interference with different enzymes. Lead inactivates these enzymes by binding to the SH-groups of proteins or by displacing some essential metal ions. Lead is known to inhibit three enzymes involved in the heme pathway: delta-aminolevulinic acid dehydratase, ferrochelatase, and coproporphyrinogen oxidase, but the major effectsareon ALAD activity. The δ-aminolevulinic acid dehydratase is the second enzyme of the heme pathway. This enzyme catalyzes the condensation of two molecules of δ-aminolevulinic acid (ALA) to form the monopyrrole porphobilinogen (PBG) [10]. In subsequent steeps, PBG is assembled into tetrapyrrole molecules, which constitute the prosthetic groups of hemoglobin [11]. Lead inhibition of ALAD activity results in accumulation of δ-aminolevulinic acid. ALA has been associated with oxidative damage by causing formation of reactive oxygen species (ROS), such as superoxide, hydroxyl radical, and hydrogen peroxide [12–14].

Negative correlations between blood lead concentration and ALAD activity have been reported, even at low levels of lead in blood [9,15,16]. On the other hand, positive correlations have been found between ALAD activity and malondialdehyde (MDA) levels [16]. Thus, ALAD activity is thought to be a sensitive indicator of early effect of lead as well as a biomarker of oxidative stress in the lead-exposed hematological system [17]. Blood lead has been considered a reliable indicator for the evaluation of lead exposure, whereas inhibition of ALAD activity has been considered one of the primary detectable parameters of lead poisoning [2].

Activity of ALAD is easily assayable in samples of peripheral blood. This enzyme has a high sensitivity to divalent lead ions, so it can be used as an indirect biomarker to estimate exposure to lead in humans [18]. ALAD activity test is considered appropriate for screening purposes, due to the progressive inactivation of this enzyme by lead over a range corresponding to subclinical intoxication [19]. In addition, ALAD activity is more sensitive than ALA in urine to evaluate the amount of circulating lead [9,20].

Previous epidemiological studies on the association between blood lead levels (BLLs) and ALAD activity showed divergent views. Studies reporting high levels of lead in blood revealed significant negative correlations between blood lead concentrations and ALAD activity [12,21,22]. However, some authors have demonstrated that ALAD inhibition occurs at levels of lead in blood around 5 μg/dL [15,16,23]. Most studies regarding the association between BLLs and ALAD activity have been conducted in occupationally exposed people and in children. Nevertheless, no significant variation of enzymatic ALAD activity has been reported in children at mean blood lead of 2.58 ± 0.30 μg/dL [13].

In a previous study, conducted by our research group, blood lead levels and some risk factors for lead exposure in pregnant women were determined, but ALAD activity was not evaluated [24]. The present cross-sectional study was designed to investigate the association between BLLs and ALAD activity in pregnant women from Durango, Mexico.

2. Materials and Methods

2.1. Subjects

This cross-sectional study was carried out between January 2014 and June 2016. The study subjects consisted of 633 clinically healthy pregnant women who received prenatal health care by the Secretariat of Health, State of Durango, Mexico. All pregnant women presented for prenatal care in health centers were asked to participate in the study. Those who accepted gave their written informed consent before being enrolled. Patients with renal failure, infectious disease or multifetal pregnancy were excluded. Participants were informed of the aims of the investigation and received information on ways to minimize their lead exposure. Each subject answered a questionnaire that contained sociodemographic data and information on reproductive history and sources of lead exposure. The study was conducted in accordance with the Declaration of Helsinki, and the research protocol was approved by the Ethical Committee of Durango General Hospital (approval number: 366/013).

2.2. Sample Collection

For determination of ALAD activity, a venous blood sample was drawn for each patient and collected in vacutainer tubes using sodium heparin as an anticoagulant. A second sample was collected in lead-free vacutainer tubes containing ethylenediaminetetraacetic acid (EDTA), and separated in two portions; one for hematological analysis, and the remaining aliquot for lead level determination. Blood samples were collected before fasting. After collection, blood samples were transported in ice boxes to the Clinical Analysis Laboratory, Scientific Research Institute, Juarez University of the State of Durango. Samples were stored and transported in a lead-free environment to avoid any contamination, handled by trained personnel and kept in reserve at 4 °C.

2.3. Measurement of ALAD Activity

Enzyme activitywas assayed spectrophotometrically by the standardized European method [25]. The enzyme was incubated with excess δ-aminolevulinic acid at 37 °C. The porphobilinogen which was formed in 1 h was mixed with modified Ehrlich reagent. The color developed was measured spectrophotometrically at 555 nm against a blank. Results were expressed as δ-aminolevulinic acid, μmol/min per liter erythrocytes (U/L). The activity was determined no later than 10 h after the sample collection.

2.4. Hematological Analysis

Hematological parameters were determined using an automated hematology analyzer (Abbott CELL-DIN 1400), at the Clinical Analysis Laboratory, Scientific Research Institute, Juarez Universityof the State of Durango. Red blood cells count (RBC), hemoglobin (Hb), hematocrit, meancorpuscular volume (MCV), mean corpuscular hemoglobin, and meancorpuscular hemoglobin concentration were determined. The hematocrit value was used for the calculation of the enzyme

activity. Only hemoglobin value was presented in the results because of the possible relationship between hemoglobin and blood lead levels.

2.5. Determination of Lead in Blood

Blood samples were transferred to the Laboratory of Environmental Toxicology, Faculty of Medicine, Juarez University of the State of Durango, Gomez Palacio Campus. This laboratory participates in the Wisconsin State Laboratory Program of Hygiene proficiency testing (WSLPHT). Blood lead was measured using a graphite furnace atomic absorption spectrometer Perkin-Elmer AAnalyst 800 with Zeeman-effect background correction. Duplicates of blood samples were analyzed according to Miller et al. [26]. Lead in bovine blood from the National Institute of Standard and Technology (NIST) was used as standard reference material. Each sample duplicate was analyzed twice and those with variation coefficient above 5% were reanalyzed.

2.6. Statistical Analysis

The sociodemographic and reproductive characteristics were shown as mean ± standard deviation. The study population was divided into two groups: those with BLLs < 5 μg/dL and those with BLLs ≥ 5 μg/dL, and Student's *t*-test was used to estimate differences between groups. To reduce the influence of extreme values on the statistical analysis, blood lead levels were analyzed by quartiles. One-way ANOVA was applied to compare the means between quartiles and the post-hoc comparisons were done using Tukey's test. Pearson correlation analysis was carried out to evaluate the relationship of blood lead concentration with hemoglobin and ALAD activity in all groups. Multiple linear regression was performed to evaluate the association of ALAD activity with BLLs. Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) software for Windows, version 15.0. A value of $p < 0.05$ was considered statistically significant.

3. Results

Table 1 summarizes the main characteristics, blood lead levels, and ALAD activity of women enrolled in this study. The mean age, education, gestational age, body mass index and hemoglobin of the studied population were 22.85 years, 10.04 years, 13.44 weeks, 25.61 kg/m^2 and 13.00 g/dL, respectively. The mean income per capita accounted 99.55 United States Dollars (USD) per month (1 USD = 17.0 Mexican pesos). The mean level of blood lead was 2.09 ± 2.34 μg/dL; and the mean ALAD activity was 57.59 ± 21.12 U/L.

Table 1. Main characteristics of the studied subjects (n = 633). ALAD: delta-aminolevulinic acid dehydratase.

Variables	Mean ± SD *	Range
Age (years)	22.85 ± 6.35	13–43
Education (years)	10.04 ± 2.67	0.0–21.0
Gestational age (weeks)	13.44 ± 4.86	3.0–28.0
Body mass index (kg/m^2)	25.61 ± 5.25	16.0–54.4
Income per capita (USD ** per month)	99.55 ± 89.68	4.41–970.59
Hemoglobin, g/dL	13.00 ± 1.27	8.8–23.1
Blood lead levels, μg/dL	2.09 ± 2.34	0.48–26.85
ALAD activity, U/L	57.59 ± 21.12	3.28–138.81

Note: * SD = standard deviation; ** USD = United States Dollars.

Table 2 shows some characteristics for women with lead levels <5 μg/dL, and for women with lead levels ≥5 μg/dL. No significant differences between the groups were observed in age, education, gestational age, body mass index, monthly income per person and hemoglobin. However, ALAD activity was significantly lower in women with lead levels ≥5 μg/dL ($p = 0.002$).

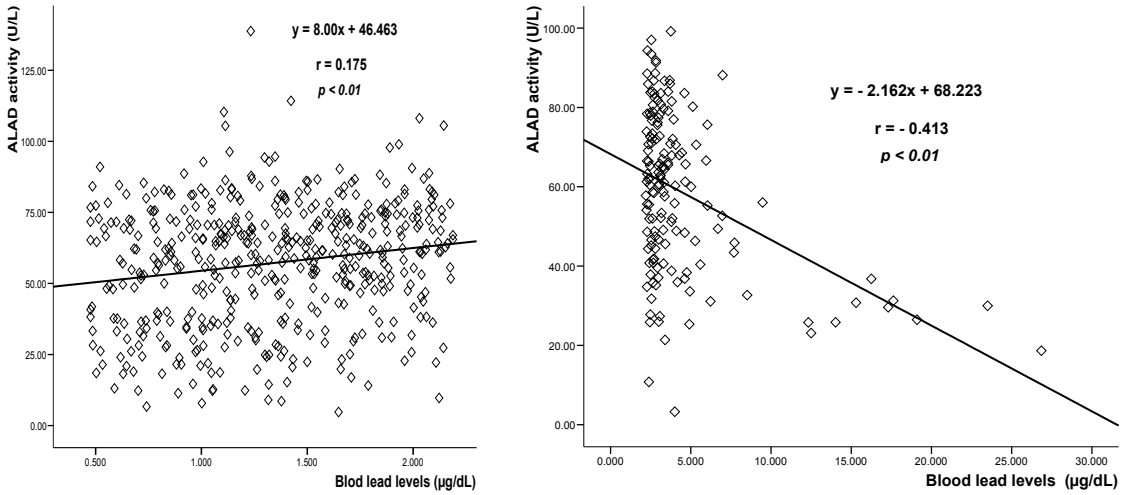
Table 3 shows sociodemographic variables, hemoglobin and ALAD activity by quartiles of blood lead. A significant variation of ALAD activity was observed ($p < 0.001$). According to the Tukey test, women in the first quartile had the lowest ALAD activity. On the other hand, enzyme activity decreased between the third and the fourth quartiles. On the basis of these results, Pearson correlation was performed to determine the relation of blood lead concentration with hemoglobin and ALAD activity by quartiles of BLLs (Table 4). The correlation of BLLs with hemoglobin was not statistically significant. However, significant negative correlation between BLLs and ALAD activity was observed in the fourth quartile (r = −0.413; $p < 0.01$).

Table 2. Main characteristics of women with blood lead levels <5 μg/dL and ≥5 μg/dL. BLL: blood lead levels.

Variables	BLLs < 5 μg/dL (n = 607)	BLLs ≥ 5 μg/dL (n = 26)	*p* *
	Mean ± SD	Mean ± SD	
Age (years)	22.87 ± 6.36	22.42 ± 6.13	0.728
Education (years)	10.06 ± 2.68	9.58 ± 2.52	0.372
Gestational age (weeks)	13.46 ± 4.85	12.95 ± 5.06	0.612
Body mass index (kg/m^2)	25.53 ± 5.20	27.36 ± 5.92	0.082
Income per capita (USD per month)	99.76 ± 78.70	94.32 ± 69.27	0.776
Hemoglobin, g/dL	13.00 ± 1.28	13.00 ± 1.04	0.974
ALAD activity, U/L	58.13 ± 21.05	45.10 ± 19.22	0.002

Note: * *p*-value was calculated from Student's *t*-test.

Taking into account the lower limit of blood lead for the third quartile, linear regression analysis was performed to determine the strength of the relationship between BLLs and ALAD activity in women with blood lead concentrations lower 2.2 μg/dL, and in those with BLLs ≥ 2.2 μg/dL (Figure 1). No significant association was observed between ALAD activity and BLLs for women with BLLs < 2.2 μg/dL. However, the results demonstrated a significant negative correlation (r = −0.413; $p < 0.01$) for women with BLLs ≥ 2.2 μg/dL.



(**A**) (**B**)

Figure 1. Linear regression between blood lead levels and δ-ALAD activity for women with BLLs < 2.2 μg/dL (**A**); and for thus with BLLs ≥ 2.2 μg/dL (**B**). The linear equation, correlation coefficient and *p* value are shown in the plot.

Table 3. Change in demographic characteristics, hemoglobin and ALAD activity by quartiles of blood lead levels.

Variables	First Quartile	Second Quartile	Third Quartile	Fourth Quartile	*p* *
n	160	158	158	157	
BLLs (μg/dL)	<1.09	1.09–1.61	1.62–2.19	>2.19	
Age, years	22.50 ± 6.84	23.60 ± 6.13	23.10 ± 6.08	23.20 ± 6.36	0.696
Education (years)	10.10 ± 2.70	10.18 ± 2.73	9.81 ± 2.60	10.05 ± 2.72	0.637
Gestational age (weeks)	13.69 ± 4.98	13.47 ± 4.73	13.71 ± 4.94	12.86 ± 4.79	0.375
Body mass index (kg/m^2)	24.90 ± 5.31	25.92 ± 5.39	26.01 ± 5.27	25.58 ± 4.98	0.254
Income per capita (USD per month)	98.41 ± 76.47	96.10 ± 100.04	95.99 ± 71.45	108.07 ± 106.64	0.614
Hemoglobin (g/dL)	12.88 ± 1.13	12.93 ± 1.20	12.95 ± 1.04	13.23 ± 1.64	0.070
ALAD activity, U/L	51.51 ± 21.82	59.10 ± 22.18	61.02 ± 19.10	58.82 ± 20.14	0.000

Note: * *p*-value was calculated from one-way ANOVA.

Table 4. Pearson correlations of blood lead levels with hemoglobin and ALAD activity by quartiles of blood lead levels.

Quartile of BLLs	Hemoglobin	ALAD Activity
First	0.027	−0.013
Second	−0.042	−0.043
Third	0.076	0.116
Fourth	−0.087	−0.413 **
All subjects	0.017	−0.113 **

Note: ** = Statistically significant correlation ($p < 0.01$).

To deepen the exploration of the relationship between blood lead concentration and ALAD activity in women with BLLs ≥ 2.2 μg/dL, multiple linear regression was applied (Table 5). Blood lead levels were inversely associated with ALAD activity ($p < 0.001$). However, no significant associations were found for age, educational level, gestational age, body mass index and hemoglobin. The model represents 21.9% of the predictive capability.

Table 5. Multiple linear regression model for ALAD activity in women with BLLs ≥ 2.2 μg/dL (n = 142).

Variable	Coefficient β	Standard Error	*p*-Value
Age, years	0.239	0.261	0.361
Educational level, years	0.689	0.578	0.235
Gestational age, weeks	0.202	0.339	0.553
Body mass index (kg/m^2)	−0.443	0.338	0.192
Hemoglobin (g/dL)	1.841	0.958	0.057
Blood lead levels (μg/dL)	−1.961	0.404	<0.001

Note: $R^2 = 0.219$.

4. Discussion

The mean blood lead concentration of 2.09 ± 2.34 μg/dL reported here is lower than those observed in other studies carried out in Mexican population. In Mexico City, Borja-Aburto found blood lead concentrations of 12.03 μg/dL in pregnant women who suffered spontaneous abortion and 10.09 μg/dL in a control group [4]. Another study of blood lead levels in pregnant women from Mexico City reported a mean blood lead concentration of 6.24 g/dL [27]. In a previous study carried out by our research group in pregnant women from Durango, Mexico, a mean blood lead level of 2.79 ± 2.14 μg/dL was observed, and 26 women (8.7%) had BLLs above the CDC recommended level of 5 μg/dL [24]. In the present research, also 26 women had levels of lead in blood above 5 μg/dL, but they represent 4.1% of the studied population.

Some authors have suggested that lead intoxication is characterized by high blood lead concentration and low ALAD activity [27,28]. For that reason, some researchers have recommended use of ALAD inhibition as an indicator of lead intoxication [12,21,29]. In our study, ALAD activity was significantly lower in women with BLLs $\geq$ 5 μg/dL compared with those with BLLs below 5 μg/dL. This finding is in an agreement with earlier published data. Similar results were observed in urban male adolescents from Lucknow, India [12], in children with neurological diseases from India [16], in lead workers from Taiwan [29], and in children from Southern Brazil [22].

Chiu et al. reported an inverse association between blood lead and ALAD activity when they compared lead workers from Taiwan with a control group (blood lead levels 19.5 $\pm$ 14.7 μg/dL and 2.9 $\pm$ 1.9 μg/dL, respectively) [29]. They concluded that the possible threshold value of blood lead for ALAD activity is around 10 μg/dL, and thus, ALAD activity may be usedas a biomarker for evaluation of lead toxicity in humans. Similar results were reported by Fecsa et al.; who analyzed lead dose-dependent effects for 18 lead exposed individuals and 12 normal volunteers [21]. Jasim et al. also reported a decrease of ALAD activity in battery manufacturing factory workers compared to non-exposed group; furthermore, this decrease became even more evident with increased duration of exposure [28]. The levels of lead in blood were 13.15 μg/dL in the control group, and more than 34.3 μg/dL in the exposed workers, respectively. In India, children residing in urban zones showed a negative correlation ($p < 0.001$) between blood lead levels (mean 11.8 $\pm$ 11.96 μg/dL) and ALAD activity [30].

Recent findings have suggested that ALAD inhibition may occur at low levels of lead in blood. Ahamed et al. reported a significant negative correlation between blood lead levels and ALAD activity in children with blood lead concentration lower than 10 μg/dL [15]. Moreover, Sakai and Morita considered that the threshold value of blood lead for ALAD inhibition is around 5 μg/dL [23]. Nevertheless, Martínez et al. did not find inhibition of enzymatic ALAD activity in children from Argentina, with mean blood lead of 2.58 $\pm$ 0.30 μg/dL [13].

Blood lead levels in our study were lower than in some prior studies on blood lead and ALAD activity [12,13,15,22,23,29,30]. Nevertheless, we observed a significant association between blood lead and ALAD activity at blood lead levels of 2.2 μg/dL, well below the CDC recommended level of 5 μg/dL for children and pregnant women [31]. To our knowledge, a similar result has not yet been reported in the literature.

It is well established that ALAD inhibition results in an increase of δ-ALA levels in blood, which can intensify oxidative stress and release iron from proteins such as ferritin [32]. For that reason, some authors have considered that decrease in ALAD activity has the potential to be used as an indicator of oxidative stress [32–34]. On the other hand, pregnancy is a condition that increases susceptibility to oxidative stress because of the mitochondria-rich placenta. During pregnancy, lipid peroxidation increases due to mitochondrial activity and hormone synthesis in placenta. Iron, which is abundant in the placenta, is important in the production of free radicals, and subjects the fetus to oxidative stress [35].

Importantly, our results also show that a small percent of pregnant women have blood lead concentrations above 5 μg/dL. Similar results were reported in a previous study carried out in Durango, Mexico [36]. A study conducted in Argentina, Mexico and Uruguay estimated 316,703 individuals in these countries are at risk of lead exposure, approximately 0.19% of the total population of all three countries. Of this population, 80,021 were women at childbearing age [37].

Researchers have documented that women with BLLs between 5–10 μg/dL have more probability of having a miscarriage compared to those with BLLs below 5 μg/dL [4]. It is thus necessary to identify and reduce the sources of exposure for these women. Recent research suggested a low threshold for the effect of maternal blood lead on birth outcomes, and recommended that exposure to lead during pregnancy should be kept as low as possible to minimize adverse outcomes [38]. Therefore, the growing evidence regarding the association between low levels of lead in blood and adverse pregnancy outcomes should be taken into account in the development of prevention politics.

We recognized some limitations in our study. In Figure 1 samples with blood lead between 5 and 10 μg/dL show quite a dispersion, but even in this segment the correlation is negative. In contrast, samples with blood lead below 2.2 μg/dL showed a slight increase of ALAD activity. It is well established that ALAD activity is specifically inhibited by lead at concentrations between 5 and 50 μg/dL [9]. In spite of this, significant correlations were observed only in the fourth quartile (BLL >2.19 μg/dL). In the other hand, we did not evaluate some biomarkers of oxidative stress that may be associated with blood lead [39], which could have resulted in uncontrolled confounding. Alcohol consumption may affect ALAD activity, but it was not considered because only a few women recognized they had this habit. Nonetheless, to our knowledge, this is the first study which has analyzed the relationship between blood lead levels and ALAD activity in Mexican pregnant women. Moreover, in the revised literature, there is no such data evaluating the effect of lead exposure on enzymatic ALAD activity in pregnant women, who constitute one of the most vulnerable sections of the population.

5. Conclusions

In summary, the results of our study suggest that even very low lead exposure may cause a decrease of ALAD activity, at least in pregnant women. We propose that ALAD inhibition may occur at very low levels of lead in blood due to lead exposure and pregnancy conditions.

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Conflicts of Interest: The authors declare no conflicts of interest.

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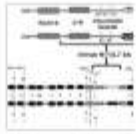

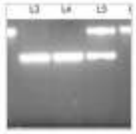

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Research article

H1/H2 *MAPT* haplotype and Parkinson's disease in Mexican mestizo population

Ernesto G. Miranda-Morales [a], Ada Sandoval-Carrillo [a], Francisco X. Castellanos-Juárez [a], Edna M. Méndez-Hernández [a], Osmel La Llave-León [a], Gerardo Quiñones-Canales [b], Luis A. Ruano-Calderón [c], Oscar Arias-Carrión [d], Jose M. Salas-Pacheco [a]

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Highlights

- No-association was observed between genotypes and PD risk in Mexican population.
- No-association was maintained when stratifying our groups by region.
- No-association was found when stratifying our groups by familial and

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H1/H2 *MAPT* haplotype and Parkinson's disease in Mexican mestizo population

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ABSTRACT

Parkinson's disease (PD) is characterized by bradykinesia, resting tremor, rigidity and postural instability as well as early symptoms. Previous studies that evaluated the association between H1/H2 *MAPT* haplotype and PD were mostly conducted in European populations in which the H1 haplotype was a reported risk factor for PD. Despite those findings, some studies have suggested that the association may be ethnically dependent. Since studies conducted in Latin American population have been scarce, we genotyped the H1/H2 *MAPT* haplotype in Mexican mestizo population as part of a PD case-control study. DNA was extracted from peripheral blood leucocytes in 108 cases and 108 controls and detection of the H1/H2 haplotypes was achieved by determining the MAPT_238 bp deletion/insertion variant at intron 9 through end-point PCR followed by visual 3% agarose gel electrophoresis interpretation. We observed no-association between genotypes and PD risk [OR/CI (Odds ratio/95% Confidence Interval) of 1.60 (0.78–3.29) for H1/H2 genotype and 2.26 (0.20–25.78) for H2/H2]. No-association was maintained when stratifying our groups by central ($p = 0.27$) and northern regions ($p = 0.70$). Our data suggest that H1/H2 *MAPT* haplotype is not a risk factor to PD in our population.

1. Introduction

1.1. Pathological mechanisms

Parkinson's disease (PD) is the second most common neurodegenerative disease and is characterized by bradykinesia, resting tremor, rigidity and postural instability as well as early symptoms such as hyposmia, constipation and sleep disorders, among others [1]. Pathological mechanisms include the death of melanin and dopamine-producing neurons in the Substantia Nigra Pars Compacta (SnPC) and the loss of Neuromelanin (NM) as a post-mortem feature [2]. Reports also identified alpha-synuclein [3] and tau [4] aggregates in Lewy Bodies. While the presence of metal ions and mitochondrial reactive oxygen species (ROS) formation have also been demonstrated [5]. Genetic causes were found in familial and sporadic PD [6]. Microtubule Associated Protein Tau (*MAPT*) gene has been highly associated [7] and studies reported an over-representation of the MAPT H1 haplotype in various neurodegenerative disorders including progressive supranuclear palsy [8], Alzheimer's Disease (AD) [9], and PD [10].

1.2. MAPT H1/H2 structure

The *MAPT* locus contains two reported haplotypes: the directly oriented H1 and the inverted H2 [11–13]. The H1 and H2 haplotypes may be distinguished by identifying one or more of the eight reported single nucleotide polymorphisms (SNPs) in absolute linkage disequilibrium. Another characteristic of H2 is the presence of a 238 bp deletion within intron 9 (Fig. 1) [8].

1.3. MAPT H1/H2 associations

A copious amount of studies have been conducted to determine the possible association between H1/H2 haplotypes and PD with contradictory results. A recent meta-analysis determined that the *MAPT*_238 bp deletion/insertion might modulate the risk of PD [14]. Also, studies in Greek and Serbian populations reported association

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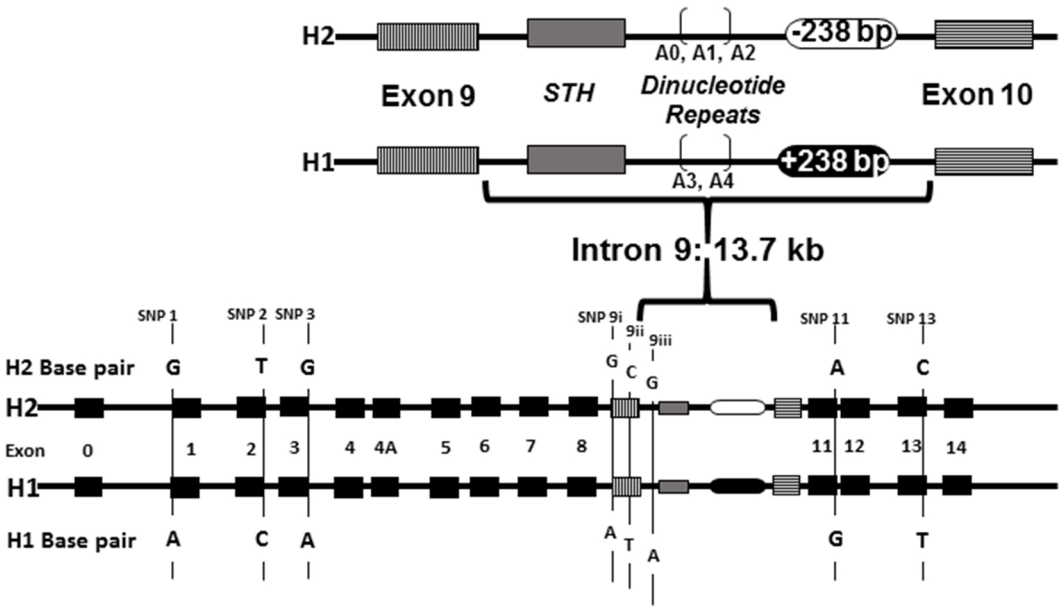

Fig. 1. Schematic representation of The *MAPT* region of interest. H1 and H2 contain 8 distinct SNPs (vertical lines with respective base pairs) and the MAPT_238 bp deletion (white oval)/insertion (black oval) variant at Intron 9. Black boxes indicate exons. Gray box indicates Saitohin (*STH*).

between H1 Haplotype and PD [15–17] and a report in UK Caucasian population found the H2 haplotype to be a protective factor [18]. However, reports in German, Indian, Greek and Finnish populations suggested that there is no correlation between H1/H2 haplotypes and PD [17,19,20]. The main goal of this work was to determine if there is an association between H1/H2 haplotypes and PD in a Mexican mestizo population.

2. Materials and methods

2.1. Information about participants

The subjects were recruited from three public hospitals. General Hospital Dr. Manuel Gea González in Mexico City (central region of Mexico), General Hospital 450 in Durango (northern region of Mexico) and General Hospital Santiago Ramón y Cajal in Durango (northern region of Mexico). PD was diagnosed using the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria (UKPDSBB). Only those with late-onset disease (after 50 years of age) were included. The ethics committee from Dr. Manuel Gea González General Hospital authorized the study. Procedures were in accordance with the ethical standards of the Helsinki Declaration. A life-style interview was applied and written consent forms were signed prior to any intervention. Subjects were programmed for a fasting peripheral blood draw using the BD Vacutainer® collection system.

2.2. Genotyping methods

Samples were stored at 1°–6 °C. The DNA was extracted from peripheral blood leucocytes using the QIAamp DNA Blood Mini Kit® by QIAGEN® and quantified using a Thermo Scientific™ NanoDrop 2000 spectrophotometer. The H1/H2 haplotypes were determined analyzing the MAPT_238 bp deletion/insertion by PCR using the primer sequences GGAAGACGTTCTCACTGATCTG (forward) and AGGAGTCTGGCTTCA GTCTCTC (reverse). The 238 bp deletion was determined by the amplification of one distinct band at a size of 246 bp (H2/H2 haplotype); the amplification of two distinct bands (484 bp and 246 bp) corroborated the H1/H2 haplotype; and finally, the amplification of a 484 bp band only, corroborated the H1/H1 haplotype (Fig. 2).

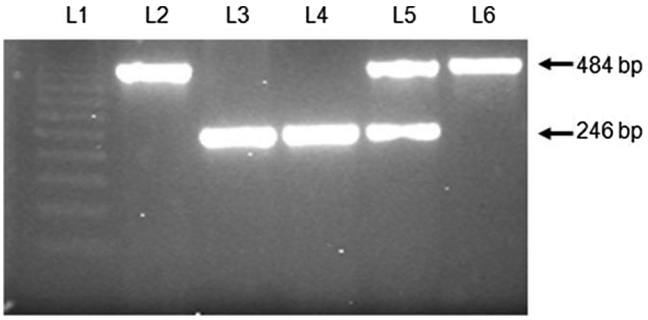

Fig. 2. Genotypification of H1/H2 haplotype using end point PCR (Genomic DNA in 3% agarose gel stained with ethidium bromide). L1, 50 bp DNA marker; L2 and L6, H1/H1 genotype; L3 and L4, H2/H2 genotype; L5, H1/H2 genotype.

2.3. Genotyping data analysis

For our genotypic analysis we utilized an on-line program provided by Institut Català d'Oncologia (https://snpstats.net/) as well as IBM SPSS Statistics for Windows (Version 21.0. Armonk, NY: IBM Corp.) for additional statistical analyses. For the purposes of this study p values < 0.05 were considered significant.

3. Results

3.1. General data about participants

In this work we included 108 cases and 108 controls. 39 paired cases resided in the central region versus 69 paired cases in the northern region. A total of 78 participants lived in the central region including Mexico City and surrounding states while 138 participants lived in the northern region including the city of Durango and rural areas of the state. The total age range of the participants was from 52 to 94 years with a mean age of 70.10 (± 9.16). Of these, 106 (49.1%) were women while 110 (50.9%) were men. For cases, the mean age at onset was 64.80 years (± 9.52). 18.51% of PD cases reported a family history of one or more first or second-degree relative(s) with PD. The mean evolution in years was 5.54 (± 4.11). Mean UPDRS III score was 43.00 (± 19.67), while total UPDRS score was 72.27 ± 33.29.

Table 1
Allelic and genotypic frequencies of H1/H2 haplotype and risk estimation to PD.

Haplotype	Controls n = 108	Cases n = 108	*p* value	OR (95% CI)	*p* value
H1	199 (0.92)	190 (0.88)	0.148*	1 (reference)	0.15
H2	17(0.08)	26 (0.12)		1.60 (0.84–3.04)	
H1/H1	92 (0.85)	84 (0.78)	0.363*	1 (reference)	0.36
H1/H2	15 (0.14)	22 (0.20)		1.60 (0.78–3.29)	
H2/H2	1 (0.01)	2 (0.02)		2.26 (0.20–25.78)	

* Pearson's Chi-squared is significant at $p \leq 0.05$.

3.2. Allelic and genotypic frequencies

The allelic and genotypic frequencies are shown (Table 1). Only one control and two cases presented the H2/H2 haplotype. No statistically significant differences were observed between groups in both, allelic (p = 0.148) and genotypic (p = 0.363) frequencies. The *odds ratio* estimation showed that neither the H2 allele (OR = 1.60, CI_{95} = 0.84–3.04) nor the H1/H2 (OR = 1.60, CI_{95} = 0.78–3.29) or H2/H2 (OR = 2.26, CI_{95} = 0.20–25.78) genotype are a risk factor for PD (Table 1).

3.3. Stratified allelic and genotypic frequencies

Subsequently, we stratified based on central or northern region from Mexico (Table 2). When comparing allelic frequencies in both controls and cases between regions we found no statistically significant differences (p = 0.098 and p = 0.595, respectively). Like the results observed when analyzing the total population, we found no differences in either the central or the northern region when comparing both allelic or genotypic frequencies between cases and controls (Table 2).

3.4. Stratified familial and sporadic PD allelic and genotypic frequencies

Lastly, we analyzed genotypic frequencies based on stratification by familial PD (n = 26) and sporadic PD (n = 82). No association for both familial PD (p = 0.48) or sporadic PD (p = 0.32) was observed (Table 3).

4. Discussion

4.1. Summary of previous studies

Although several studies have been carried out to evaluate the possible association between H1/H2 *MAPT* haplotype and PD, these have mainly been conducted in European populations. In this regard, in spite of the H1 haplotype being recognized as a risk factor for PD in caucasians [14], this association was not observed in German, Greek and Finnish populations [17,19], and thus suggests that it is ethnically dependent. With respect to Latin American populations, the only previous work was performed in population from the central region of Mexico, highlighting the need for more studies to determine the role of the H1/H2 haplotype in PD for these populations.

4.2. Regional genetic diversity in Mexican mestizo population and MAPT H1/H2

Mexican population, which is predominantly mestizo (composed of Amerindian, European, and, to a minor degree, African ancestries) has demonstrated regional genetic diversity that may affect biomedical traits in diseases [21,22]. Accordingly, our work included population from both the central and northern regions of the country. Although these genetic differences were reflected through a greater presence of H2 allele and H1/H2 genotype in cases and controls from the northern region compared to the central region, they were not statistically significant.

4.3. Multifactorial mechanisms for MAPT activation and PD?

We found no association between H1/H2 *MAPT* haplotype and PD risk, even after analyzing the population of each region independently. These results are consistent with those previously reported in Mexican mestizo population from the central region of Mexico [23] As PD is a multifactorial disease, perhaps our finding represents a distinct mechanism in the activation of *MAPT* in Mexican PD population; one that may very well be controlled by both genetic or epigenetic factors, including diet and environmental conditions. Future studies should consider additional analyses of current as well as new polymorphisms. Also, analysis of epigenetic changes of *MAPT* should be performed.

4.4. Study limitations

Finally, we would like to point out that our study has some limitations. We did not include a population from southern Mexico, which would allow a representation of the entire mestizo population of the country. Additionally, we did not determine the reported H1 subhaplotypes.

5. Conclusion

In conclusion, our results confirm no association between H1/H2 *MAPT* haplotype and PD in Mexican mestizo population and could serve as a useful reference when comparing among other ethnic groups in future studies.

Table 2
Allelic and genotypic frequencies of H1/H2 haplotype stratified by region and risk estimation to PD.

Region	Haplotype	Controls	Cases	*p* value	OR (95% CI)	*p* value
Central	H1	75 (0.96)	70 (0.90)	0.117*	1 (reference)	0.132
	H2	3 (0.04)	8 (0.10)		2.85 (0.72–11.20)	
	H1/H1	36 (0.92)	32 (0.82)	ND	1 (reference)	0.27
	H1/H2	3 (0.08)	6 (0.15)		2.25 (0.52–9.74)	
	H2/H2	0 (0)	1 (0.03)		ND	
Northern	H1	124 (0.90)	120 (0.87)	0.452*	1 (reference)	0.453
	H2	14 (0.10)	18 (0.13)		1.32 (0.63–2.79)	
	H1/H1	56 (0.81)	52 (0.75)	0.697*	1 (reference)	0.70
	H1/H2	12 (0.17)	16 (0.23)		1.44 (0.62–3.32)	
	H2/H2	1 (0.02)	1 (0.02)		2.26 (0.07–17.66)	

ND, not determined.
* Pearson's Chi-squared is significant at $p \leq 0.05$.

Table 3
Allelic and genotypic frequencies of H1/H2 haplotype stratified by familial and sporadic PD and risk estimation.

PD	Haplotype	Controls	Cases	*p* value	OR (95% CI)	*p* value
Familial	H1	47 (0.90)	45 (0.87)	0.539*	1 (reference)	0.541
	H2	5 (0.10)	7 (0.13)		0.68 (0.20–2.31)	
	H1/H1	21 (0.81)	20 (0.77)	ND	1 (reference)	0.48
	H1/H2	5 (0.19)	5 (0.19)		0.95 (0.21–4.36)	
	H2/H2	0 (.00)	1 (0.04)		ND	
Sporadic	H1	152 (0.93)	145 (0.88)	0.186*	1 (reference)	0.190
	H2	12 (0.07)	19 (0.12)		0.60 (0.28–1.28)	
	H1/H1	71 (0.87)	64 (0.78)	0.336*	1 (reference)	0.32
	H1/H2	10 (0.12)	17 (0.21)		0.52 (0.22–1.22)	
	H2/H2	1 (0.01)	1 (0.01)		0.88 (0.05–14.55)	

ND, not determined.
* Pearson's Chi-squared is significant at $p \leq 0.05$.

Contributions

EGM-M and JMS-P were involved in the experimental design and drafted the manuscript. OA-C and AS-C were involved in the experimental process and revised it critically for important intellectual content. EMM-H, FXC-J, and OL-L gave approval for the version to be published and were involved in revising it critically. LAR-C and GQ-C were involved in the clinical aspects of the study and revised the intellectual content of the manuscript.

Disclosure statement

The authors disclose no actual or potential conflicts of interest.

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Author information

Abstract

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RESEARCH ARTICLE Open Access

Arsenic exposure and risk of preeclampsia in a Mexican mestizo population

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Abstract

Background: Exposure to arsenic in drinking water has been associated with various complications of pregnancy including fetal loss, low birth weight, anemia, gestational diabetes and spontaneous abortion. However, to date, there are no studies evaluating its possible association with preeclampsia.

Methods: This case–control study involved 104 preeclamptic and 202 healthy pregnant women. The concentrations of arsenic in drinking water and urine were measured using a Microwave Plasma-Atomic Emission Spectrometer.

Results: We found relatively low levels of arsenic in household tap water (range of 2.48–76.02 μg/L) and in the urine of the participants (7.1 μg/L vs 6.78 μg/L in cases and controls, respectively).

Conclusions: The analysis between groups showed for the first time that at these lower levels of exposure there is no association with preeclampsia.

Keywords: Preeclampsia, Arsenic, Drinking water

Background

Preeclampsia (PE) is a disorder peculiar to pregnancy and a major cause of maternal death and adverse fetal outcome [1]. In developing countries where access to health care is limited, PE is a leading cause of maternal mortality, with estimates of more than 60,000 maternal deaths per year [2] Although the exact pathophysiologic mechanisms of PE remain elusive, studies to date have implicated multiple processes, including the following: abnormal trophoblastic invasion, vasospasm, platelet activation, imbalance in the vasomotor-regulating factors and placental ischemia [3]. PE is characterized by increased oxidative stress due to the imbalance between lipid peroxidation and antioxidant defense mechanisms, leading to endothelial dysfunction and free radical mediated cell injury [4].

Arsenic-contaminated drinking water represents a major public health problem internationally [5–8]. The World Health Organization (WHO) and U.S. Environmental Protection Agency (EPA) standard for arsenic level in drinking water is 10 μg/L [9, 10]. Arsenic (As) is an established carcinogen and is also associated with a wide range of other chronic illnesses, such as diabetes, hypertension, and vascular diseases [11].

Oxidative stress has been identified as an important mechanism of As toxicity and carcinogenicity. In particular, As induces oxidative DNA damage and lipid peroxidation [12–16]. Oxidative stress and disrupted antioxidant systems have been shown to be involved in a wide range of pregnancy complications such as impaired fetal growth, PE, and miscarriage [17, 18].

Besides the generation of oxidative stress as a possible mechanism by which As may be associated with PE, Shin Le et al. reported that exposure to environmentally relevant concentrations of As (2.5 μM of AsNaO2) inhibit the migration of EVT cells (a human extravillous trophoblast cell line) in vitro, therefore, a similar mechanism may be occurring in vivo [19].

Several studies have been conducted to determine the association between chronic As exposure and adverse pregnancy outcome. Excess spontaneous abortion,

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stillbirth, and preterm birth rates among women with chronic As exposure have been reported [20–23]. However, to date there are no reports that show an association between As exposure and PE. This study evaluates whether As exposure from drinking water is associated with PE in a population of northern Mexico.

Methods

Patient recruitment

This prospective case–control study was approved by the Research Ethics Committee of the General Hospital of the Ministry of Health of Durango, Mexico in accordance with the Code of Ethics of the Declaration of Helsinki. Signed informed consent was obtained from all patients and controls before participation in the study. The sample size was calculated using the formula $n = (Z_{\alpha/2} + Z_{\beta})^2\ \dot{p}\ (1-\dot{p})\ (r+1)/d^2r$. The n needed to achieve 80 % power with an alpha of 0.05 was 94 (cases) and 188 (controls). Finally, we recruited 104 women diagnosed with PE (cases) and 202 healthy pregnant women (controls). The inclusion criteria were all those women diagnosed with mild PE (blood pressure (BP) ≥ 140/90 mmHg and proteinuria ≥ 30 mg/dL), severe PE (BP ≥ 160/110 mmHg and proteinuria ≥ 2000 mg/dL) and eclampsia (defined as occurrence, in a woman with PE, of seizures that cannot be attributed to other causes). The control group was conformed by healthy pregnant women attending the same hospital; without hypertensive, pathological or metabolic disorders during pregnancy. Follow up was given to the control group to corroborate the normality of the blood pressure values.

Sample collection

Within 1–3 weeks of delivery, a drinking water sample was collected at the homes of each of the study participants. Drinking-water samples were collected based on the subject's primary drinking water source. Maternal spot urine samples were collected at the hospital before delivery and immediately transported to the laboratory. Samples were stored at −80 °C until processing.

Detection of As in drinking water and urine

The concentrations of As in drinking water (DW) and urine were measured in the toxicology laboratory of Scientific Research Institute of the Universidad Juárez del Estado de Durango (UJED) using a Microwave Plasma-Atomic Emission Spectrometer (MP-AES 4100). The Trace Elements in Water standard reference material (SRM 1643e) (National Institute of Standards and Technology, Gaithersburg, MD) was used for quality control. The limit of detection for As in DW by MP-AES was 0.5 μg As/L. For urine analysis, six point calibration curves were prepared. To compensate for variation in the dilution of the urine (caused by variation in fluid intake, time of sampling, temperature, and physical activity), we adjusted the concentrations by specific gravity.

Statistical analysis

Independent sample Student's *t*-tests were performed using SPSS software (version 15.0; SPSS Inc., Chicago, IL, USA). Odds ratios (ORs) as estimates of relative risk of the disease were calculated with 95 % confidence intervals (95 % CIs). The ORs were adjusted for variations in age and weeks of pregnancy by means of a multivariate logistic regression model. Mann–Whitney *U* test was used when the data were not normally distributed. For analysis, our patients were stratified into 3 groups based on As levels in DW (Table 3). The Group 1 (G1) presented levels lower than 10 μg/L, group 2 (G2) levels between 10.1 μg/L and 25 μg/L and group 3 (G3) levels above 25.1 μg/L

Results

Clinical characteristics for controls and cases are shown in Table 1. Of the 104 women diagnosed with PE, 13 had mild PE, 72 severe PE and 19 eclampsia. Variables that showed a difference between groups were family history of PE, systolic and diastolic blood pressure (mm Hg), weeks of pregnancy and body mass index (Table 1). The range of As concentration in household tap water was 2.48–76.02 μg/L with more than 95 % of the participants having As levels higher than 10 μg/L. The mean concentration of As in DW was 39.58 μg/L and 40.49 μg/L for cases and controls, respectively; there were no statistically significant differences (Table 2, $p = 0.816$). While the WHO sets a maximum concentration of 10 μg/L in DW, the authorities in Mexico have set a maximum concentration of 25 μg/L (NOM-127-SSA1-1994) [24]. For this reason, the OR was estimated stratifying our patients into 3 groups based on As levels in DW. The results of Table 3 show that although the group exposed to concentrations above 25 μg/L presents an increased risk (OR = 1,715). This difference is not statistically significant ($p = 0.214$).

Table 1 Clinical characteristics for cases and controls

Clinical features	Controls (*n = 202*)	Cases (*n = 104*)	P-*value*
Age (years)	24.30 (7.078)[a]	24.39 (7.349)[a]	.92[b]
Weeks of pregnancy	37.49 (3.96)[a]	35.82 (3.97)[a]	0.001[b]
Systolic BP (mm Hg)	111.74 (10.82)[a]	158.36 (16.41)[a]	<0.0001[b]
Diastolic BP (mm Hg)	70.39 (9.97)[a]	101.21 (10.3)[a]	<0.0001[b]
Number of pregnancies	2.26 (1.40)[a]	2.34 (2.49)[a]	0.718[b]
Body mass index	24.61 (5.22)[a]	27.63 (5.82)[a]	<0.0001[b]
PE antecedent	13/202	14/104	0.045[c]

[a]Mean ± Standard deviation
[b]Independent sample *T* test
[c]Chi square test

Table 2 Water and urine arsenic levels in cases and controls

Arsenic μg/L	Controls (*n = 202*)	Cases (*n = 104*)		P-*value*
Water	40.49 (16.40)[a]	39.58 (26.43)[a]		0.816[b]
Urine	6.78 (3.48)[a]	7.1 (5.74)[a]		0.428[c]
		Mild PE *n* = 13	Severe PE/eclampsia *n* = 91	P-*value*
Water		46.03 (20.65)[a]	38.62 (26.87)[a]	0.519[b]
Urine		7.82 (6.87)[a]	7.03 (5.67)[a]	0.788[c]

[a] Mean ± Standard deviation
[b] Independent sample *T* test
[c] Mann–Whitney *U* test

Total urinary As concentration (U-tAs) was also evaluated. The mean concentration of U-tAs was 7.1 μg/L and 6.78 μg/L for cases and controls, respectively; there were no statistically significant differences (Table 2, $p = 0.428$). With the intention to establish whether As may be associated with the severity of PE, the cases were stratified in mild PE and severe PE/eclampsia. The results of Table 2 show that there is no statistically significant differences in the U-tAs (p =0.788). The risk of PE by U-tAs was estimated piling up to the patients in tertiles. The results in Table 3 show that at these levels, U-tAs is not a risk for PE.

Finally, we evaluated the correlation between As in DW and U-tAs. We observed an increase in the U-tAs associated with higher levels of As in DW. G1 presented a mean of 3.39 μg/L, G2 of 6.67 μg/L and G3 of 7.8 μg/L. However, the correlation coefficient was very low ($R^2 = 0.036$).

Discussion

To our knowledge this is the first study that evaluates if As exposure from DW is associated with PE. The As concentrations in household tap water (2.48–76.02 μg/L) were consistent with those previously found by our working group in the wells that provide DW to the city of Durango [25, 26]. Although these concentrations are not as high as those reported in other countries [27–30] or even in other regions of our own locality [31], there is a tremendous interest in the evaluation of regions with low or moderate As exposure in accordance with the increasingly clear evidence that relatively low levels of As can have health effects. Our comparative analysis between controls and cases evidenced no statistically significant differences. In addition, no differences were found in the analysis based on the severity of the PE.

The analysis of U-tAs showed a mean of 7.1 μg/L for cases and 6.78 μg/L for controls. These U-tAs levels are clearly lower than those reported among pregnant women in Bangladesh (80 μg/L) [32] and even lower than those reported in pregnant women in the nearby region known as Comarca Lagunera (23.3 μg/L) [33]. In our study we didn't find an association between U-tAs and PE or an association with the severity of PE. Recently, Joy-Mendez et al. found no association between serum As levels and blood pressure in a cohort of pregnant women from Mexico city [34]. They reported a mean of 15.2 μg/L of As in serum. Although they don't evaluate PE, our results can be considered similar.

In contrast to our results, several reports have associated As exposure with pregnancy complications including low weight of the newborn [35], fetal death [36], gestational diabetes [32], anemia [37] and spontaneous abortions [38], however, these associations appear at significantly higher levels of As (e. g., fetal death, U-tAs >200 μg/L or spontaneous abortions, As in DW >100 μg/L).

Our results could be interpreted on the one hand, as a confirmation of no association between As and PE, at least at these low levels. On the other hand, they might suggest that we need higher levels of As exposure to be able to observe the association.

Our study has some limitations. Although the participants state that their main source of water is from the tap, we can't rule out that As can come from other sources of drinking water (e.g., bottled water), some

Table 3 Odds ratio estimation by ranges of arsenic in water and urine

Water arsenic	OR* (95 % CI)	P-*value*	Urine arsenic	OR* (95 % CI)	P-*value*
Group 1[a] *n = 10*	Reference		Tertile 1[d] *n = 102*	Reference	
Group 2[b] *n = 69*	1.486 (0.200–11.025)	0.698	Tertile 2[e] *n = 102*	1.400 (0.748–2.621)	0.698
Group 3[c] *n = 227*	1.715 (0.732–4.019)	0.214	Tertile 3[f] *n = 102*	0.788 (0.411–1.512)	0.214

[a] DW As < 10 μg/L
[b] DW As 10.1–25 μg/L
[c] DW As >25 μg/L
[d] U-tAs ≤7.4956 μg/L
[e] U-tAs >7.4956 ≤ 11.4911 μg/L
[f] U-tAs >11.4911 μg/L
* ORs were adjusted for age and weeks of pregnancy

food, or by some occupational exposure. Another limitation is that we didn't find high levels of U-tAs, so we can't establish in our study if higher levels of urinary As are or are not associated with PE.

The evaluation of pregnant women with higher levels of As as well as the analysis of other factors (e.g., genetic or nutritional) becomes necessary to confirm and strengthen our findings.

Conclusions

First, it is shown that the majority of our population is exposed to As levels higher than that established by the WHO. In addition, our work suggests for the first time that there is no association between As exposure and PE.

Abbreviations

As, arsenic; DW, drinking water; EPA, environmental protection agency; ORs, odds ratios; PE, preeclampsia; UJED, Universidad Juárez del Estado de Durango; U-tAs, urinary arsenic concentration; WHO, World Health Organization

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Availability of data and materials

The data will not be shared in order to protect the participants' anonymity.

Authors' contributions

EMMH, ATV and OLL carried out the statistical analysis and helped to draft the manuscript. EIAS, SMSP, FVA and MBS carried out the integration of groups and sampling of household tap water. FXCJ and MAD carried out the arsenic determinations. JMSP and ASC conceived of the study, and participated in its design and coordination and drafted the manuscript. All authors have read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of the General Hospital of the Ministry of Health of Durango, Mexico. Informed signed consent was obtained from study participants.

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TNF-α Polymorphisms and Maternal Depression in a Mexican Mestizo Population.

Sandoval-Carrillo A[1], Alvarado-Esquivel C[2], Salas-Martinez C[2,3], Mendez-Hernandez EM[1], Sifuentes-Alvarez A[2,3], Martínez-Martinez AL[2], Castillo-Orona JM[2], Hernandez-Tinoco J[1], Antuna-Salcido EI[1], Sanchez-Anguiano LF[1], Velez Velez LM[1], Salas-Pacheco SM[1], Castellanos-Juarez FX[1], Llave-Leon O[1], Arias-Carrion O[4], Salas-Pacheco JM[1].

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Abstract

BACKGROUND: Depressive disorders are common during pregnancy. There is compelling evidence that the inflammatory response system is important in the pathophysiology of depression. Higher concentrations of proinflammatory cytokines including tumor necrosis factor-alpha (TNF-α) in depressed subjects have been described. Because several polymorphisms in the TNF-α promoter region are known to affect its gene expression, the aim of this study was determine whether TNF-α - 857C/T, -308G/A, and -238G/A polymorphisms confer susceptibility to depression during pregnancy in a Mexican mestizo population.

METHODS: This case-control study involved 153 depressed pregnant women and 177 controls. Polymorphisms were genotyped using real-time PCR. Odds ratios (OR) and 95% confidence intervals adjusted by age, body mass index, number of pregnancies, months of pregnancy and number of abortions were used to estimate risk.

RESULTS: The -857CT genotype was found to increase the risk for depression (OR= 1.73, 95% CI= 1
genotype reduced the risk (OR= 0.33, 95% CI= 0.14-0.72). The - 308G/A polymorphism was not asso
the C857-G308-A238 haplotype was associated with a decreased risk of depression (OR= 0.35, 95%

CONCLUSION: Our results show for the first time an association between TNF-α -857C/T and -238G/
depression in Mexican mestizo population.

KEYWORDS: Depressive disorders; TNF-α; polymorphism; prenatal depression; risk population; tumor necrosis fa

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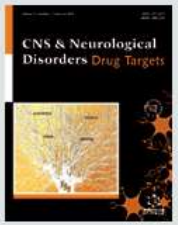

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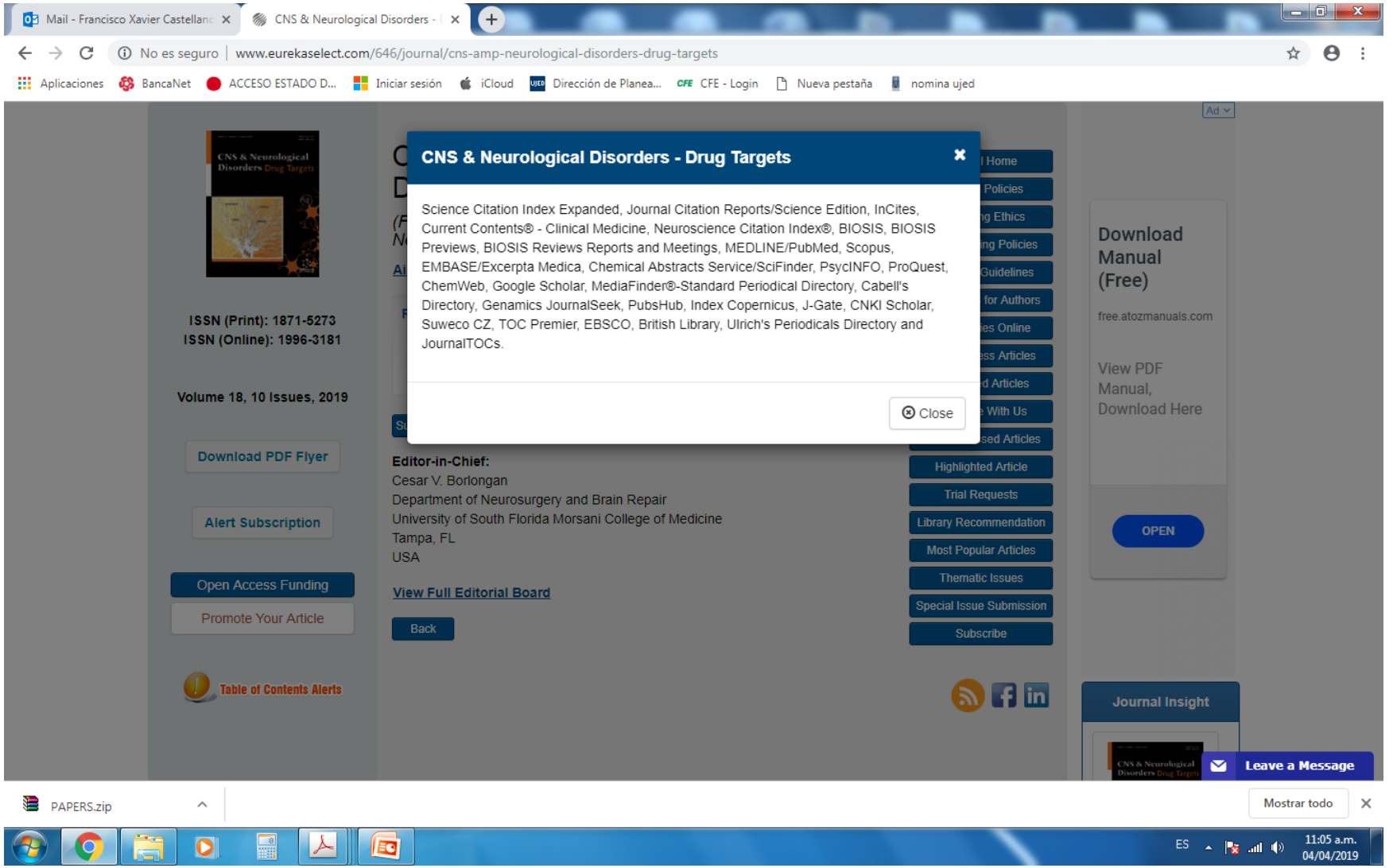
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RESEARCH ARTICLE

TNF-α Polymorphisms and Maternal Depression in a Mexican Mestizo Population

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Abstract: ***Background***: Depressive disorders are common during pregnancy. There is compelling evidence that the inflammatory response system is important in the pathophysiology of depression. Higher concentrations of proinflammatory cytokines including tumor necrosis factor-alpha (TNF-α) in depressed subjects have been described. Because several polymorphisms in the TNF-α promoter region are known to affect its gene expression, the aim of this study was determine whether TNF-α -857C/T, -308G/A, and -238G/A polymorphisms confer susceptibility to depression during pregnancy in a Mexican mestizo population.

Methods: This case-control study involved 153 depressed pregnant women and 177 controls. Polymorphisms were genotyped using real-time PCR. Odds ratios (OR) and 95% confidence intervals adjusted by age, body mass index, number of pregnancies, months of pregnancy and number of abortions were used to estimate risk.

Results: The -857CT genotype was found to increase the risk for depression (OR= 1.73, 95% CI= 1.06-2.82). In contrast, the -238GA genotype reduced the risk (OR= 0.33, 95% CI= 0.14-0.72). The -308G/A polymorphism was not associated with risk for depression. Finally, the C857-G308-A238 haplotype was associated with a decreased risk of depression (OR= 0.35, 95% CI= 0.15-0.82).

Conclusion: Our results show for the first time an association between *TNF-α* -857C/T and -238G/A polymorphisms and prenatal depression in Mexican mestizo population.

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1. INTRODUCTION

Depression during pregnancy can lead to behavioral changes such as the abandonment of prenatal controls, poor adherence to medical indications, consumption of tobacco, drugs, and alcohol with potentially devastating consequences for both mother and baby. Almost 10% of pregnant women are diagnosed with depression. This percentage may be increased depending on cultural and socioeconomic conditions [1]. A number of factors have been associated with depression during pregnancy: lack of family or social support, stressful life events, tobacco use, hormonal changes, anxious temperament, history of mental illness and genetic predisposition, are some examples [2].

Besides this, several reports suggest that depression is an inflammatory disorder mediated by proinflammatory cytokines, such as interleukins 2, -6, and -12 and tumor necrosis-alpha (TNF-α) [3-5].

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TNF-α is a proinflammatory cytokine that strongly contributes to inflammatory and immune responses by inducing a cascade of various inflammatory cytokines; it is produced by monocytes, macrophages and T and B lymphocytes, and also by microglia in the central nervous system [6].

The role of TNF-α in depression has been evaluated in both epidemiological studies and animal models. A meta-analysis showed that TNF-α is commonly elevated in depressed patients [7]; also, the administration of TNF-α to rats induces a spectrum of behavioral changes including social withdrawal, decreased motor activity, reduced food intake and sleep alterations [8].

The TNF-α gene is located on chromosome 6p21.3, within the class III region of MHC [9, 10]. Single nucleotide polymorphisms (SNPs) in the TNF-α gene, including -238G/A (rs361525), -308G/A (rs1800629), and -857C/T (rs1799724) have been described [11]. Because these SNPs in the TNF-α promoter region have been associated with different TNF-α expression profiles and circulating TNF-α levels, they can modulate inflammatory processes, disease development and response to treatment [12]. For that reason, the main goal of our study determined if -238G/A, -308G/A and -857C/T polymorphisms of TNF-α gene confer susceptibility to depression during the prenatal period in a Mexican mestizo population.

2. MATERIALS AND METHOD

2.1. Patient Recruitment

Blood samples were obtained from patients of a previous study conducted at General Hospital of the Secretary of Health in Durango City from March 2015 to February 2016 [13].

2.2. DNA Extraction and Genotyping of Samples

The DNA extraction from blood samples was performed using the QIAamp DNA blood extraction kit (Qiagen, Hilden, Germany). The genotypes were assessed using TaqMan assays (Applied Biosystems) as described previously [14]. The predesigned assays were C-11918223-10, C-7514879-10, and C-2215707-10 (-857C/T, -308G/A, and -238G/A, respectively.

2.3. Statistical Analysis

The clinical characteristics were expressed as mean and were compared using the Student's *t*-test. The allele and genotype frequencies were calculated by direct counting. Deviation from the Hardy-Weinberg equilibrium (HWE) constant was tested using a χ^2 test with 1 degree of freedom. The differences of distributions of the polymorphisms were performed by χ^2 analysis using SPSS software (version 15.0; SPSS Inc., Chicago, IL, USA); $p < 0.05$ was considered statistically significant. The odds ratio was calculated from allelic and genotype frequencies with 95% confidence intervals (95% CI) using the SNPstats software program (Catalan Institute of Oncology).

3. RESULTS

A total of 330 pregnant women were enrolled in the study (153 depressed pregnant women and 177 controls). Of the 153 women diagnosed with depression, 93 had mild depression and 60 severe depression. Only the body mass index showed a difference between groups ($p = 0.036$, Table **1**).

Allelic and genotypic frequencies of -857C/T, -308G/A, and -238G/A TNF-α polymorphisms are shown in Table **2**. All polymorphisms were in HWE. The allelic frequencies of -857C/T and -238G/A showed statistically significant differences between groups ($p= 0.030$ and $p= 0.0019$, respectively). Also, these differences were observed in the genotypic frequencies of -857C/T polymorphism ($p = 0.047$). No differences in allelic or genotypic frequencies between cases and controls were observed in -308G/A polymorphism (Table **2**, $p > 0.05$).

The risk of depression by the presence of these polymorphisms was determined. A logistic regression model adjusted for age, body mass index, number of pregnancies, months of pregnancy and number of abortions was used. The results of Table **3** showed that the -857CT genotype is a risk factor (OR= 1.73, 95% CI= 1.06-2.82) and that the -238GA genotype is a protector factor (OR= 0.33, 95% CI= 0.14-0.72) for depression in pregnant women. Furthermore, a significant trend was observed for both polymorphisms (p for trend = 0.035 and 0.001). Finally, haplotype analysis showed that the C857-G308-A238 haplotype was significantly associated

Table 1. Clinical characteristics of depressed (cases) and healthy pregnant women (controls).

Clinical Features	Cases, *n* = 153	Controls, *n* = 177	*p*-value
Age (years) [a]	23.49 (8.72)	23.58 (8.05)	0.925 [b]
BMI [a]	27.99 (5.71)	26.71 (5.32)	0.036 [b]
Number of pregnancies [a]	2.21 (1.52)	2.12 (1.51)	0.606 [b]
Months of pregnancy [a]	6.54 (1.52)	6.82 (1.42)	0.086 [b]
Number of abortions [a]	0.13(0.38)	0.17 (0.49)	0.439 [b]

[a]Mean (± Standard deviation).

[b]Independent sample *T* test.

Table 2. Allele and genotype frequencies of TNF-α polymorphisms in depressed pregnant women (cases) and healthy pregnant women (controls).

		Cases *n* = 153	Controls *n* = 177	*p*-value
-857C/T	C	0.77	0.84	0.030 [a]
	T	0.23	0.16	
	C/C	0.59	0.72	0.047 [a]
	C/T	0.37	0.25	
	T/T	0.04	0.03	
-308G/A	G	0.94	0.94	0.929 [a]
	A	0.06	0.06	
	G/G	0.89	0.90	0.175 [a]
	G/A	0.11	0.08	
	A/A	0	0.02	
-238G/A	G	0.97	0.92	0.0019 [a]
	A	0.03	0.08	
	G/G	0.95	0.84	ND [a]
	G/A	0.05	0.16	
	A/A	0	0	

[a] Pearson's Chi-squared is significant at $p \leq 0.05$.

ND, not determined.

Table 3. TNF-α polymorphisms association with depression in pregnant women.

		Cases n	Controls n	OR	95% CI	p-value
-857C/T	C/C	90	126	1.00	(referent)	0.078
	C/T	57	45	1.73	(1.06-2.82)	
	T/T	6	6	1.54	0.44-5.40	
	p value for trend					0.035
-308G/A	G/G	136	160	1.00	(referent)	0.14
	G/A	17	14	1.42	0.66-3.05	
	A/A	0	3	ND	ND	
	p value for trend					0.960
-238G/A	G/G	145	148	1.00	(referent)	0.0035
	G/A	8	29	0.33	0.14-0.72	
	A/A	0	0	ND	ND	
	p value for trend					0.001

ND, not determined.

with a decreased risk of depression (OR= 0.35, 95% CI= 0.15-0.82, Table **4**).

4. DISCUSSION

The continued search for risk markers in depressed pregnant women remains of great interest because of the wide range of negative outcomes such as social isolation [15], marital discord [16], child delays in motor or intellectual development [17], restricted fetal growth and elevated stress reactivity in infants [18, 19], among others.

Peripheral inflammation can lead to depression through several immune-mediated pathways that transmit the signal from the periphery to the central nervous system. Patients with major depressive disorder exhibit all of the cardinal features of an inflammatory response, including increased

Table 4. Frequencies and association of TNF-α (−857C/T, −308G/A and -238G/A) haplotypes with depression in pregnant women.

Haplotypes	Cases	Controls	OR	95% CI	*p*-value
C857-G308-G238	0.69	0.70	1.00	(referent)	
T857-G308-G238	0.225	0.161	1.39	(0.91 - 2.12)	0.12
C857-A308-G238	0.054	0.056	1.03	(0.53 - 2.00)	0.93
C857-G308-A238	0.024	0.081	0.35	(0.15 - 0.82)	0.016
C857-A308-A238	0.001	0	ND	ND	ND

ND, not determined.

expression of pro-inflammatory cytokines and their receptors and increased levels of acute-phase reactants, chemokines and soluble adhesion molecules in peripheral blood and cerebrospinal fluid [20]. In this context, SNPs that modulate the expression of TNF-α or any other pro-inflammatory cytokine may have a potential role in susceptibility to depression.

The polymorphisms evaluated in this work have previously been associated with differences in TNF-α gene expression. Furthermore, they also have been associated with some disorders including attempt suicide [21], schizophrenia [22], obsessive-compulsive disorder [23], major depressive disorder [24] and post-stroke depression [25]. However, there are no studies evaluating their possible role in prenatal depression.

Our results showed that the -857CT and -238GA genotypes increase and reduce the risk to develop depression in our population, respectively. These results are consistent with evidence suggesting an increase in proinflammatory cytokines in depressed patients. The TNF-α-857T allele was reported to be associated with high TNF-α production in *in vitro* cell proliferation studies [26]. Also, the T allele was associated with increased transcription of TNF-α in a Chinese population and high serum levels of TNF-α in the Indian and Japanese population [12, 27-29]. On the other hand, the −238A allele was reported to down-regulate TNF-α expression [30, 31]. Moreover, the −238G allele was related to high TNF-α mRNA expression and high serum TNF-α concentrations in rheumatoid arthritis and in knee osteoarthritis patients [32, 33].

Concerning -308G/A SNP, the literature is controversial. Studies with both increased [34-36] and decreased [37-40] TNF-α plasma or mRNA levels associated with the −308A allele have been published. Also, some works suggest an association of this SNP with depression [24, 25] but others not [41, 42]. Our results suggest no association between the -308G/A SNP and prenatal depression.

In relation to the genotypic frequencies, previous studies reported a frequency of 0.746 CC, 0.248 CT and 0.004 TT for -857CT SNP, 0.93 GG and 0.07 GA for -308G/A SNP and 0.89 G/G and 0.11 G/A for -238G/A SNP [32, 43]. We found very similar results for our group of controls.

Interestingly, the C857-G308-A238 haplotype was associated with a decreased risk of depression. As already mentioned, we would expect higher levels of proinflammatory cytokines in patients with depression. Therefore, our results suggest that the presence of the C857 allele (associated with decreased transcription of TNF-α) would have a greater effect than that of the C857 allele (associated with increased transcription of TNF-α) and consequently, lower amounts of TNF-α protein would be produced in those individuals who have the C857-G308-A238 haplotype. However, further experimentation will be needed to prove it.

There are some limitations in our study. First, the effect of SNPs on TNF-α gene expression or circulating TNF-α levels was not evaluated. These data would be of great interest, in particular regarding the controversial -308G/A SNP findings in previous reports. Second, only pregnant women from the northern region of México were included. To establish these polymorphisms as risk markers in the general Mexican population, it will be necessary to carry out additional studies that include women from all regions of the country, based on the demonstrated genetic differences between subpopulations from different regions throughout México [44].

CONCLUSION

Our results show for the first time an association between TNF-α -857C/T and -238G/A polymorphisms and prenatal depression in a Mexican mestizo population.

LIST OF ABBREVIATIONS

HWE = Hardy-Weinberg Equilibrium

SNP = Single Nucleotide Polymorphism

TNF-α = Tumor Necrosis Factor-alpha

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Ethics Committee of the General Hospital of the Secretary of Health in Durango City, Mexico approved this study, and written informed consents were obtained from all participants and from the next of kin of minor participants.

HUMAN AND ANIMAL RIGHTS

The study was conducted in accordance with the Helsinki Declaration.

CONSENT FOR PUBLICATION

Written informed consents were obtained from all participants and from the next of kin of minor participants.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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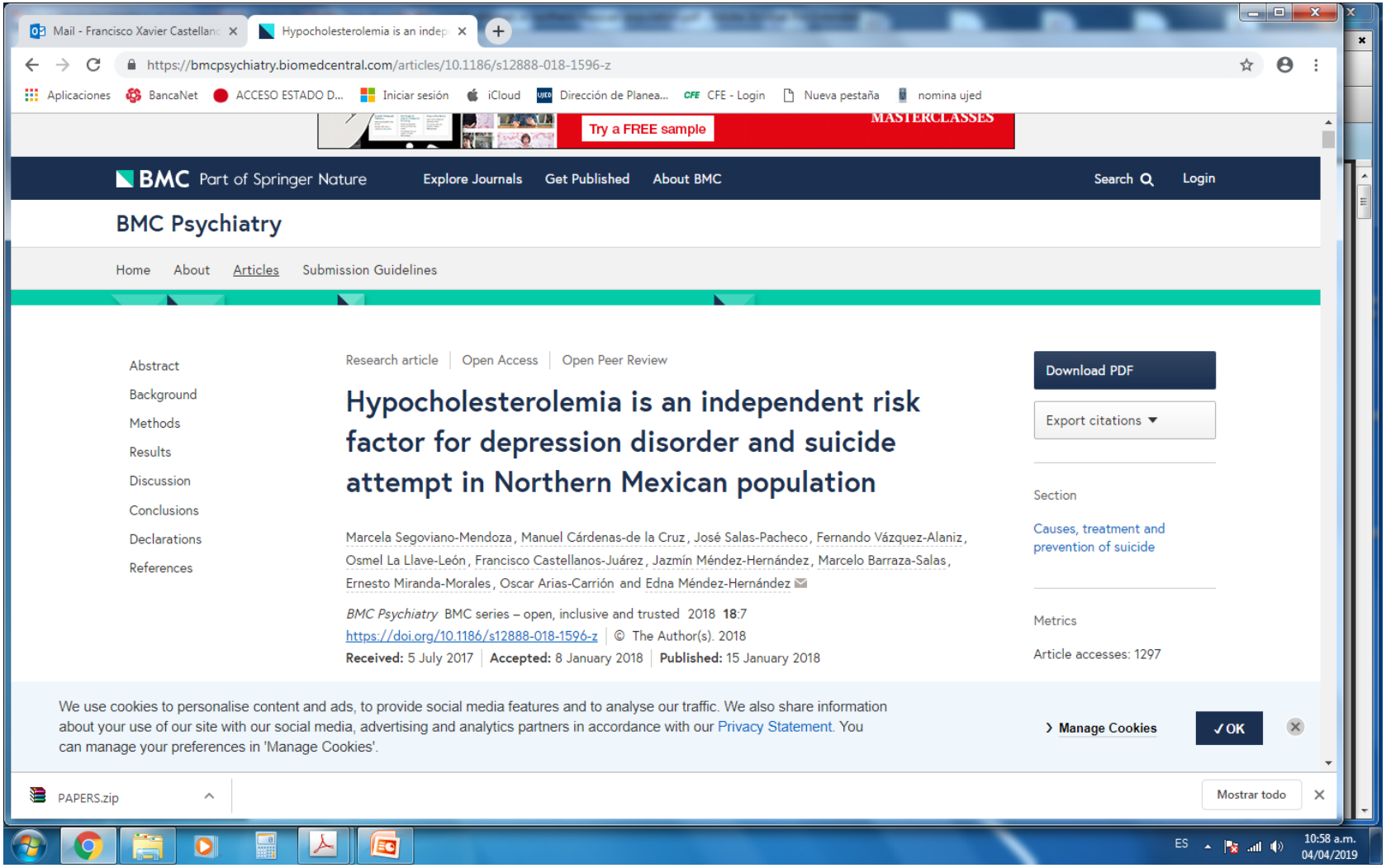
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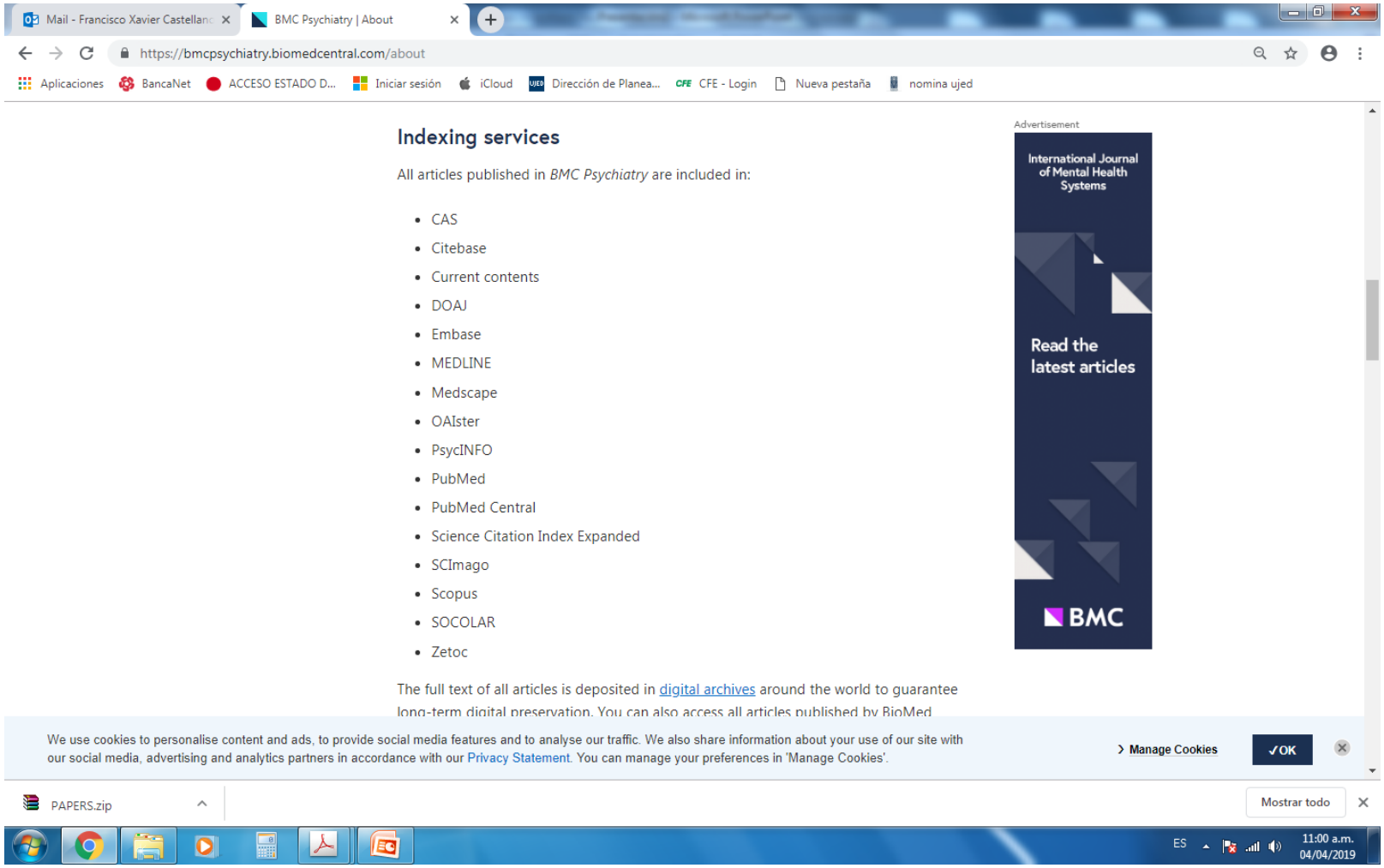
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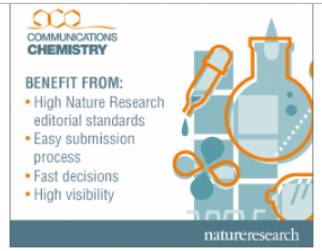

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RESEARCH ARTICLE Open Access

Hypocholesterolemia is an independent risk factor for depression disorder and suicide attempt in Northern Mexican population

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Abstract

Background: Cholesterol has been associated as a risk factor for cardiovascular disease. Recently, however, there is growing evidence about crucial requirement of neuron membrane cholesterol in the organization and function of the 5-HT_{1A} serotonin receptor. For this, low cholesterol level has been reported to be associated with depression and suicidality. However there have been inconsistent reports about this finding and the exact relationship between these factors remains controversial. Therefore, we investigated the link between serum cholesterol and its fractions with depression disorder and suicide attempt in 467 adult subjects in Mexican mestizo population.

Methods: Plasma levels of total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-c) and low density lipoprotein cholesterol (LDL-c) were determined in 261 MDD patients meeting the DSM-5 criteria for major depressive disorder (MDD), 59 of whom had undergone an episode of suicide attempt, and 206 healthy controls.

Results: A significant decrease in total cholesterol, LDL-cholesterol, VLDL-cholesterol and triglyceride serum levels was observed in the groups of MDD patients and suicide attempt compared to those without suicidal behavior ($p < 0.05$). After adjusting for covariates, lower cholesterol levels were significantly associated with MDD (*OR* 4.229 *CI* 95% 2.555 – 7.000, $p<.001$) and suicide attempt (*OR* 5.540 *CI* 95% 2.825 – 10.866, $p<.001$)

Conclusions: These results support the hypothesis that lower levels of cholesterol are associated with mood disorders like MDD and suicidal behavior. More mechanistic studies are needed to further explain this association.

Keywords: Suicide attempt, depression, cholesterol

Background

Suicide is one of the most disastrous outcomes of psychiatric disorders [1]. It is a significant public health problem and is one of the leading causes of death worldwide [2–4]. In Mexico the rate of suicide is a current health problem that is accentuated by the fact that it is a country with an emerging market economy. In recent years, Mexico has presented an increase in its suicide rate. For example, between 2000 and 2014 there was an increase in the suicide rate from 3.5 to 5.2 cases per 100,000 inhabitants (http://bibliodigitalibd.senado.gob.mx/handle/123456789/3181) [5].

Suicidal behavior includes a wide spectrum of behaviors, such as completed suicides, high-lethality suicide attempts, and low-lethality suicide attempts [6, 7]. Although roughly 60% of all suicides occur in the context of depressive disorders [7, 8] it is still challenging for clinicians to predict suicide risk in patients with depression. For this reason, increased attention has been paid to potential biomarkers for suicide in patients with major depressive disorder (MDD) and suicidal behavior [1, 9].

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Many studies have confirmed that biological markers might be linked to suicidality, among which serum lipid levels might play an important role [2, 10–12]. However, there has been considerable controversy about the association between serum lipid levels and suicidality. Some human studies showed that suicide attempters had lower cholesterol levels [2, 11, 13, 14]others reported positive associations between cholesterol and completed suicide[2, 15–17]and some others indicated that there was no evidence for an association between serum cholesterol and suicidality [18, 19].Although the mechanism behind hypocholesterolemia and suicide has not been clearly defined, previous studies have suggested that altered cholesterol at synaptic lipid rafts may cause a reduction in serotonin communication [2].

In the Mexican population, very few studies have examined the association between serum lipid levels and the presence of depression and suicide attempt, and none have reported the frequency of hypocholesterolemia in depressed patients and suicide attempters. Here, we hypothesized that: 1) serum lipid levels are reduced in subjects with depression and suicide attempt; 2) Hypocholesterolemia is a risk factor associated with depression and suicide attempt.

Methods

Study population

After the approval of protocol by Research and Ethics Committee of the General Hospital 450 (No. 12/0306-2015), a case-control study was conducted with 261 MDD adult patients, 59 of these also had a recent episode of suicide attempt and 206 healthy adult volunteer controls of both genders; all subjects provided informed consent. Study subjects were recruited from the Mental Health Hospital "Dr. Miguel Valle Bueno" (Secretary of Health) and psychiatry service of the General Hospital 450 (Secretary of Health) and General Hospital "Dr. Santiago Ramón y Cajal" (ISSSTE), in Durango City, Mexico, from June2015to December 2016.

MDD diagnosis was made by trained psychiatrists according to DSM-5 criteria. We defined suicide attempt as "a non-fatal, self-directed, potentially injurious behavior with an intent to die as a result of the behavior" as defined by the Center for Disease Control and Prevention (https://www.cdc.gov/violenceprevention/suicide/definitions.html) [20]. For our recruitment, we considered only participants that required hospitalization.Subjects in the case group were matched with subjects in the control group based on age, sex and body mass index (BMI).The latter, in order to exclude nutritional state as a confounding factor and due to previous association between BMI and cholesterol levels. [21]. Control subjects were apparently healthy persons without any symptoms or signs of MDD based on a clinical examination at inclusion. Use of lipid lowering drugs, such as statins was considered a confounding factor due to the diverse effects it may have on cellular mediation of inflammation and immunity [22] in conjunction with its known effect on depression [23] and was, therefore, an exclusion criterion. Lastly, we excluded those with chronic diseases (hepatic disorders, diabetes mellitus, hypertension, cardiovascular disease) due to their association with dyslipidemia. [24, 25]

Lipid profile

Blood samples were obtained by venous puncture of all participants after an overnight fasting period. The lipid profiles were determined using the A15 Clinical Chemistry and Turbidimetry Systems (BioSystems) according to the manufacturer's instructions. The level of serum lipids was evaluated based on total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG).Hypocholesterolemia was defined as a total cholesterol concentration of less than 150 mg/dl.

Statistical Analyses

Numerical data were presented as mean±standard deviation (*SD*). Categorical variables were presented as proportions. Differences between the two case groups (MDD and MDD associated with suicide attempt) and control group (healthy subjects) were estimated using ANOVA (Kruskall Wallis test for skewed data) for numerical variables with an additional Bonferroni post-hoc test, and the chi-squared test for categorical variables. Additionally, our analysis was stratified by sex and logistic regression analysis was performed to determine the association between hypocholesterolemia (independent variable) and the presence of depression and suicide attempt (dependent variables). Values of $p<0.05$ were considered statistically significant. The Statistical Package for the Social Sciences (SPSS) for Windows version 21.0 (SPSS Inc., Chicago, IL) was used for data management and statistical analysis. Odds ratio (*OR*) and 95% confidence interval (95%*CI*) were determined, while p value <0.05 defined the statistical significance.

Results

Clinical characteristics and laboratory parameters of the 467 enrolled subjects are shown in Table 1. The comparative analysis of the serum lipid levels between the study groups showed significant differences in the total cholesterol, LDL-cholesterol, VLDL-cholesterol, triglycerides serum levels and, hypocholesterolemia frequency ($p<0.05$). No significant difference in HDL levels were observed between groups.

Post-hoc analysis between the two groups comprised of patients with MDD with suicide attempt ($p<0.001$) and MDD only ($p<0.001$) showed significantly lower total cholesterol levels compared to the control group. Also, patients with MDD who were associated with suicide attempt had

Table 1 Mean cholesterol levels and hypocholesterolemia frequency according to mental impairment categories

	Healthy subjects	MDD	MDD associated w/suicide attempt	*P* value
n	206	202	59	–
Age, years	36.8 ± 6.6	37.3 ± 10.0	35.2 ± 10.5	0.363
Females / Males, n (%)	166 (80.5) /40 (19.5)	169 (83.7) /35 (16.3)	42 (71.2) /17 (28.8)	0.139
Obesity frequency (IMC>30 kg/m^2), n (%)	55 (26.8)	63 (32)	15 (25.4)	0.431
Total cholesterol serum level, mg/dl	172.5 ± 25.3	167.9± 45.1	152.2 ± 39.0	<.001‡,*,†
HDL cholesterol serum level, mg/dl	46.0 ± 11.6	43.8 ± 14.5	46.0± 18.7	0.198
LDL cholesterol serum level, mg/dl	96.7 ± 29.4	84.0 ± 39.5	76.9 ± 32.5	0.014*
VLDL cholesterol serum level, mg/dl	28.9± 14.8	41.2± 23.0	37.6± 21.3	<.001‡,†
Triglyceridesserum level, mg/dl	142.7 ± 87.1	208.3± 119.7	172.8 ± 88.1	<.001‡,*,†
Hypocholesterolemia frequency (<150 mg/dl), n (%)	28 (13.6)	79 (38.2)	29 (49.2)	<.001

MDD Major depression disorder
Values are mean ± standard deviation
*Statistically significant difference between Healthy subjects and MDD associated with suicide attempt
†Statistically significant difference between MDD and MDD associated with suicide attempt
‡Statistically significant difference between Healthy subjects and MDD

significantly lower total cholesterol levels compared with MDD only (p 0.016).

LDL levels were lower in the MDD associated with suicide attempt group with respect to the control group (p 0.013). Subjects with depression presented higher VLDL (p<0.001) and triglyceride levels (p<0.001) compared with healthy controls. Similarly, subjects with depression presented higher VLDL (p 0.043) and triglyceride levels (p 0.039) compared with MDD with suicide attempt. The frequency of hypocholesterolemia was significantly higher in the MDD and MDD with suicide attempt groups compared with the control group (p<0.001).

A subgroup analysis by gender was performed in order to separately assess the magnitude of the association between lipid serum levels in men and women with MDD and suicide attempt (Table 2). Both, men and women showed significantly lower total cholesterol levels in subjects with MDD associated with suicide attempt compared with the control group (p<0.05). However, only in women, did we observe a significant difference between the MDD-only

Table 2 Analysis by gender of clinical characteristics and laboratory parameters

	Male			*p* value	Female			*p* value
	Healthy subjects	MDD	MDD associated w/suicide attempt		Healthy subjects	MDD	MDD associated w/suicide attempt	
n	40	36	17		166	171	42	
Age, years	38.1 ± 6.1	35.8 ± 10.5	37.3 ± 11.9	*0.592*	36.5 ± 6.7	37.5 ± 10.0	34.3 ± 9.9	*0.133*
Obesity frequency (IMC>30 kg/m^2), n (%)	10 (25)	6 (17.1)	3 (17.6)	*0.664*	45 (27.3)	57 (34.8)	12 (28.6)	*0.322*
Total cholesterol serum level, mg/dl	182.5 ± 42.5	164.8 ± 48.6	140.2 ± 32.1	*0.002*‡,*	170.1 ± 18.4	168.5 ± 44.4	157.1 ± 40.8	*0.017**
HDL cholesterol serum level, mg/dl	46.4 ± 14.5	41.7 ± 15.8	44.1 ± 12.4	*0.566*	45.8 ± 10.2	44.2 ± 14.2	46.8 ± 20.9	*0.301*
LDL cholesterol serum level, mg/dl	100.8 ± 35.9	71.2 ± 37.2	71.7 ± 24.5	*0.011*‡	94.8 ± 26.2	86.7 ± 39.5	78.9 ± 35.3	*0.165*
VLDL cholesterol serum level, mg/dl	30.9 ± 17.0	55.4 ± 33.4	29.8 ± 10.1	*0.002*‡,†	28.1 ± 13.9	38.1 ± 18.9	34.9 ± 18.7	*0.004*‡
Triglycerides serum level, mg/dl	137.7 ± 66.9	277.1 ± 167.2	157.6 ± 60.2	<.001‡,†	143.9 ± 91.4	193.7 ± 101.8	179.0 ± 97.2	<.001‡,*
Hypocholesterolemia frequency (<150 mg/dl), n (%)	8 (20)	17 (47.2)	9 (52.9)	*0.015*	20 (12)	62 (36.3)	20 (47.6)	<.001

Values are mean ± standard deviation
*Statistically significant difference between Healthy subjects and MDD associated with suicide attempt
†Statistically significant difference between MDD and MDD associated with suicide attempt
‡Statistically significant difference between Healthy subjects and MDD

group versus the control group. No such relationship was seen in males. The comparative analysis of the hypocholesterolemia frequency between the study groups showed significant differences in both genders ($p<0.05$).

A bivariate logistic regression using data matched on age, sex, and BMI showed a statistically significant association between hypocholesterolemia and MDD (*OR* 4.229 *CI* 95% 2.555 – 7.000, $p< 0.001$). In the same way, a statistically significant association between hypocholesterolemia and suicide attempt was observed (*OR* 5.540 *CI* 95% 2.825 – 10.866, $p<0.001$). Additionally, triglycerides were analyzed and we found the following Odds Ratios and 95% Confidence Intervals: for hypertriglyceridemia in MDD [3.528 (2.326-5.352); $p<0.001$]; for hypertriglyceridemia in MDD with suicide attempt [2.626 (1.411-4.885); $p=0.002$]. Upon further analysis, no significant association in the other variables.

Discussion

Here, we show that lower serum cholesterol levels are linked with MDD and suicide attempt. Age and sex-adjusted analyses showed a clear association between serum cholesterol levels and the risk of depression and suicide attempt.

Previously, some studies have also shown an association between low cholesterol and increased risk of death due to injuries or suicide [2, 9, 26–29], but not in other reports [1, 30–33], even elevated cholesterol levels have been associated with suicide mortality in other studies [15, 33].

In Mexican subjects, there is only one research paper that has examined the possible link with hypocholesterolemia and suicide attempt in subjects with depression [34]. This study found no difference in lipid profiles between patients who had attempted suicide and those who had not. However, these authors studied only 33 patients with a major depressive episode (moderate to severe) comparing 18 subjects who had attempted suicide versus subjects who had never attempted suicide.

Although there is evidence of a link between low serum cholesterol levels and suicide in patients with depression [35, 36], the mechanism that may link serum lipids with suicidality is still unclear. It has been established that nearly all brain cholesterol is produced *in situ* through de novo synthesis and that adequate prevention of its uptake from the bloodstream is provided by selectivity of the blood-brain barrier [37–39]. Nonetheless, it is viable that decreased peripheral cholesterol in those individuals with psychiatric disorders occurs concurrently with cholesterol modifications that take place in distinct synaptic lipid rafts in neurons (by a common regulatory mechanism). This could produce the minimized activity of serotonergic communication and, consequently, give rise to instinctive responses and violent suicidal behavior [2, 40].

Cholesterol is the paramount constituent of cellular membranes in higher eukaryotes and is essential in membrane function and organization as well as dynamics and sorting. It is commonly found dispersed in a non-random form in specific areas (domains) in both biological and model membranes [41–43]. These areas, often denominated as 'lipid rafts' [43, 44], are thought to be fundamental in the preservation of the structure and function of the membrane. However, describing the spatiotemporal resolution of these domains has turned out to be a difficult task [43, 45]. It has been suggested that these formations be membrane domains in which signaling from a neurotransmitter may arise via a group of receptors, such as serotonin$_{1A}$ (5-HT$_{1A}$) receptor [46].

Previous studies demonstrated the imperative necessity of membrane cholesterol in the function and organization of the 5-HT$_{1A}$ receptor [45, 47–52]. Results from additional studies showed that the fluidity of lipids considerably regulates the binding of serotonin (5-HT) in murine brain membranes. It is therefore expected that decreased levels of cholesterol would increase the fluidity of the cellular membrane. While, at the same time, minimal exposure of the 5-HT receptors would be found in the synaptic cleft [2, 53].

Reportedly, disturbance of rafts by cholesterol deficiency notably lowers agonist binding and coupling of G protein to 5-hydroxytryptamine 1A (5-HT1A) serotonin receptors in bovine hippocampal membranes [46, 47]. Serotonin$_{1A}$ receptors typify one of the most formidable, evolutionarily primitive, yet largely conserved families of seven transmembrane *G* protein-coupled receptors (GPCRs) that span the membrane [45, 54]. Also, serotonergic signaling constitutes an important part in the formation and regulation of a multitude of functions such as behavioral, cognitive, and developmental [45]. Moreover, studies have demonstrated that there is an association between decreased 5-HT activity and suicide [2, 55].

It is noteworthy to mention that recent studies described crystal structures of GPCRs, including serotonin$_{1A}$ receptor, that demonstrated structural proof of cholesterol binding sites [45, 56, 57].Currently, two conceivable pathways have been proposed by which membrane cholesterol could affect the structure and function of GPCRs: (i) by way of a direct/specific interaction with GPCRs, or (ii) via an indirect pathway by modifying the physical properties of the membrane in which the receptor is inserted, or as a result of an integration of both [45, 58].

About cholesterol levels and their relation to gender, our study showed that the decrease in total cholesterol levels occurred in both men and women. Other authors have reported a relationship between reduced cholesterol and suicidal tendencies only in males [13, 59–62]. However, it is worth noting that additional studies on the association between gender and serum cholesterol have been unconvincing.

A lack of consistency between different published reports coupled with the fact that, to date, it has not been possible to identify a cholesterol threshold level capable of precipitating a psychiatric disorder, suggests the presence of a non-linear relationship.

The existence of reports in which depression has been associated with increased cholesterol levels would support this hypothesis. A possible explanation for this, proposed the involvement of monoamine oxidase (MAO). The aforementioned model studies associated hypercholesterolemia with depression in hypercholesterolemic mice via monoaminergic metabolism. Specifically, they reported increased monoamine oxidase (MAO) A and B activity in the hippocampus of mice [63, 64]. Thus providing one possible reason why elevated levels of cholesterol are able to produce depression much like decreased levels are able to, but via independent mechanisms.

Besides total cholesterol, other studies that investigated the link between triglycerides, HDL cholesterol and LDL cholesterol, observed contrasting results between different populations. Our results showed higher levels of triglycerides in subjects with MDD and MDD associated with suicide attempt. These findings do not coincide with data previously reported in 2015 that observed decreased levels of triglycerides in subjects with suicidal attempts [65]. However, other authors report conflicting findings, even suggesting a positive association between triglyceride levels and the risk of suicidal behavior [15]. Considering LDL cholesterol levels, our results coincide with the conclusions of a meta-analysis published in 2016, which included a total of 36 different studies and found overall association between lower LDL levels and depression [66]. With respect to VLDL levels, which were significantly higher in MDD versus healthy controls, it is worth noting that few studies report VLDL levels. Taking this into consideration, our result is different from the result reported in a previous study [67] that showed significantly lower levels while our results demonstrate higher levels. With respect to HDL cholesterol levels, our results did not demonstrate significant differences when comparing subjects with MDD, subjects with MDD associated with suicide attempt and the control group. This fact contrasts with previous studies in which significant differences in HDL cholesterol between subjects with attempted suicide and healthy controls were shown [59, 68].

Lastly, we found a significant association between elevated triglyceride levels versus MDD and MDD with suicide attempt. Our finding coincides with a previous study which found a correlation between depressive symptoms and triglyceride levels [69] and suggestions by others which postulate that high triglyceride levels are associated with Type A personality traits, such as hostility, anger and domineering attitudes [70].

Several limitations of this study deserve to be mentioned. First, because our study is based on a case-control design, temporality could be not inferred with certainty. Whether hypocholesterolemia is a risk factor for developing depression and suicide attempt or merely an associated epiphenomenon can not be assured with certainty; second, we did not measure 24 S-hydroxycholesterol levels, which is a peripheral biomarker of brain cholesterol metabolism. However, it is expected that reduction of total cholesterol would reduce 24 S-hydroxycholesterol [71]. Besides, we did not evaluate dietary intake; however, because subjects in the groups of the study were enrolled from the same socio-cultural and economic background, it is expected that customary diets were similarly distributed. Finally, an additional limitation of our study is that we did not analyze the cardiovascular risk associated with serum cholesterol concentrations. In the future, it will be important to profoundly analyze the contradictory results reported with regard to cholesterol's role in depression. [63, 64]. This would help to verify if cholesterol is, in fact, a viable biomarker for neuropsychiatric disorders. It is evident that these results may be extrapolated only to a population that is similar to our own with similar exclusion criteria. Strengths of our study include the inclusion of incident cases of suicide attempt, which is a recognized tool to minimize analysis bias in the cross-sectional studies; also, the exclusion of individuals with lipid-lowering drugs allows us to control the potential source of bias.

Conclusions

In conclusion, our results show that hypocholesterolemia is independently associated with depression and suicide attempt in adults of the Mexican population .This finding, if consistent in more studies in our population, could influence public health policies focused in the prevention of mental health disorders. Measuring cholesterol levels could be a minimally invasive, inexpensive and simple way to predict suicide risk in our population. The use of cholesterol levels as a biomarker would permit clinicians to efficiently obtain a laboratory result that, once combined with clinical evaluations and symptoms, could permit a more timely diagnosis. Additionally, it would be necessary to calculate the sensibility and specificity of this test in our population.

Abbreviations

CHOL: Cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; MDD: Major depressive disorder; VLDL: Very low-density lipoprotein

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
EMH and FCJ conceived and designed the experiments; MCC, EMM and MSM performed the experiments; OLL and JSP analyzed the data; OAC and MBS contributed analysis tools; FVA, JMH and EMM wrote the paper. All authors read and approved the final manuscript

Ethics approval and consent to participate
The protocol was approved by the Ethics Committee for Research of the General Hospital 450, Secretary of Health of Durango (No. 12/0306-2015). Informed consent was obtained from participants was in written form.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests

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