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LUIS GUILLERMO IBARRA IBARRA

Investigación en Discapacidad

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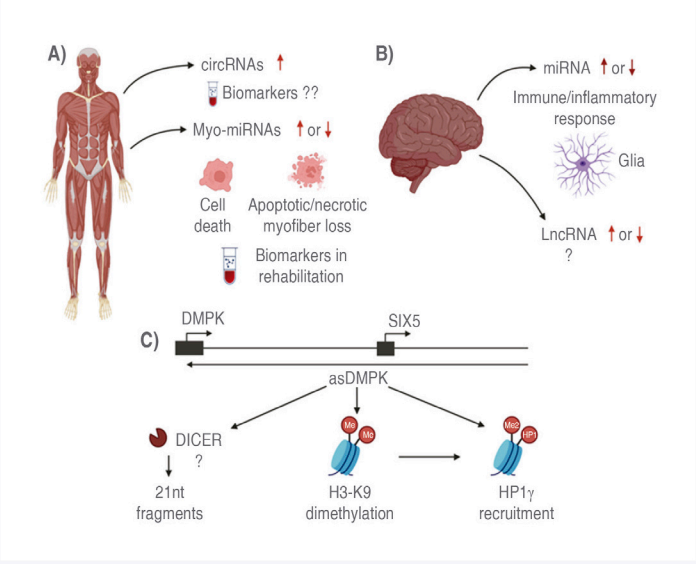

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Investigación en Discapacidad

COMITÉ EDITORIAL

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LUIS GUILLERMO IBARRA IBARRA

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Imagen de la portada: *siRNA is derived from long double-stranded RNA molecules, which can be cut by the DICER enzyme into RNA fragments of 19-24 nt, with the resulting RNA fragments exercising their functions when loaded onto Argonaute (AGO) proteins.*

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Y el periplo continúa: hacia una nueva época de la Revista *Investigación en Discapacidad*

And the journey continues: towards a new era for the Investigación en Discapacidad

Carlos Pineda,* Hugo Sandoval‡

Hace 16 años se afincó en el Instituto Nacional de Rehabilitación «Luis Guillermo Ibarra Ibarra» (INR LGII) el proyecto de divulgar los avances en el estudio, diagnóstico, prevención, tratamiento y rehabilitación integral de las discapacidades.[1] En mayo de 2012 ese noble proyecto culminó con la publicación del primer número de la Revista *Investigación en Discapacidad*, órgano de difusión científica oficial de nuestra Institución.

A partir de ese momento y durante siete años, hasta el 2018, nuestra revista evaluó todos sus manuscritos sometidos mediante el sistema de revisión por pares, mantuvo la regularidad de su publicación y alcanzó visibilidad nacional e internacional. De su buen comienzo y exitosos años iniciales dan testimonio más de 400 mil visitas acumuladas, provenientes de más de 110 países, registradas en el sitio *web* de Medigraphic (https://www.medigraphic.com/).

Investigación en Discapacidad destacó, asimismo, por su expedita indexación en diversos repositorios regionales como Latindex, Google Académico, BIBLAT y PERIÓDICA.[2] Nuestra revista también ha sido indexada en algunas bibliotecas prestigiadas, entre las que resaltan la del Instituto de Biotecnología de la UNAM; The *Library of the Carinthia University of Applied Sciences,* en Austria, y la *Wissenschaftszentrum Berlin fur Sozialforschung,* en Alemania.

Gracias a la entusiasta participación entonces alcanzada, a partir del año 2014 *Investigación en Discapacidad* modificó su periodicidad, de cuatrimestral a trimestral; agregó un suplemento dedicado a la divulgación de los resúmenes del Congreso Internacional de Investigación en Discapacidad (con un tiraje de 2,500 ejemplares); obtuvo su *International Standard Serial Number* (ISSN) y registró, ante el Instituto Nacional del Derecho de Autor, su Reserva de Derechos al Uso Exclusivo.

Durante esta fructífera época, la revista promovió reuniones con algunas revistas científicas del CONACYT, contó con la visita del Editor en jefe de una revista de muy alto impacto; facilitó el encuentro de algunas editoriales en las instalaciones del INR LGII y elaboró manuales en apoyo de su operación.

HACIA EL RESCATE DE LA REVISTA

Pese a los buenos resultados descritos, *Investigación en Discapacidad* fue prácticamente cancelada a partir del 2019. La revista se ha quedado sin publicaciones nuevas desde ese año, y dejó de publicarse en formato impreso a partir del 2017.

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A pesar de lo anterior, la revista ha seguido dando alentadores signos de actividad, gracias a la consulta de su acervo acumulado, que cuenta con miles de visitas durante 2019, 2020 y 2021, tal y como se muestra en la *Tabla 1*. Además de México, los países que más la visitan incluyen a los EE. UU., Colombia, Ecuador, Argentina, Bolivia, Chile, Perú, España y Nicaragua.

La nueva dirección del INR LGII se ha propuesto apoyar decididamente el resurgimiento de *Investigación en Discapacidad*, con el objetivo de retomar la publicación continua de sus artículos hasta lograr, progresivamente, avanzar en la Clasificación Cualitativa de Revistas Periódicas y Libros, y pasar del grupo I al II.

El rescate institucional de la revista es un trabajo colectivo en marcha, que busca colocarla de nuevo como el órgano de difusión científica oficial del INR LGII. Nuestra visión es que *Investigación en Discapacidad* se convierta en una publicación indizada en los principales repositorios institucionales nacionales (incluyendo el índice de Revistas Mexicanas de Investigación Científica y Tecnológica del CONACYT) e internacionales, como Medline/PubMed.

ACCIONES ESPECÍFICAS POR DESARROLLAR

Para alcanzar su objetivo y la nueva visión propuesta, se realizarán las siguientes actividades:

1. Rescatar a la revista del abandono institucional en el que actualmente se encuentra, mediante una reestructuración a fondo de su Comité Editorial y equipo de trabajo.
2. Incorporar a investigadores nacionales miembros del SNI, y a líderes internacionales de alto prestigio y reputación científica.
3. Regularizar su publicación periódica e incrementar, paulatinamente, el número de trabajos originales en cada número.
4. Fomentar una mayor participación de investigadores provenientes de otras instituciones de salud y de universidades de prestigio.
5. Ampliar su distribución y difusión en congresos nacionales e internacionales.
6. Consolidar su reputación como medio de comunicación científica y referente de investigación en materia de rehabilitación de las discapacidades.
7. Publicar una mayor cantidad de artículos en idioma inglés.
8. Desarrollar un sistema electrónico para la gestión de los manuscritos sometidos a revisión.
9. Incluir en su Comité Editorial a un editor de redes sociales.

HACIA UN NUEVO HORIZONTE

Investigación en Discapacidad volverá a ser un foro incluyente, plural, abierto y participativo, disponible para toda aquella investigadora o investigador, nacional o internacional, que desee participar en la investigación biomédica y tecnológica en materia de rehabilitación de las discapacidades.[3]

Queremos impulsar nuevos contenidos enfocados en la prevención de las discapacidades, la investigación tecnológica, la ingeniería biomédica, los estudios sociomédicos, la detección de condiciones discapacitantes en etapas preclínicas, el estudio de biomarcadores y de factores de riesgo, entre otros. Con el soporte editorial de Medigraphic, la revista proporcionará acceso abierto y gratuito a todas sus publicaciones.[4]

Tabla 1: Investigación en Discapacidad. Número de visitas y artículos consultados en versión completa (PDF) 2013-2021.

Año	Países	Total de visitas	Promedio diario	Total de consultas	Promedio diario
2013	44	15,628	43	25,308	69
2014	62	63,861	175	90,706	266
2015	83	171,988	471	215,435	590
2016	58	214,296	586	207,061	567
2017	61	265,613	724	211,618	580
2018	54	303,011	830	315,450	864
2019	**46**	**366,799**	**1,005**	**230,388**	**631**
2020	**96**	**399,538**	**1,098**	**234,830**	**643**
2021*	**113**	**426,723**	**1,286**	**219,514**	**661**

* Información registrada al mes de noviembre del año 2021. Fuente: Medigraphic.

Con la publicación de este primer número enero-abril de 2022, resurge de manera cuatrimestral el órgano oficial de difusión científica oficial del INR LGII, en medio de un periodo de transición gubernamental de gran trascendencia para nuestro país. Le damos la más cordial bienvenida a esta ave fénix.

Nos complace presentar ante todos ustedes, amables lectores, la nueva época de la Revista *Investigación en Discapacidad*, con la seguridad de que la disfrutarán tanto como nosotros.

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Conflicto de intereses: Se declara que no existe conflicto de intereses por parte de los autores.

ORIGINAL ARTICLE

INVESTIGACIÓN en DISCAPACIDAD
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Volumetric bone mineral density measured by quantitative computed tomography: reference values for the mexican pediatric population

Densidad mineral ósea volumétrica medida por tomografía de cálculo cuantitativo: valores de referencia para la población pediátrica mexicana

Elisa Martínez Coria,* Cinthya Lourdes Toledo Peral,‡ Norma Pilar Castellanos Abrego,§ Martín Luna Méndez,* Josefina Gutiérrez Martínez‡

Keywords:
Peak bone mass, quantitative computed tomography, volumetric bone mineral density, Pediatric vBMD, DXA.

Palabras clave:
Masa ósea máxima, tomografía computarizada cuantitativa, densidad mineral ósea volumétrica, Pediátrica vBMD, DXA.

Abstract

Introduction: Nowadays, childhood diseases as Duchenne muscular dystrophy (DMD) have raised interest in pediatric bone densitometry, since long-term steroid therapy is a serious risk factor for osteoporosis. Even though dual energy X-ray absorptiometry (DXA) is the most used technique to measure bone mineral density (BMD), quantitative computed tomography (QCT) is the most exact way to assess bone health. But the reference values are available for adult populations, and only for a few pediatric populations. **Objective:** The aim of this study is to measure volumetric BMD (vBMD) values using QCT to determine the reference values of healthy Mexican pediatric population. **Material and methods:** This is an observational transversal study to measure vBMD from three images of healthy trabecular lumbar spine using QCT. **Results:** vBMD data has a sigmoid behavior in both genders, with a delayed start for males; the difference in values during puberty have a moderate significant correlation (-0.546, p = 0.004). vBMD values for both genders are 40% lower than the reported for Caucasian pediatric population. **Conclusion:** These results encourage us to continue this study to increase the confidence of the obtained vBMD reference values for Mexican pediatric population. This will have a high impact in diagnosis accuracy, particularly in chronically ill children, with DMD and other musculoskeletal diseases.

Resumen

Introducción: *En la actualidad, enfermedades infantiles como la distrofia muscular de Duchenne (DMD) han despertado el interés en la densitometría ósea pediátrica, ya que la terapia con esteroides a largo plazo es un factor de riesgo grave para la osteoporosis. Aunque la absorciometría de rayos X de energía dual (DXA) es la técnica más utilizada para medir la densidad mineral ósea (DMO), la tomografía computarizada cuantitativa (QCT) es la forma más exacta de evaluar la salud ósea. Pero los valores de referencia están disponibles para poblaciones adultas y solo para unas pocas poblaciones pediátricas.* ***Objetivo:*** *El objetivo de este estudio es medir los valores de DMO volumétrica (vDMO) utilizando QCT para determinar los valores de referencia de la población pediátrica mexicana sana.* ***Material y métodos:*** *Este es un estudio transversal observacional para medir vDMO a partir de tres imágenes de*

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columna lumbar trabecular sana utilizando QCT. ***Resultados:*** *Los datos de vDMO tienen un comportamiento sigmoide en ambos sexos, con un inicio tardío para los hombres; la diferencia de valores durante la pubertad tiene una correlación significativa moderada (-0.546, p = 0.004). Los valores de vDMO para ambos sexos son un 40% más bajos que los reportados para la población pediátrica caucásica.* ***Conclusión:*** *Estos resultados nos animan a continuar con este estudio para aumentar la confianza de los valores de referencia de vDMO obtenidos para la población pediátrica mexicana. Esto tendrá un gran impacto en la precisión del diagnóstico, especialmente en niños con enfermedades crónicas, DMD y otras enfermedades musculoesqueléticas.*

INTRODUCTION

Strong bones are a very important part of children and adults health. A bone mineral density (BMD) test is the best way to assess bone health. Bone density refers to the ratio of weight to volume or area of the bones. It compares the bone density, or mass, to that of a healthy young subject.[1] The peak bone mass (PBM) is the maximum amount of body tissue present at the end of skeletal maturation and is the reservoir that a person has for the rest of their life. PBM is typically reached in the early 20s for both males and females. The bone mass of a given part of the skeleton is directly dependent upon both its volume or area and the density of the mineralized tissue contained within the periosteum. During puberty, the bone mass difference due to gender is expressed. The difference responds to a more prolonged bone maturation period in males than in females, with a larger increase in bone size and cortical thickness. But by the end of pubertal maturation there is no significant gender difference in the volumetric trabecular density.[2] PBM is reached at the end of the twenties, which makes childhood and teenage years the best time for bone growth, although this is a controversial period.[3]

The adult human skeleton is composed of 80% cortical bone and 20% trabecular bone. Different bones and skeletal sites within bones have different ratios of cortical to trabecular bone. Bone is composed of 50 to 70% mineral, 20 to 40% organic matrix, 5 to 10% water, and less than 3% of lipids. The mineral content of bone is mostly calcium hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$], with small amounts of carbonate, magnesium, and acid phosphate.[1] Due to its high porosity and large surface area, trabecular bone is a better indicator of bone remodeling that cortical bone.[4] 75% of BMD is regulated by genetic, environmental factors,[5] and physical activity during childhood;[6] the middle prenatal and early postnatal environments determine the remaining 25%.[7] So, it is essential to know the factors that can adversely affect bone growth and mineralization.[8]

Low bone mass (LBM) has several causes, which may include genetic history, not developing good bone mass during childhood and adolescence, having certain physical conditions, or being treated with drug therapies. Osteoporosis is a complex and multifactorial condition characterized by a reduction in bone mass and deterioration of microarchitecture caused by the depletion of calcium and bone protein, which predisposes a person to fractures. It is more common in older adults, e.g., postmenopausal women, and in patients undergoing long-term steroid therapies, like children with Duchenne muscular dystrophy (DMD).[9] LBM that is not low enough to be osteoporosis is called osteopenia which results when osteoid synthesis is not sufficient to replace normal osteoid lysis. Not everyone who has LBM gets osteoporosis, but they present a higher risk.

The most common method for measuring bone mass is called dual energy X-ray absorptiometry (DXA) which was introduced in the 1980s.[10] The presence or absence of osteoporosis is based on two standards known as age-matched (Z-score) or young normal (T-score) that compares a measured BMD value to the PBM of a healthy 25-year-old person of the same sex. The World Health Organization (WHO)[11] defines osteoporosis as a bone density value at least 2.5 standard deviations (SD) below PBM. A standard deviation from mean PBM is known as one T-score. Thus, osteoporosis is defined as one SD, or T-score, of lumbar spine or 2.5 standard deviations below the norm for a measure at the hip. Likewise, from 0 to -1 SD the BMD value is considered normal, and from -1 to -2.5 SD is considered osteopenia. There is evidence that race has an influence on BMD, as is shown in a Brazilian women study, where lumbar spine and femoral neck mean BMD values are lower than

American and European women,[12] unlike for Argentine women who had similar values.[13] Reference Z-score based on American population has been shown to be not-acceptable for Britannic population.[14] Ethnicity has an influence on BMD, e.g., Hispanics also have a bone density about 2-4% higher.[15] In Mexico, BMD reference values for healthy Mexican population (7-80 years old) taken from a manufacturer measurement has an underestimated number of abnormal BMD values.[16]

It is important to note that T-scores com-pare BMD values of adults with normal or average height at PBM (950 mg/cm^2 for Caucasian woman/men at 25 years old). So, T-score classification is not appropriate for pediatric population. For children, BMD is given by Z-score which compares to the normal range for children of the same age and sex. When it is below 2 SD, children are considered to have LBM for chronological age, according to the International Society for Clinical Densitometry (ISCD).[1,17]

In recent years, bone densitometry in children has gained interest as a result of the wide variety of chronic diseases that influence bone growth and present high risk of fractures as: osteogénesis imperfecta, DMD, inflammatory bowel disease, and cerebral palsy. Even though DXA is widely used to measure BMD, there are few guides indicating that it should be studied in populations different to postmenopausal women. WHO classification cannot be used in pediatric population; up to 2003, all densitometry techniques were designed, developed, and validated for adult populations.[18] Besides, the ISCD establishes that the osteoporosis diagnosis in children should not be applied on a single densitometry criterion.[19]

DXA presents some limitations for diagnosis of osteoporosis in pediatric population: a) normal pediatric BMD reference values have not been validated,[20] b) some ethnical groups and/or pubertal stages have no reference values, c) BMD measurement is performed in two dimensions (g/cm^2), disregarding bone thickness, so it underestimates systematically the density of shorter patients and those with smaller bones, d) DXA measurement does not distinguish between trabecular and cortical bone structure and each brand uses different reference values for BMD, f) patients with chronic diseases represent a challenge for interpretations.[20]

A volumetric BMD (vBMD) study in pediatric populations requires further analysis in the regions where changes are observed, e.g., microarchitecture of trabecular bone in the dorsal spine. Quantitative computed tomography (QCT) is a true volumetric bone densitometry technique which yields the vBMD expressed as grams of $Ca_{10}(PO_4)_6(OH)_2$ per cm^3. Most studies using QCT assess vBMD at L1-L4. An advantage of QCT is its capability of separating dense cortical bone from trabecular bone. The latter has much higher metabolic activity and is affected by age, diseases and therapy-related changes earlier and more often than cortical bone. So, QCT of the spine has the advantage over DXA to detect changes earlier.[21]

QCT should be considered the gold standard in vBMD,[22] even requiring a higher dose of radiation than DXA. Even though, this is the reason why its application to pediatrics has been difficult. There are reports of lumbar QCT where the trabecular vBMD is constant during childhood up to the start of puberty, but it has a large increment during puberty.

In different studies,[23,24] BMD using DXA for healthy children classified by gender, age and ethnicity were reported. In Mexico, a study of 6,479 healthy mestizo Mexican population performed with DXA, reported that PBM and T-scores differ significantly from the reference values of US commercial manufacturer's Hispanic database that includes children.[16,25]

These studies evidenced the discrepancies found in pediatric population, between DXA and QCT. DXA shows a growing BMD during the first years of childhood and a high increment during puberty that stabilizes around 17 years old. On the contrary, the findings using the lumbar QCT show that bone density is constant during a large portion of childhood and then at puberty it has a remarkable jump.[26,27] Using QCT, the PBM seems to be reached with sexual maturity, and with DXA it is observed a rise after the longitudinal growth ceases.[3]

It is crucial to have a diagnosis tool reliable and effective to determine bone health, osteopenia, or osteoporosis in pediatric patients. Plus, there is no reference value for vBMD classification by age and gender for Mexican pediatric population. Particularly, for the Instituto Nacional de Rehabilitación «Luis Guillermo Ibarra Ibarra» (INRLGII), this is an essential diagnosis tool because the Institute provides medical care to children with chronic diseases, such as DMD, to whom is not possible to establish accurately a fracture risk index, which is increased in the early stages of the disease and in cases when they present excess abdominal fat.

So, the aim of this paper is to determine the reference values of vBMD data for Mexican pediatric population using QCT of trabecular lumbar spine, and to compare them to other pediatric populations measures of QCT or DXA reported in literature.

MATERIAL Y METHODS

An observational, transversal, descriptive study, with a measurement of vBMD in pediatric population identified as healthy, was carried out. vBMD was measured using lumbar QCT in pediatric patients, ranging from two to 25 years old randomly, and stratified into four groups: 2-7, 8-13, 14-19, and 20-25 years old; and at the same time, classified by gender: male and female, and from whom was recorded height, weight, dietary habits, and lifestyle activity (e.g., sports) and if presented any diseases. The protocol was approved by the INRLGII Research and Ethical Committees (Protocol No. 21/10), and a letter for informed consent was signed by the parents.

In a single sample, three images of trabecular bone were taken in the lumbar area (L2, L3, and L4) to obtain a vBMD measure, calculated as an average of the three vertebrae individual values. A single physician radiologist analyzed and validated the measurement that the QCT scan performed automatically in the center of each vertebral body, to avoid observer variation. vBMD was measured by automatically selecting the Region of Interest (ROI), which is compared against a solid mineral phantom reference (0, 125, and 250 mg/cm^3 solid hydroxyapatite equivalent) placed in a pad under the subject during CT image acquisition, also used for simultaneous calibration (CT-T bone densitometry package; GE© Medical Systems).

The radiation dose was of 0.27 mSv, way under the maximum value allowed by the official Mexican norm NOM-229-SSA1-2002[28] of 5 mSv as the annual limit, making its use in healthy subjects reasonable.[29,30] The parameters of voltage and current were controlled by a 64-slices GE© LightSpeed VCT scan (120 kVp, 120 mA). Subjects had gonad protection.

Elimination criteria included a vBMD lower than 120 mg/cm^3 or noisy images due to patient movements. Body mass index (BMI) was determined, and percentile values were allocated according to age and weight to determine if they were low weight or obese, as exclusion criteria. Children that presented alterations of height respect to age, patients with genetic or congenital pathologies, patients with alterations of bone complexion, or occupational lesions of space that implicate the area of study, patients with metabolic pathologies or neoplasia, patients under treatment with steroids and/or hormonal therapy and subjects that had suffer from fractures are excluded of this study.

The vBMD values were recorded and the mean values were compared among the groups and genders. Classification by group was considered when the values differ from the previous age group by at least 5 mg/cm^3, as reported by Gilsanz, et al.[26] A vBMD value is considered to be the PBM when it differs less than 5 mg/cm^3 for all subsequent age groups, and also when a linear regression analysis did not result in a significant increasing or decreasing slope over age. The correlation between vBMD and anthropometric parameters (weight, size, and BMI) are examined using the Pearson and Spearman correlation tests, accordingly. Also, these tests were performed to compare vBMD values between male and female subjects in each age group. The confidence interval is 95% for the statistical analysis, which was performed using the software IBM® SPSS Statistics V 17.0.

Table 1: Antropometric and vBMD values for Mexican female and male pediatric population, divided by four age groups, n shows the sample size per group. Normal distribution test (Shapiro-Wilk) for vBMD values, p > 0.05 indicates normal distribution. The increment between groups is presented (> 5 mg/cm^3).

Gender	Age group (years)	n	BMI ± SD (mg/cm^2)	vBMD ± SD (mg/cm^2)	Increment intergroup SD (mg/cm^3)
Females	2 - 7	10	16.03 ± 1.58	158.5 ± 23.07	——
	8 - 13	11	21.08 ± 3.05	168.49 ± 14.04	+ 6.5
	14 - 19	10	24.34 ± 3.24	187.78 ± 34.68	+ 22.42
	20 - 25	10	24.86 ± 3.17	203.13 ± 24.94	+ 8.35
Males	2 - 7	14	15.94 ± 1.09	154.39 ± 20.41	——
	8 - 13	16	18.19 ± 3.33	146.19 ± 20.41	- 8.58
	14 - 19	10	26.04 ± 4.22	168.57 ± 22.67	+ 23.60
	20 - 25	10	24.80 ± 2.99	180.57 ± 20.36	+ 8.97

BMI = body mass index; vBMD = bone mineral density; SD = standard deviation.
* Age group with normal distribution. ** Age group with not normal distribution.

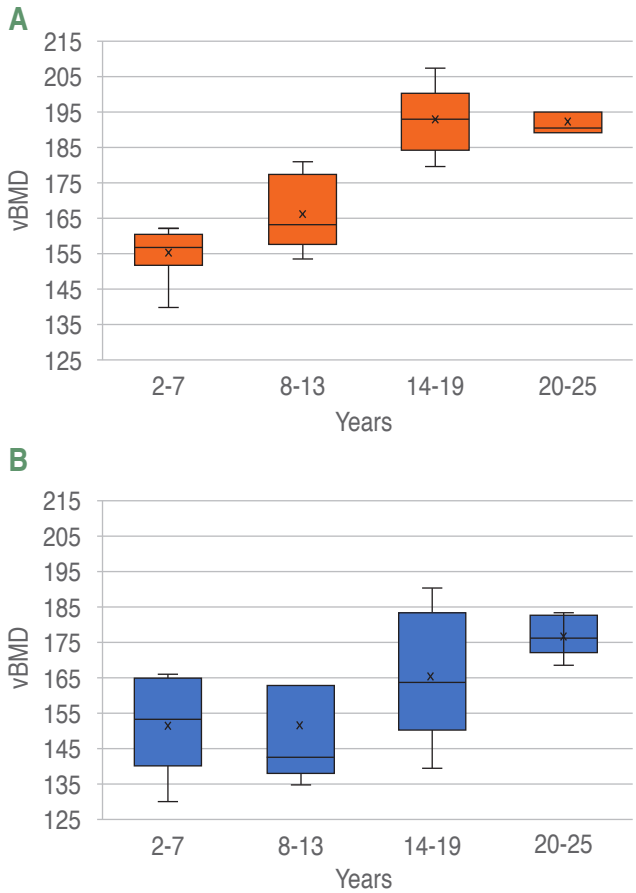

Figure 1: vBMD values of age groups: 2-7, 8-13, 14-19 and 20-25 years old, in Mexican pediatric population. **A)** Female vBMD measured values, expressed in mg/cm^3; **B)** Male vBMD measured values, expressed in mg/cm^3.

RESULTS

A random sampling was made, without replacement or correction for finite population. A sample size of 91 Mexican children [41 females (45.05%) and 50 males (54.95%)] ranging from two to 25 years old, stratified by age into four groups (2-7, 8-13, 14-19, and 20-25 years old). For the groups for each gender, a confidence level of 95% (Z = 1.96) and a SD of 27.15 mg/cm^3 was calculated. Regarding the sample size, the precision is d = 16.82 mg/cm^3, according to n = $Z2^*S^2/d^2$.[31] The time required to complete the QCT scans was approximately 15 minutes per subject. Tomography images are taken at the midportion of L2, L3, and L4 vertebrae; the effective radiation dose was approximately 0.27 mSv per study. Measurements were eliminated when children BMI indicated low weight or obesity, according to the percentile BMI pediatric tables for both genders.

Table 1 shows the mean and standard deviation values for BMI and vBMD values for Mexican female and male pediatric population, for age groups from two to 25 years old. The BMI for both genders ranges from 13.75 to 28.73 kg/m^2, which are within the normal limits. In *Figure 1A*, for females it is observed an almost average constant value for trabecular vBMD during childhood (~140 to ~170 mg/cm^3) until early puberty, and a vBMD increase during puberty (+16.33 mg/cm^3), between eight and 13 years old. From that point on, slow growths are maintained (+12.37 mg/cm^3), at 14 to 15 years old and there are progressive increments until 19 years old, and a final increment (+8.35 mg/cm^3) from 20 to 25 years old; graphically this resembles a sigmoid behavior. In the case of males, *Figure 1B*, there is a decrement of the mean vBMD values measured, between childhood and puberty, but later increments are closer to that of females (+23.60 mg/cm^3). The final increment (+8.97 mg/cm^3) is present in the 20 to 25-year-old group.

For all age groups, and both genders, Shapiro-Wilk normality tests of data distribution were performed, p-values by age group and gender are shown in *Table 1*. Data distribution is not normal for all groups.

So, Spearman and Pearson correlation tests were performed comparing values of vBMD versus anthropometric parameters (weight, size and BMI), accordingly. The correlation values do not show statistical significance ($p < 0.05$) for female subjects vBMD values and anthropometric variables, anyway, the three variables show a positive moderate correlation value to vBMD for males (20 to 25 years), and for BMI in females (8 to 13 years).

Table 2 show the differences in vBMD values between genders, using Student t-test and Mann-

Table 2: Correlation fro vBMD measured values between genders fro each age group.

Age group (years)	Correlation between Male and Female vBMD values	p
2 - 7	0.157*	0.880
8 - 13	-0.546**	0.004***
14 - 19	-0.010*	0.327
20 - 25	-0.049*	0.968

* Pearson correlation. ** Spearman correlation. *** Statistically significant

Whitney U test (depending distribution of data, respectively). The differences between female and male data along age groups were significant in the eight to 13 years group with a significance of p = 0.004, where changes in vBMD values are larger.

As *Table 1* shows, the increments between age groups for both genders are higher than 5 mg/cm^3 and are similar according to age groups. The highest increments are present during the teenage years and then a slower but still incremental change is achieved at 20 to 25 years hinting that the PBM is reached at this stage. For both genders, it resembles a sigmoid behavior; but apparently, it is shifted in years between male and female population.

Finally, in *Figure 2*, it can be observed that the measured vBMD values for females (2a) and males (2b) for the 20 to 25 years group stay within the limits of the gold standard values when compared to the reference curves from the QCT-5000^{TM} software used (CT-T bone densitometry package; GE$^{©}$ Medical Systems).

DISCUSSION

Accurate methods for vBMD measurement in pediatric population are very important to assess bone health in children during their development to determinate metabolic risk factors, establish correct diagnosis, and monitor therapeutic interventions. Metabolic activity is affected by age, disease, and corticosteroid therapy. DXA is considered the preferred method to evaluate the mineral state in practical clinic, due to its speed, precision and low exposition to radiation. Unfortunately, acquisition and interpretation of DXA in growing children is more complex than in adults; since it does not account for bone thickness neither allows to distinguish between trabecular and cortical bone. There are flaws in the recognition of problems in pediatrics densitometry that can lead to misdiagnosis; the lack of standardized data and/or effective diagnostic tool are main problems. vBMD measured in the microarchitecture of trabecular bone at lumbar spine by QCT is the best technique to assess bone mass by volume, because the sensitivity to detect early changes in vBMD is increased.

The main disadvantage of vBMD is a higher radiation dose compared with DXA; but with an adequate management for reduction of risk factors it can yield greater benefits. Studies reported in international literature[3,23,24,26,32,33] have shown the use of QCT in healthy children to obtain references

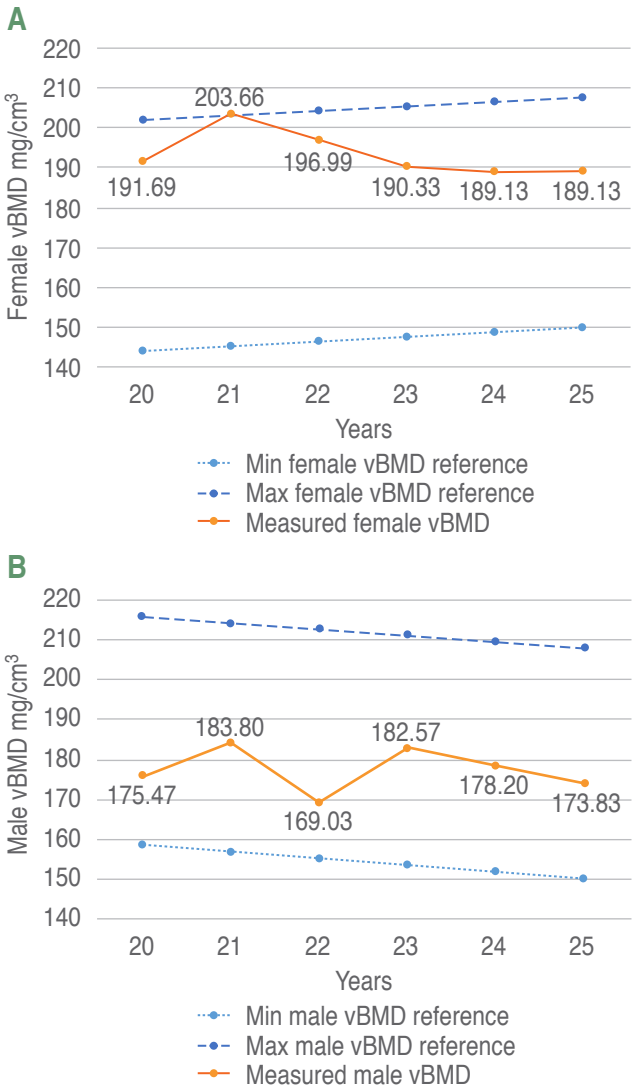

Figure 2: Measured values vs gold standard reference values (QCT-5000TM measure of bone density). **A)** Female vBMD measured values and reference range, **B)** Male vBMD measured values and reference range.

values, in which the research was under the review of the ethics committee of the institution accompanied by parents written consent. Our QCT protocol was designed to keep radiation exposure under 5 mSv and to take proper protection measures; and it was approved by a Research and an Ethical Committee and written consent was obtained from parents.

Likewise, WHO offers few guides over the indications that should be considered in poplations different to postmenopausal women, so its classification should not be used in pediatric population. We also

want to emphaticize that vBMD values for Caucasian pediatric population are not a valid reference for the Mexican pediatric population; the values obtained for Mexican population in this study suggest that the vBMD average values are about 35 to 40% lower than those of a Caucasian pediatric population,[26] so any measure based on these values as reference simply does not yield a valid outcome.

Our results, that show a sigmoid behavior of vBMD along childhood, differs from the behavior shown by DXA studies.[32] There are larger studies for Latin America including children[16] using the DXA technique. For pediatric population (seven to 18 years old) DXA showed steady increments of BMD (g/cm^2) with age, and a slight gain during puberty until 18 years old, as reported for a European pediatric population.[16,18]

The results shown from this work for Mexican pediatric population compared to those found increments of vBMD between age groups is shown in *Table 1*. The maximum velocity of bone mass gain is found between 10 and 16 years old for both genders, which means that maximum bone gain is independent of gender and maybe more related to hormonal behavior during this stage, as seen in *Figure 1*.

More samples are required to evaluate the differences by year of age. Anyway, the obtained values show that the vBMD differences are not significant between genders before eight to 10 years old. Then, there is a moderate positive correlation between genders at puberty, meaning that the observed differences *(Table 1)* are statistically significant ($p = 0.004$). Regarding PBM, females reach it at around 20-25 years old (251.37 mg/cm^3), while for males PBM may be reached later (219.57 mg/cm^3 for 20 to 25 years old group).

CONCLUSION

Our results show that vBMD values have ups and downs as children grow and enter puberty and teenage years, a fact that agrees with studies from other populations, and resembles a sigmoid behavior similar to the data presented by Gilsanz et al[26] even with a smaller sample.

Using the criteria established by Mexican norms regarding radiation exposure,[28] this study shows the importance of choosing the adequate measurement technique to achieve the most accurate data. And with it will be possible to have a Mexican vBMD reference table stratified by age and gender that could have a major impact in the proper identification of bone density and fracture risk index for chronically ill children. These reference values would make it possible to confirm a diagnosis, to handle better the risk of fracture and to indicate the most adequate treatment. This is especially valuable in chronically ill children, e.g., DMD or other musculoskeletal diseases, who might present delay in bone maturity.

Preliminarily, these first measures show vBMD Mexican pediatric population values and encourage us to increase the sample size, to improve the precision of the results and to be able to calculate properly the Z-score. In addition, the PBM value and age for both genders need to be more precisely identified to eventually contribute to establish the reference values for the Mexican pediatric population.

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Sleep disorders in patients with acquired brain damage, associated factors and their impact on functionality

Desórdenes de sueño en pacientes con daño cerebral adquirido, factores asociados y su impacto sobre la funcionalidad

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Stroke, brain traumatic injury, sleep disorders, functionality.

Palabras clave:
Enfermedad vascular cerebral, trumatismo craneoencefálico, trastornos en el sueño, funcionalidad.

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Abstract

Objective: To identify the prevalence of sleep disorders in chronic post-stroke and post-traumatic brain injury (TBI) patients, to determine the risk factors and their impact on functionality in activities of daily life. **Material and methods:** Cross-sectional clinical study that included adults ≥ 18 years with a history of acquired brain damage (post-stroke or post-TBI). Sociodemographic data and clinical history were obtained, and the following instruments were applied: Pittsburgh Sleep Quality Index, the Epworth Sleepiness Scale, the Berlin Questionnaire© Sleep Apnea, the Barthel's functionality index, the Hamilton Depression Rating Scale and the Beck Anxiety Inventory. **Results:** We included 116 patients, 91 post-stroke (78.4%) and 25 post-TBI (21.6%), mean age was 56.58 years (SD = 19.37). In post-stroke patients, the following risk factors were identified: diabetes (OR = 3.01; 95% CI = 1.13-8.01 for poor sleep quality), multiple comorbidities (OR = 3.78; 95% CI = 1.04-13.67 for quality of sleep), depression (OR = 2.46; 95% CI = 2.46-25.80 for apnea; OR = 7.94; 95% CI = 1.25-10.82 for insomnia) and anxiety (OR = 17.84; 95% CI = 2.28-139.64 for insomnia). In post-TBI patients, the following were identified as risk factors: overweight/obesity (OR = 11.25; 95% CI = 1.64-76.84 for poor sleep quality) and coma (OR = 2.33; 95% CI = 1.42-3.82 for sleepiness). The risk factor for functional loss in post-stroke is apnea (OR = 2.63; 95% CI = 1.05-6.54) and in post-TBI the poor quality of sleep (OR = 8.25; 95% CI = 1.15-50.03). **Conclusion:** Post-stroke and post-TBI patients have a high prevalence of sleep disorders and its comorbidities increase the risk of chronic sleep disorders and functional loss.

Resumen

Objetivo: *Identificar la prevalencia de trastornos en el sueño en pacientes post-stroke y post-TCE, determinar los factores de riesgo y su impacto en la funcionalidad en actividades de la vida diaria.* ***Material y métodos:*** *Estudio clínico transversal que incluyó adultos ≥ de 18 años con antecedente de daño cerebral adquirido (post-stroke o postraumatismo craneoencefálico). Se obtuvieron datos sociodemográficos y antecedentes clínicos, y se aplicaron los siguientes instrumentos: Pittsburgh Sleep Quality Index, the Epworth Sleepiness Scale, the Berlin questionnaire sleep apnea, the Barthel's*

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functionality index, the Hamilton Depression Rating Scale and the Beck Anxiety Inventory. ***Resultados:*** *Se incluyeron 116 pacientes, 91 post-stroke (78.4%) y 25 post-TBI (21.6%), media de edad fue 56.58 años (DE = 19.37). En pacientes post-stroke se identificaron como factores de riesgo: diabetes (OR = 3.01; IC 95% = 1.13-8.01 para mala calidad de sueño), múltiples comorbilidades (OR = 3.78; IC 95% = 1.04-13.67 para calidad de sueño), depresión (OR = 2.46; IC 95% = 2.46-25.80 para apnea; OR = 7.94; IC 95% = 1.25-10.82 para insomnio) y ansiedad (OR = 17.84; IC 95% = 2.28-139.64 para insomnio). En el pacientes post-TBI, se identificaron como factores de riesgo: sobrepeso/obesidad (OR = 11.25; IC 95% = 1.64-76.84 para pobre calidad de sueño) y antecedente de coma (OR = 2.33; IC 95% = 1.42-3.82 para somnolencia). El factor de riesgo para pérdida funcional en post-stroke es la apnea (OR = 2.63; IC 95% = 1.05-6.54) y en post-TBI la mala calidad de sueño (OR = 8.25; IC 95% = 1.15-50.03).* ***Conclusión:*** *Los pacientes post-stroke y post-TBI presentan comorbilidades que incrementan el riesgo de presentar trastornos del sueño crónicos y pérdida funcional.*

INTRODUCTION

Sleep disorders are common consequences of acquired brain damage. In patients with a history of cerebrovascular disease (post-stroke), a prevalence of 1.1 to 27% of sleepiness, 50-70% of apnea[1] and 20-56% of insomnia[2] have been identified previously. In patients with a history of traumatic brain injury (post-TBI), sleep disturbances may occur as part of the TBI spectrum or may occur after the injury.[3] The prevalence of sleep disturbances is reported in 30-70%,[3] 41.7% have sleepiness or fatigue (41.7%), 36% apnea, 30% poor quality of sleep and insomnia.[4]

The causes of sleep disorders in patients with acquired brain damage include a complex interrelation between pathophysiological (structural, electrical or neurochemical) processes, variables associated with the injury (severity, site and extent of injury, loss of consciousness, time of evolution), previous sleep habits and alterations, psychological factors (mood changes, neuropsychiatric sequelae), environmental factors (noise, light, invasive treatments, adverse effect of medications), another type of injury sequelae (pain, immobility), social factors (type of care, family role), among others.[2-5]

In addition to altering daytime energy levels, sleep disorders can exacerbate other conditions such as cognitive deficits (predominantly in attention and memory), pain, fatigue, mood disturbances, and contribute to poor rehabilitation achievements, which can have an impact on functional recovery and lead to low quality of life.[2,5,6]

For the diagnosis of sleep disorders, polysomnography (PSG) has been considered the gold standard, providing objective and quantitative information of physiological indicators in a transversal manner, however, its complexity, low availability and high costs make it difficult for it to be widely available in all patients. Therefore, an alternative method to study these disorders is the application of validated scales and questionnaires in which the patient describes different aspects related to the quality and duration of sleep in relation to a longer period of time. These being easily administered and low-cost, the scales are largely used as a resource to improve the initial characterization of patients and identify the parameters to be evaluated in a PSG.[7,8]

Although there are numerous studies that have described the sequelae in sleep after acquired brain damage,[1-4,9] little is known about the chronicity of this type of manifestations and the differential characteristics between post-stroke and post-TBI patients, which may be interesting considering the high prevalence of this type of lesion and its impact on functionality.

The objective of this study was to identify the prevalence of sleep disturbances in post-stroke and post-TBI patients and to determine the risk factors for these disturbances. As a secondary objective, the impact of sleep disorders on functionality in activities of daily life was analyzed.

MATERIAL AND METHODS

Study design and participants. Cross-sectional clinical study conducted in a third-level hospital in Mexico City that included men and women over the age of 18 who met the following inclusion criteria: 1) history of acquired brain damage (first event of ischemic or hemorrhagic stroke or presence of TBI, corroborated by neuroimaging study), 2) absence of neurological, psychiatric or previously diagnosed sleep disturbances (obstructive apnea, narcolepsy, chronic insomnia, hypersomnia, parasomnias), 3) evolution time of at least one month from brain injury, 4) absence of severe cognitive or physical impairment that would prevent the application of the assessment instruments, 5) absence of additional uncontrolled

or untreated medical conditions affecting the sleep, mood or cognition.

Instruments. After having signed the informed consent, a semi-structured interview was conducted in which information about sociodemographic variables and clinical history was obtained. For the evaluation of sleep disorders, functional and mental state the following instruments were applied: Pittsburgh Sleep Quality Index (PSQI ≥ 6), the Epworth Sleepiness Scale (ESS ≥ 10), the Berlin questionnaire sleep apnea (BQ ≥ 3), the Barthel's functionality index (≥ 80), the Hamilton Depression Rating Scale (HDRS ≥ 8) and the Beck Anxiety Inventory (BAI, 1 mild anxiety). Evaluations were conducted by qualified personnel in individual cubicles with appropriate conditions.

Statistical methods. Descriptive statistics were used to analyze the characteristics of the sample. The Shapiro-Wilk test was used to determine the normal distribution of variables. Student t and Mann-Whitney U tests were used to compare means between groups and χ^2 to compare proportions. Multiple linear regressions were performed to identify variables associated with the presence of sleep disturbances and variables associated with functional loss and odds ratio (OR) were determined with a 95% confidence interval (CI). All analyses were performed with the SPSS 21 statistical program. To establish significant differences and correlations, a value of $p \leq 0.05$ was considered.

RESULTS

The sample consisted of 116 patients, 91 post-stroke (78.4%) and 25 post-TBI (21.6%), the mean age was 56.58 years (SD = 19.37), with the post-TBI group being younger in a statistically significant way (37.64, SD = 19.80 with respect to post-stroke: 61.79, SD = 15.74, p 0.001), 56.8% of the total sample were men, 50.5% of the post-stroke group and 80% of the post-TBI group. In both groups there was predominance of right manual laterality (96.7% in post-stroke and 100% in post-TBI). The average evolution time was 17.9 months, the post-TBI group had a longer evolution time (27.75, SD = 39.27) than the post-VC group (15.08, SD = 18.49), however, this was not statistically significant. In post-stroke patients, the most prevalent type of lesion was ischemic (64.8% with respect to 34.1% hemorrhagic), predominantly left (50.8%). In post-TBI patients, 73.9% had a right hemisphere lesion, 84% had a history of coma, and 60% required surgical treatment *(Table 1)*.

Regarding the clinical variables, the post-stroke group presented a greater number of comorbidities (3.31 with respect to 2.20, p = 0.005), a higher prevalence of hypertension (65.9% with respect to 4%, p = 0.001) and diabetes (34.1% with respect to 8%, p = 0.011) with respect to the post-stroke, while the post-TBI group had a higher prevalence of alcoholism compared to the post-stroke group (56% compared to 15.4%, p = 0.001) *(Table 1)*.

Table 1 shows the clinical scales used to assess sleep disorders (quality of sleep, sleepiness and apnea), mood (depression and anxiety), as well as functionality in both groups of patients. Only statistically significant differences were identified between groups in the symptoms of apnea, with the post-stroke group having the highest score (3.21, SD = 1.61 with respect to 2.12, SD = 1.39 in post-TBI, p = 0.002).

Prevalence of sleep disturbances in post-stroke and post-TBI patients. The post-stroke group had a higher prevalence of poor sleep quality (61.3% with respect to post-TBI: 52%), risk of apnea (63.4% with respect to post-TBI: 44%) and insomnia (26.9% with respect to post-TBI: 12%). The post-TBI group had a higher prevalence of sleepiness (52% with respect to post-stroke: 36.6%). None of the differences were statistically significant *(Table 1 and Figure 1)*.

Risk factors for sleep disturbances in post-stroke and post-TBI patients. In post-stroke patients, the presence of diabetes (OR = 3.01; 95% CI = 1.13-8.01) and multiple comorbidities (OR = 3.78; 95% CI = 1.04-13.67) were identified as risk factors for poor sleep. For sleepiness, only the presence of diabetes was identified as a risk factor (OR = 3.98; 95% CI = 1.59-9.91). For apnea, the presence of diabetes (OR = 4.57; 95% CI = 1.55-13.45) and depression (OR = 7.97; 95% CI = 2.46-25.80) were observed as risk factors. Depression and anxiety were the risk factors identified for insomnia (OR = 3.68; 95% CI = 1.25-10.82 and OR = 17.84; 95% CI = 2.28-139.64, respectively).

In the post-TBI group, overweight or obesity were identified as risk factors for poor sleep quality (OR = 11.25; 95% CI = 1.64-76.84), while the history of coma was identified as a risk factor for sleepiness (OR = 2.33; 95% CI = 1.42-3.82) *(Table 2)*.

Effect of sleep disorders on functionality. In the post-stroke group, apnea was the only sleep disturbance that represents a risk factor to generate

Table 1: General characteristics of the sample.

Variable	Total	Post-stroke	Post-TBI	p
Sociodemographic variables				
n	116 (100)	91 (78.4)	25 (21.6)	
Age	56.58 (19.37)	61.79 (15.74)	37.64 (19.8)	0.001*
Sex (men)	65 (56.8)	46 (50.5)	20 (80)	0.008*
Laterality	73 (97.3)	59 (96.7)	25 (100)	0.492
Variables associated with the lesion				
Evolution time	17.87 (24.94)	15.08 (18.49)	27.75 (39.27)	0.142
Stroke type				
Ischemic	—	57 (64.8)	—	—
Hemorrhagic	—	30 (34.1)	—	—
Injured hemisphere (right)	50 (50)	33 (42.9)	17 (73.9)	0.009*
History of coma	21 (84)	—	21 (84)	—
Surgical treatment	—	—	12 (60)	—
Clinical variables				
Total comorbidities	3.03 (1.75)	3.31 (1.73)	2.20 (1.47)	0.005*
Stroke preious	9 (11.8)	9 (12.5)	0 (0)	0.102
Hypertension	61 (52.6)	60 (65.9)	1 (4)	0.001*
Diabetes	33 (28.4)	31 (34.1)	2 (8)	0.011*
Dyslipidemia	30 (25.9)	25 (27.5)	5 (20)	0.450
Depression	19 (16.4)	18 (19.8)	1 (4)	0.059
Heart disease	15 (12.9)	13 (14.3)	2 (8)	0.407
BMI	24.89 (3.92)	24.77 (3.85)	25.35 (4.19)	0.505
Alcoholism	28 (24.1)	14 (15.4)	14 (56)	0.001
Smoking	30 (25.9)	23 (25.3)	7 (28)	0.783
Clinical scales				
PSQI	7.88 (4.91)	8.18 (5.16)	7.08 (3.91)	0.361
ESS	8.40 (6.21)	8.21 (6.45)	8.6 (5.58)	0.618
BQ	2.98 (1.61)	3.21 (1.61)	2.12 (1.39)	0.002*
Hamilton	8.69 (7.86)	8.92 (8.04)	8 (7.48)	0.721
Beck	4.80 (5.59)	5.06 (5.90)	3.92 (4.51)	0.448
Barthel	57.80 (38.68)	59.41 (39.20)	51.82 (36.84)	0.329
Prevalence of sleep				
Por quality of sleep	70 (59.3)	57 (61.3)	13 (52)	0.401
Dayitme sleepiness	47 (39.8)	34 (36.6)	13 (52)	0.161
Apnea risk	70 (59.3)	59 (63.4)	11 (44)	0.079
Insomnia	28 (23.70)	25 (26.9)	3 (12)	0.120

TBI = traumatic brain injury; BMI = Body mass index; PSQI = Pittsburgh Sleep Quality Index; ESS = Epworth Sleepiness Scale; BQ = Berlin questionnaire sleep apnea. * Statistically significant

functional dependence (OR= 2.63; 95% CI = 1.05-6.54), however, risk factors are also identified as age over 60 years (OR = 3.75; 95% CI = 1.50-9.36) and the presence of depression (OR = 3.60; 95% CI = 1.07-12.09).

In the post-TBI group, the only risk factor for functional dependence was poor sleep quality (OR = 8.25; 95% CI = 1.15-59.03) *(Table 3)*.

DISCUSSION

Acquired brain damage is a major cause of disability that generates several sequelae, with sleep disorders being one of the most frequent. Given the effect of sleep disorders in other conditions that can affect the patient's recovery, it is necessary to detect, characterize and consider this type of

alterations in the management of patients with acquired brain damage.

The present study found a high prevalence of sleep disturbances, 61.3% of post-stroke patients and 52% of post-TBI patients reported poor sleep quality. In post-stroke patients, there was a high prevalence of risk of apnea (63.4%) and insomnia (26.9%). These results agree with what was described by various authors,[1,2,9,10] who have described 50-70% prevalence of apnea and 20-56% insomnia, however, the prevalence of daytime sleepiness in the present study at 17.9 months (36.6%) was slightly higher than that reported by Hermann and Bassetti[1], who reported 27% to 21 months; and does not agree with what was identified by Winward et al.[10] who described a significant reduction in sleepiness six months after injury in patients with minor stroke. The increased severity of the patients included in this study is likely to explain the permanence of daytime sleepiness several months after injury.

Risk factors for sleep disturbances in post-stroke patients. According to our results, the presence of diabetes mellitus and multiple comorbidities have an impact on the quality of sleep of post-stroke patients. It has been described that the quality of sleep may be affected by the medical conditions of patients, so the presence of various comorbidities, including diabetes, can exacerbate poor sleep quality. Specifically, diabetes has been

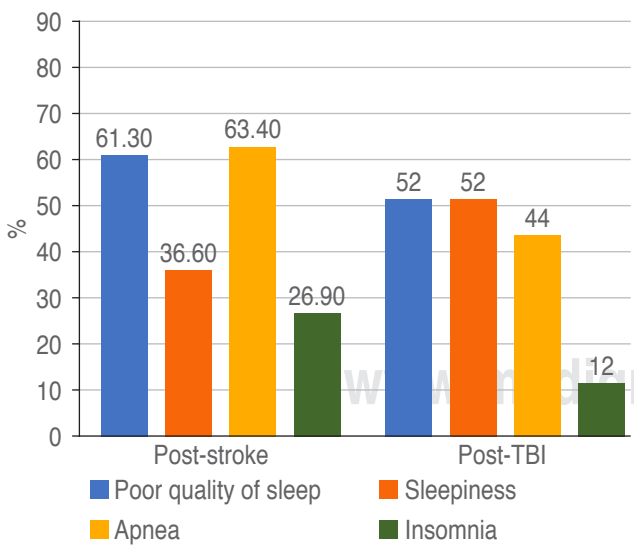

Figure 1: Prevalence of sleep disturbances between post-stroke and post-TBI patients.

Table 2: Risk factors of sleep disturbances in post-stroke and post-TBI patients.

Variables	OR (95% CI)
Post-stroke	
Sleep quality	
Diabetes	3.01 (1.13-8.01)
More than one comorbidity	3.78 (1.04-13.67)
Sleepiness	
Diabetes	3.98 (1.59-9.91)
Apnea	
Diabetes	4.57 (1.55-13.45)
Depression (self report)	2.87 (1.19-6.89)
Depression (Hamilton scale)	7.97 (2.46-25.80)
Insomnia	
Depression	3.68 (1.25-10.82)
Depression (Hamilton scale)	7.97 (2.46-25.80)
Anxiety (Beck scale)	17.84 (2.28-139.64)
Post-TBI	
Sleep quality	
Overweight/obesity	11.25 (1.64-76.84)
Sleepiness	
Coma	2.33 (1.42-3.82)

OR = odds ratio; CI = confidence interval; TBI = traumatic brain injury.

associated with numerous sleep disorders, the most prevalent being apnea, hypersomnia and insomnia. This has been explained by both the effects of diabetes on the central control of breathing that can trigger episodes of apnea and by glycemic imbalances during the day that can exacerbate hypersomnia that can generate effects in night sleep generating insomnia.[11]

Various studies have shown that patients with diabetes have worse quality of night sleep, so they have excessive daytime sleepiness. Some of the causes that explain sleep disorders in patients with diabetes are the presence of pain due to the presence of peripheral neuropathy, or nocturia generated by poor glycemic control. In addition, a specific abnormal breathing pattern has been identified in patients with diabetes, which is still confusing.[12-14]

In our study, the presence of diabetes was associated with the presence of apnea. Several studies have described that the presence of diabetes affects central respiratory control and that this can promote the presence of apnea, being observed in some studies

prevalence of 27% in diabetes compared to 15.6% in non-diabetic, and in others, presence of apnea in more than half of patients with type 2 diabetes. It should be emphasized that these variables are associated regardless of age and degree of obesity.[11]

Regarding the relationship between depression and sleep apnea, several studies have shown the interrelation between these variables, so that the presence of sleep disturbances such as apnea have repercussions on mental health and, on the other hand, the presence of mood disturbances can contribute to the exacerbation of sleep disturbances. Given the lack of clarity of the pathophysiological mechanisms that explain this relationship, it has been proposed that both sleep disorders and mental health disorders could be a consequence of the same neurobiological process.[14]

There is a great deal of evidence to support the interrelationship between mood disturbances (such as anxiety and depression) and their relationship to sleep. Some studies have shown that genetic factors related to the etiology of insomnia overlap with those related to depression and anxiety, however, there are various biological mechanisms, psychosocial and environmental factors involved in the presence of these symptoms.[15]

Risk factors for sleep disturbances in post-TBI patients. Obesity and overweight have been considered one of the factors of greater risk to present alterations in sleep through various pathogenetic mechanisms, However, it has also been described those subjects with sleep disturbances are also more likely to be overweight and obese.[16] Some studies have identified that a mechanism that links obesity to sleep disorders is the quality of the diet, because of nutrients acting on inflammation or hormonal responses involved in the mechanisms of hungersatiety, energy metabolism and circadian rhythm.[17] On the other hand, it has been described that in obesity, the cephalic displacement of the diaphragm by abdominal fat affects lung volumes, producing a restrictive pattern characterized by the reduction of functional residual capacity and expiratory reserve volume that affects the quality and quantity of sleep.[18]

Although there is no direct link between post-TBI coma and daytime sleepiness, it has been reported that in general almost half of people with a history of severe TBI have a pathological level of sleepiness with latency times of less than 10 minutes. The association between history of coma and the presence of sleepiness is likely to be associated with direct injury of histaminergic tuberomammillary alert neurons, which are reduced by about 40% after severe traumatic brain injury.[19-21]

Table 3: Risk factors of functional dependency in post-stroke and post-TBI.

Variables	OR (95% CI)
Post-stroke	
Age over 60 years	3.75 (1.50-9.36)
Depression	3.60 (1.07-12.09)
Apnea	2.63 (1.05-6.54)
Post-TBI	
Poor quality of sleep	8.25 (1.15-59.03)

OR = odds ratio; CI = confidence interval; TBI = traumatic brain injury.

Effect of sleep disorders on functionality. In this study, it was identified that in post-stroke patients, the age over 60 years, depressive symptoms and apnea, are risk factors to present a lower functionality, while the poor quality of sleep affects the functional capacity in post-TBI patients. These findings correspond to what has been described in various studies, in which it has been considered that sleep disorders impact the rehabilitation capacity of patients with acquired brain injury and functional recovery.[22]

Limitations of the study. It is recognized that the evaluation of sleep disorders was carried out clinically only with specific and standardized scales for these purposes, it was not possible to corroborate the findings with other techniques such as polysomnography. On the other hand, given that the study is cross-sectional, it is not possible to determine whether the variables identified as risk factors occurred prior to sleep disorders or whether it is an interrelation between variables. It should be noted that the sample of patients with TBI is very small and not balanced with those with stroke, so comparisons between these groups would not be completely valid.

Ethical considerations: This study was carried out in accordance with the Declaration of Helsinki (1964) and with the current national guidelines for human research. The research was evaluated and approved by the research and ethics committees of the National Institute of Rehabilitation LGII of Mexico City.

All participants signed and received a copy of the informed consent in which they voluntarily accept-ed their collaboration in the study.

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CASO CLÍNICO

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Efecto de la rehabilitación neuropsicológica en la enfermedad vascular cerebral en etapa crónica en adolescentes. Estudio de caso

Effect of neuropsychological rehabilitation in chronic stage of cerebral vascular disease in adolescents. Case study

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Palabras clave: Enfermedad vascular cerebral, rehabilitación neuropsicológica, jóvenes, cognición, funcionalidad.

Keywords: *Cerebral vascular disease, neuropsychological rehabilitation, young, cognition, functionality.*

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Resumen

Introducción: La enfermedad vascular cerebral (EVC) es rara en adolescentes; sin embargo, puede tener consecuencias más importantes a esta edad debido a que muchas funciones cognitivas aún están en desarrollo. Existen muy pocos reportes sobre el efecto de la rehabilitación neuropsicológica (RN) en adolescentes con EVC en etapa crónica. **Objetivo:** Presentar los efectos de un programa de RN en el estado cognitivo, emocional y funcional en un paciente de 19 años con secuelas crónicas de EVC. **Material y métodos:** Se presenta el caso de un masculino de 19 años que sufrió un EVC hemorrágico criptogénico en ganglios basales a los 16 años. Se realizó un programa de RN de 12 sesiones semanales de una hora de duración y evaluación antes y después de la intervención, empleando tareas del Neuropsi breve, de la batería BANFE, así como tareas orientadas para la exploración de habilidades espaciales y el inventario de depresión de Beck (BDI). **Resultados:** El programa de RN generó efectos en el registro y evocación de la tarea de memoria verbal y cálculo del Neuropsi breve; mejoró los tiempos de ejecución y aciertos en las tareas de la BANFE y logró mejor desempeño en habilidades espaciales. Disminuyó la sintomatología depresiva y a nivel funcional, el paciente logró retomar algunas actividades académicas en un contexto informal. **Conclusión:** La RN resulta un recurso terapéutico capaz de mejorar el estado cognitivo y anímico en pacientes crónicos, lo que puede facilitar la reincorporación de los pacientes a sus actividades cotidianas y académicas.

Abstract

Introduction: *Stroke is rare in teenagers, however, it may have more important consequences at this age due to the fact that many cognitive functions are still under development. There are very few reports on the effect of neuropsychological rehabilitation (NR) in teenagers with stroke in the chronic stage.* ***Objective:*** *To present the effects of a NR program on the cognitive, emotional and functional state in a 19-year-old patient with chronic sequelae of stroke.* ***Material and methods:*** *We present the case of a 19-year-old male who suffered a cryptogenic hemorrhagic stroke in the right basal ganglia at 16 years of age. A NR program of 12 weekly sessions of one hour was carried out. An evaluation was carried out before and after the intervention using tasks from the brief Neuropsi test, from the BANFE battery, as well as tasks oriented to the exploration of spatial skills and the Beck Depression Inventory (BDI).* ***Results:*** *The NR program generated effects on the registration and evocation of the verbal memory task and calculation of the brief Neuropsi test; improved execution times and successes in BANFE tasks and achieved better performance in spatial skills. Depressive symptoms decreased and*

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at a functional level, the patient was able to resume some academic activities in an informal context. ***Conclusion:*** *NR is a therapeutic resource capable of improving the cognitive and emotional state in chronic patients, which can facilitate the return of patients to their daily and academic activities.*

INTRODUCCIÓN

La enfermedad vascular cerebral (EVC) en jóvenes menores de 45 años es un evento infrecuente (4-5%).[1] La EVC en jóvenes es más heterogénea respecto a la observada en adultos mayores, debido a la inmadurez cerebral aún presente, a la variedad de posibles factores de riesgo subyacentes y a la etiología de la lesión.[2,3]

Respecto a las secuelas cognitivas de la EVC, se ha encontrado presencia de alteración en atención, funciones ejecutivas, menor desempeño intelectual, bajo rendimiento académico, así como fallas en la regulación emocional y conductual que suelen persistir hasta más de seis años.[4]

Se ha descrito que la rehabilitación neuropsicológica (RN), al promover un mejor estado cognitivo de pacientes post-EVC, puede impactar de manera positiva el estado emocional y calidad de vida,[5] lo que podría contemplarse como una estrategia terapéutica viable para dar frente a las secuelas del EVC en jóvenes.[1,6,7]

El objetivo de este trabajo es presentar los efectos de un programa de rehabilitación neuropsicológica en el estado cognitivo, emocional y funcional en un paciente de 19 años con secuelas crónicas de EVC, enfatizando la importancia de incluir la intervención neuropsicológica en los procesos de rehabilitación de pacientes jóvenes con lesión cerebral.

CASO CLÍNICO

Se trata de un paciente masculino de 19 años de edad, soltero, que cursó hasta quinto semestre de preparatoria. Como único antecedente de relevancia, el paciente consumía alcohol de manera esporádica.

Presentó hemorragia cerebral criptogénica en ganglios basales derechos, además de polineuropatía del paciente en estado crítico cuando tenía 16 años. Cursó con diversas complicaciones, entre ellas neumonía nosocomial, hidrocefalia y crisis convulsivas, por lo cual se realizó ventriculostomía, traqueostomía y gastrostomía.

Con la intención de dar seguimiento a las intervenciones realizadas previamente, cinco meses posteriores a la EVC se hospitalizó en el Instituto Nacional de Rehabilitación, en donde se realizó seguimiento médico neurológico, así como rehabilitación física y ocupacional que permitieron la recuperación paulatina del estado de alerta y movilidad.

Si bien la intervención inicial recibida en el instituto generó mejoras significativas en el estado físico y cognitivo, el paciente seguía presentando fallas para recuperar información reciente, mantenerse atento en sus actividades, refería tristeza y apatía que le seguían generando dependencia para la realización de las actividades de la vida diaria.

Evaluación neuropsicológica

Se realizó un proceso de evaluación neuropsicológica en el cual se aplicaron los siguientes instrumentos: orientación, lista de palabras y cálculo de la evaluación neuropsicológica breve en español (Neuropsi breve); Torre de Hanoi, Stroop versión A y B de la BANFE; tareas neuropsicológicamente orientadas para la exploración de habilidades espaciales (comprensión y expresión izquierda-derecha y seguimiento de rutas en un mapa) y el inventario de depresión de Beck (BDI).

Se realizó la aplicación de los inventarios de depresión y ansiedad de Beck, el índice de Katz para actividades básicas de la vida diaria, y la escala de Lawton y Brody para actividades instrumentadas.

Resultados de la evaluación inicial

Ante la evaluación inicial, el paciente se presentó en silla de ruedas con poca destreza motora en general, alteraciones en la pinza fina y en los movimientos oculares que dificultaban el rastreo visual y la coordinación ojo-mano.

Se observaron fluctuaciones en el sostenimiento atencional, alteración en el funcionamiento ejecutivo (control inhibitorio de tipo cognitivo y motor, planeación y memoria de trabajo), lo que generaba fallas en la adquisición de información (proceso de aprendizaje y memoria) audio-verbal, visual, en habilidades visuoespaciales y visuoconstructivas. Aunado a lo anterior, se identificaron fallas en habilidades espaciales, específicamente en el análisis e identificación de elementos alocéntricos.

Se identificó presencia de síntomas depresivos severos y se encontró que el paciente requería asistencia para llevar a cabo actividades básicas e instrumentadas de la vida diaria. El cuadro antes descrito era esperado, considerando las lesiones vasculares presentes en el paciente que comprometen conexiones córtico-subcorti-

cales del sistema de ganglios basales y regiones frontales. De manera adicional, las dificultades presentadas en las habilidades espaciales se asocian con alteraciones en circuitos frontoparietales que al momento de la lesión podrían aún encontrarse en desarrollo.

Programa de rehabilitación neuropsicológica

El programa de rehabilitación neuropsicológica consistió en 12 sesiones semanales de una hora, estructurado en tres etapas y tuvo como objetivo general promover los recursos atencionales y el funcionamiento ejecutivo como base para los mecanismos de memoria y aprendizaje, lo que en segunda instancia podía incidir en la optimización de las habilidades académicas básicas (lectoescritura y cálculo), necesarias para la reintegración a las actividades escolares.

La *Figura 1* presenta los procesos cognitivos abordados y objetivos de cada una de las tres etapas de la intervención y el eje transverso que se realizó durante todo el programa.

Resultados de la evaluación neuropsicológica final

El paciente logró mejor desempeño en el registro (pre = 2/alteraciones severas, post = 4/normal), evocación con claves (pre = 2/alteraciones severas, post = 3/normal) y reconocimiento (pre = 3/alteraciones severas, post = 6/normal) en la tarea de memoria verbal y cálculo (pre = 1/alteraciones moderadas, post = 2/normal) de la prueba Neuropsi breve; mejoró los tiempos de ejecución en la Torre de Hanoi (pre = 169"/alteraciones leves a moderadas, post = 129"/normal) y Stroop A (pre = 112"/alteraciones leves a moderadas, post = 103"/normal) de la BANFE, y presentó mayor número de aciertos en el Stroop A (pre = 71/alteraciones severas, post = 80/alteraciones leves a moderadas). Además, se observaron mayores puntajes en las tareas de comprensión (pre = 3, post = 5) y expresión (pre = 2, post = 5) de rutas en mapas en las tareas neuropsicológicamente orientadas dirigidas a la exploración de las habilidades espaciales. Finalmente, se logró disminución significativa en la sintomatología depresiva, pasando de un nivel de depresión severo (31 puntos) a mínimo (12 puntos) *(Tabla 1)*.

La *Figura 2* presenta el comparativo de las curvas de aprendizaje antes y después del programa de rehabilitación.

A nivel funcional, el paciente retomó las actividades académicas en un contexto informal, iniciando un curso a nivel técnico sobre habilidades informáticas.

DISCUSIÓN

Un aspecto fundamental en la EVC en jóvenes es que el tipo de secuelas identificadas no sólo corresponden

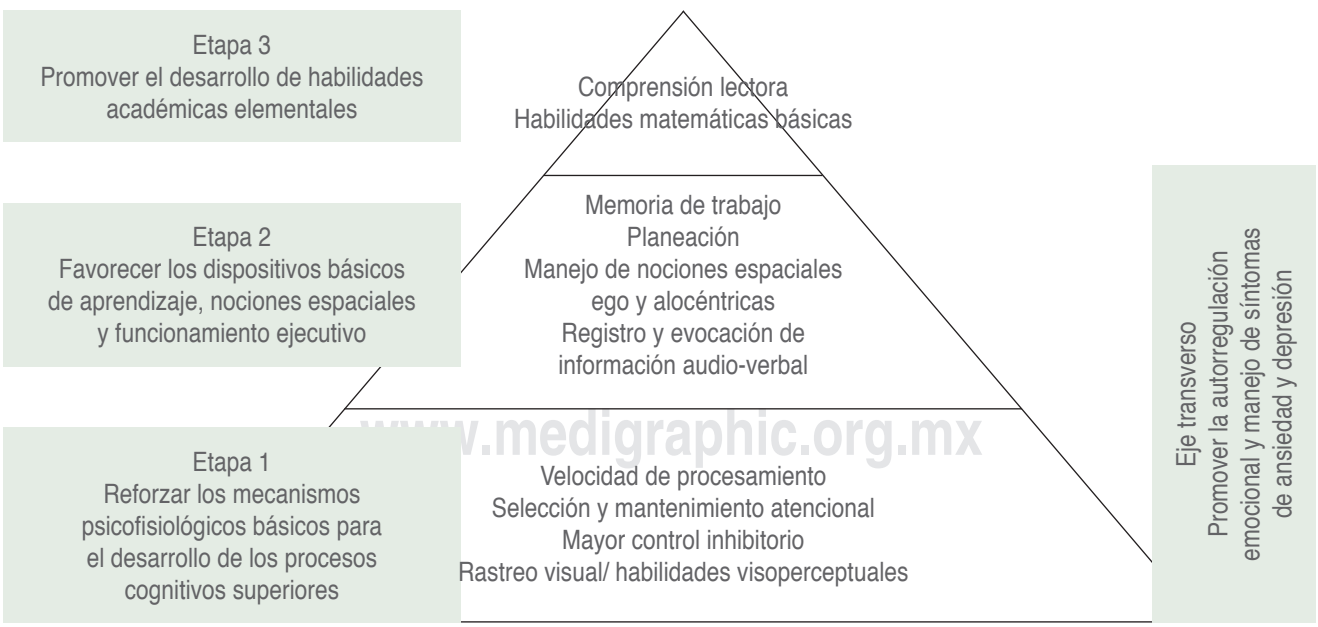

Figura 1: Estructura del programa de intervención.

Tabla 1: Puntaje alcanzado por el paciente pre- y postintervención.

Tareas	Preintervención	Rango de ejecución	Postintervención	Rango de ejecución	Comparativo
Neuropsi breve					
Orientación	5	Normal	5	Normal	Se mantiene
Memoria verbal (registro)	2	Alteraciones severas	4	Normal	Mejora
Memoria verbal (evocación)					
Espontánea	1	Alteraciones severas	2	Alteraciones severas	Se mantiene
Categorías	2	Alteraciones severas	3	Alteraciones moderadas	Mejora
Reconocimiento	3	Alteraciones severas	6	Normal	Mejora
Cálculo	1	Alteraciones moderadas	2	Normal	Mejora
BANFE					
Torre de Hanoi 3 discos (movimientos)	8	Normal	11	Normal	Se mantiene
Torre de Hanoi 3 discos (tiempo)	83	Normal	72	Normal	Se mantiene
Torre de Hanoi 4 discos (movimientos)	21	Normal	30	Normal	Se mantiene
Torre de Hanoi 4 discos (tiempo)	169	Alteraciones leves a moderadas	129	Normal	Mejora
Stroop Forma A (errores tipo stroop)	11	Alteraciones severas	4	Alteraciones severas	Se mantiene
Stroop Forma A (tiempo)	112	Alteraciones leves a moderadas	103	Normal	Mejora
Stroop Forma A (aciertos)	71	Alteraciones severas	80	Alteraciones leves a moderadas	Mejora
Stroop Forma B (errores tipo stroop)	4	Alteraciones severas	6	Alteraciones severas	Se mantiene
Stroop forma B (tiempo)	106	Alteraciones severas	105	Alteraciones severas	Se mantiene
Stroop forma B (aciertos)	80	Alteraciones severas	78	Alteraciones severas	Se mantiene
Tarea de exploración de habilidades espaciales					
Mapas					
Comprensión	3/8	No aplica	5/8	No aplica	Mejora
Expresión	2/8		5/8		
Ánimo					
Inventario de depresión de Beck	31/63	Nivel de depresión severo	12/63	Nivel de depresión mínimo	Mejora

con el sitio de lesión, sino que deben ser analizadas a la luz de procesos propios de desarrollo y de cambios neuronales del cerebro.[2]

En este trabajo se presenta el caso de un joven de 19 años, quien presentó un EVC de tipo hemorrágico en ganglios basales a los 16 años y que como secuela presentó alteración en procesos atencionales, funcionamiento ejecutivo y en habilidades espaciales.

Se ha reportado que pacientes jóvenes con EVC presentan alteraciones recurrentes en la atención y funcionamiento ejecutivo, lo cual se ha explicado, porque al momento de la lesión, debido a que el cerebro aún se encuentra en desarrollo, los proce-

sos de mayor complejidad como el funcionamiento ejecutivo, que dependen de la maduración de la red frontoparietal,[8] aún se encuentran generalizados a diversas estructuras cerebrales, lo que implica que lesiones que normalmente en adultos no interfieren en estos procesos, sí se vean afectadas en niños y jóvenes,[4] y más aún, que la falla persista si no se lleva a cabo un proceso de RN que promueva la reorganización y optimización de las redes neuronales implicadas.[4,9]

Además, se ha reconocido la implicación de los ganglios basales en el óptimo funcionamiento de las funciones ejecutivas y la regulación atencional,[4] por lo que en este caso, la ausencia de un proceso de RN podría generar que la alteración cognitiva del paciente se mantenga de manera permanente, teniendo el riesgo de cronificarse, lo que podría implicar imposibilidad para la reintegración a sus actividades de la vida diaria.

En este sentido, un elemento altamente importante en los programas de RN es considerar la experiencia y el retorno a ambientes que sean estimulantes para el paciente.[10,11] En el caso descrito en este artículo, se promovió la incorporación a actividades de la vida diaria dentro de casa y en el contexto escolar, lo que, de acuerdo con lo reportado por Ismail y colegas,[10] promueve la maduración y creación de redes neuronales propias del desarrollo y de la fase de recuperación de la lesión.

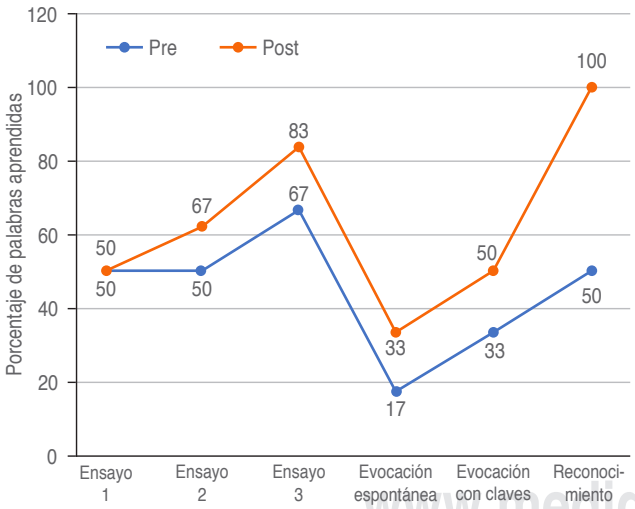

Figura 2: Comparativo entre la curva de aprendizaje en la lista de palabras pre- y postintervención.
La gráfica presenta el comparativo de las curvas de aprendizaje antes y después del programa de rehabilitación. Se identifica desempeño superior en todos los mecanismos de adquisición de información novedosa: registro (ensayos 1 a 3), evocación (espontáneo y por claves) y reconocimiento.

Dado el panorama del EVC en jóvenes, considerar la RN como parte de los programas de intervención para este tipo de paciente resulta necesario. Lo Coco y su equipo[12] han enfatizado en la importancia del trabajo multidisciplinario en el manejo de los pacientes post-EVC, pues éste permite el manejo exitoso de los factores de riesgo vascular, el óptimo manejo de la fase aguda y la generación de estrategias para mitigar las secuelas de la lesión que aumentan significativamente el costo de la atención y la utilización de los recursos de salud.[12]

Debe considerarse que actualmente las guías de práctica clínica y los programas de mejora de la calidad de vida de pacientes con lesión cerebral, recomiendan la evaluación y rehabilitación neuropsicológica.[13,14]

Zhao y colaboradores[14] reconocen la necesidad de considerar diferentes aspectos al evaluar los resultados de un programa de intervención, entre ellos: cambios clínicos en la función cognitiva general, cambios clínicos en función cognitiva de dominio específico, funcionalidad y calidad de vida. En el presente artículo se presenta evidencia de los efectos de la RN en los procesos cognitivos mayormente afectados, el estado anímico y el impacto en la funcionalidad.

CONCLUSIÓN

Debe considerarse que si el EVC ocurre en jóvenes cuando el sistema nervioso aún se encuentra en desarrollo, impone facilidades y retos que deben contemplarse dentro del proceso de intervención. La RN resulta un recurso terapéutico capaz de mejorar el estado cognitivo y anímico, lo que puede facilitar la reincorporación de los pacientes a sus actividades cotidianas y académicas.

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The role of non-coding RNAs in the pathogenesis of myotonic dystrophy type 1

El papel de los RNAs no-codificantes en la patogénesis de la distrofia miotónica tipo 1

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Palabras clave:
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Abstract

Myotonic dystrophy type 1 (DM1) is the most common muscular dystrophy in adults with a prevalence of 1/8,000 worldwide. DM1 is a multisystem disorder with a complex pathophysiology. Spliciopathy is the mechanism with the greatest impact on the pathogenesis and is also the most studied. However, other mechanisms like deregulation of non-coding RNAs (ncRNAs) have been described that contribute to the pathogenesis. ncRNAs, particularly miRNAs, participate in the development, differentiation, and regeneration of muscle tissue in DM1. The potential role of some miRNAs as DM1 biomarkers has been revealed from patient's serum studies. More recent studies, described antisense DM1 RNA, now classified as a lncRNA, with a potential role in the formation of siRNAs, chromatin modifying, and RAN translation mechanisms. Nonetheless, lncRNA have not been described in DM1, and it would therefore be interesting to investigate the role they play in this disease. It appears that ncRNAs play an important role in DM1, adding new elements to the previously described mechanisms, which improve our understanding of this complex disease, leaving still a lot to be discovered.

Resumen

La distrofia miotónica tipo 1 (DM1) es la distrofia muscular más común en adultos con una prevalencia de 1/8,000 a nivel mundial. La DM1 es un trastorno multisistémico con una patofisiología compleja. El procesamiento alternativo es el mecanismo con el mayor impacto en la patogénesis y el más estudiado actualmente. Sin embargo, se ha descrito que otros mecanismos como desregulación de RNAs no-codificantes (ncRNAs) contribuyen a la patogénesis. Los ncRNAs, particularmente miRNAs, participan en el desarrollo, diferenciación y regeneración del tejido muscular en DM1. El potencial papel de algunos miRNAs como biomarcadores de DM1 ha sido revelado a partir de estudios con suero de pacientes. Estudios más recientes describieron la presencia de RNA antisentido, ahora clasificados como lncRNA, con un potencial papel en la formación de siRNAs, modificador de la cromatina y mecanismos de traducción RAN. No obstante, lncRNAs no han sido descritos en DM1 y, por lo tanto, podría ser interesante la investigación del papel que juegan en esta enfermedad. Parece que ncRNAs juegan un papel importante en DM1, adicionando nuevos elementos a los mecanismos descritos previamente, lo cual mejora nuestro entendimiento de esta enfermedad compleja, dejando mucho aún por descubrir.

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INTRODUCTION

Expansions of unstable microsatellite sequence, notably trinucleotide repeats, were identified as a novel mutational mechanism underlying more than 30 human disorders, with neurological and neuromuscular symptoms, including myotonic dystrophy type 1 (DM1).[1,2]

DM1 is the most common muscular dystrophy in adults, with a prevalence of 1/8,000 worldwide,[3] inherited in an autosomal dominant pattern. It is caused by the expanded CTG repeats in the 3' untranslated region (3'UTR) of the dystrophia myotonica protein kinase gene (DMPK) located on chromosome 19q 13.3.

DM1 is a multisystem disorder with a complex pathophysiology;[4] the symptoms and clinical findings include myotonia, muscle wasting, cardiac conduction defects, central nervous system alterations, cataracts, and insulin resistance, among others, whereas in the congenital form of DM1, cognitive dysfunction and mental retardation have also been documented.[5]

The number of CTG repeats ranges between five and thirty-five in the normal population and increases between fifty and several thousand in DM1 patients.[5,6] At the molecular level, mutant RNA with expanded CTG repeats is retained in nuclear aggregates that sequester proteins such as muscleblind-like proteins (MBNL1, MBNL2 and MBNL3), and alter the function of specificity protein 1 (SP1) and retinoic acid receptor gamma (RARg), resulting in alternative splicing and transcription deregulation.[7-9] Spliciopathy is the mechanism with the greatest impact on the pathogenesis and is also the most studied. However, other mechanisms that contribute to the pathogenesis such as changes in gene expression, translation efficiency, misregulated alternative polyadenylation and deregulation of non-coding RNAs (ncRNAs) have been described.[10-24]

Regarding ncRNAs, it has been shown that they are critical in regulatory activity in normal cellular development, function, and pathogenesis. They have recently been described as having an important role in neurodegenerative disorders like Parkinson's disease, Huntington's disease, Alzheimer's disease and myotonic dystrophy.[25-28] ncRNAs are classified as small ncRNAs or long ncRNAs, according to their length. ncRNAs include microRNAs (miRNAs) from 19 to 24 bp, small nucleolar RNAs (snoRNAs) from 60 to 300 bp, PIWI interacting RNAs (piRNAs) from 26 to 31 bp, transcription initiation RNAs (tiRNAs) from 17 to 18 bp, promoter associated small RNAs (PASRs) from 22 to 200 bp, circular RNAs (circRNAs) with variable size and TSS associated RNAs (TSSa-RNAs) from 20 to 90 bp. Long noncoding RNAs (lncRNAs) are longer than 200 nucleotides and are a very heterogeneous group of molecules. They may be classified according to their genome localization and/or by their orientation (sense, antisense, bidirectional, intronic or intergenic lncRNAs).[29-31] In the following section, we address the most studied ncRNAs in relation to myotonic dystrophy.

miRNAs IN MYOTONIC DYSTROPHY

MicroRNAs (miRNAs) are endogenous small (21–23 nt in length) non-coding RNAs that control gene expression at the posttranscriptional level. They down-regulate gene expression by imperfect pairing with complementary sites within transcript sequences and suppress their translation, stimulate deadenylation and degradation, or induce target cleavage.

Given that DM1 has its principal symptoms at the level of skeletal muscle, studies tend to focus on muscle tissue. As a result, several changes in muscle-specific miRNAs (myo-miRNAs) have been reported for DM1. Myo-miRNAs regulate muscle function and adaptation during development (proliferation, differentiation, quiescence, regeneration) and disease.[20,32,33] In a recent study of biopsies of DM1 patients, a reduced expression of miRNA-1, miRNA-133a, and miRNA-133b was observed in the patients' muscle. Previous studies have proposed that miRNA-1 is a member of the group of «degenerative miRNAs» which may be mediators of cell death, contributing to apoptotic/necrotic myofiber loss. And they also found an overexpression of the considered «regenerative miRNA», miRNA-206, in DM1 muscle, as previously reported in DM1 and DMD.[14,23,34]

In a recent study, muscle-specific miRNAs were explored, which could be considered objective and circulating biomarkers of the efficacy of rehabilitation in DM1. Rehabilitation was used to counteract muscle atrophy and improve muscle function. In the study they have shown a significant downregulation of myo-miRNAs and myostatin after physical rehabilitation in parallel with the improvement of clinical functional tests. A significant downregulation of miR-1, miR-133a, miR-133b, and miR-206 after 12 weeks of endurance training and a decrement of miR-133a after strength training were observed. The results suggest that miR-1, miR-133a, miR-133b, miR-206, and myostatin

might be considered circulating objective biomarkers of rehabilitation efficacy in DM1, supporting the clinical outcome measures.[35]

In another study, it was shown that miR-1 and miR-335 were up-regulated whereas miR-29b, miR-29c and miR-33 were down-regulated in DM1 biopsies. Moreover, they found that potential miR-1 targets are significantly up-regulated due to a miR-1 subcellular localization which was severely disrupted, altering its function. miR-1 is a crucial regulator not only of myogenic differentiation, but also of muscle cell excitability. It is suggested that miR-1 plays an important role in DM1.[20]

An important molecule involved in myogenesis is Twist-1. Congenital DM1 cells which have a defective differentiation program have low levels of MyoD and miR-206 but high Twist-1 levels. Twist-1 is an important molecule involved in myogenesis, which belongs to the family of bHLH transcription factors. However, in mouse C2C12 myoblasts and in human embryonic stem cell (HESC)-derived embryoid bodies, Twist-1 is found to inhibit muscle cell differentiation. miR-206 is a negative regulator of Twist-1 and promotes muscle cell differentiation. Therefore, the MyoD -miR-206-Twist-1 pathway is compromised in DM1 cells that exhibit a defective differentiation program.[36,37]

In DM1, cardiac muscle is also affected, and several miRNA families are deregulated in patient heart tissues. It has been found that CUG exp RNA expression leads to an up-regulation of miR-21 and down-regulation of miR-29, miR-30 and miR-133 family members, and this study shows that tight reciprocal relationship between gain and loss of these miRNAs that target genes have a critical role in the core network in DM1 cardiac fibrosis. The miR-23a/b family regulates post-transcriptional loss of CELF1 protein during mouse postnatal heart development; reduced levels of miR-23a and miR-23b in DM1 heart tissue are expected to result in an overall increase in CELF1 protein levels, thus contributing to mis-regulation of CELF1 splicing targets. A select set of miRNAs in DM1, including miR-1, is down-regulated due to a reduced MEF2 transcriptional program. Mef2c is a transcriptional factor essential for direct reprogramming of cardiac fibroblasts into induced cardiomyocytes, and the loss of Mef2 activity causes deregulation of many miRNAs and mRNAs in a DM1 cardiac cell (culture model) and heart tissue (mouse model).[12,38]

At the molecular level, one of the best-characterized trans-dominant effects induced by the CUGexp-RNAs in DM1 is the mis-regulation of alternative splicing of a subset of premRNAs. More recently, Charlet's team has described a novel function of the RNA binding protein MBNL1 as a regulator of the microRNA miR-1 biogenesis. A Predictive bioinformatic analysis indicates that pre-miR-1 have potential MBNL1 binding site. Based on this observation, a miRNome analysis of human muscle cells showed a significant alteration of miR-1 expression in DM1 cells. MBNL1 binds to a UGC motif located within the loop of pre-miR-1 and competes for the binding of LIN28, which promotes pre-miR-1 uridylation by TUT4 and blocks dicer processing.[14,21] Consequently, miR-1 loss in the heart causes increased expression of connexin 43 and CACNA1C, as they are targets of miR-1. CACNA1C and connexin 43 encode the main calcium-and gap-junction channels in heart, respectively, and their mis-regulation could contribute to cardiac dysfunction, such as conduction defect observed in the DM1 patients.

Recently, microRNAs have been found to be present at significant levels in extracellular body fluids, including blood serum and plasma. Perfetti et al. identified a signature of nine deregulated miRNAs in plasma samples of DM1 patients and suggested that these miRNAs can be used as diagnostic biomarkers for DM1, and the muscle-specific miR-133a was included in these miRNAs.[19] In another study the muscle-specific miRNAs miR-1, miR-133a, miR-133b and miR-206 were detected in the sera isolated from DM1 patients and their levels were found to be significantly higher in progressive DM1 patients compared to non-progressive DM1 patients; this implies that these muscle-specific miRNAs presumably leak from the degraded muscle tissue during muscle wasting and enter the blood circulation of the patient. However, the increase in the serum levels of myomiRNAs observed in DM1 patients was not correlated with disease severity.[23]

Prior to these studies, deregulated plasma miRNAs in DM1 were validated. They confirmed that 8 miRNAs out of 12 were significantly deregulated in DM1 patients, including non-muscle specific miRNAs, namely miR-140, -27b, -454 and 574; indeed, since DM1 is a multisystemic disorder, it is possible that the tissue of origin of these miRNAs might not be the skeletal muscle.[39] However, a more recent study in serum, shows that only miR-21 had a significantly different expression between controls and patients. This study took previously reported miRNAs into account and there were discrepancies in the results, which can be attributed to the statistical methods or

differences in the experimental procedures used in each study.[40] Therefore, it is necessary to carry out more studies regarding the deregulation of miRNAs in patient serum due to their potential importance as biomarkers.

Regarding therapeutic studies involving miRNAs in DM1, a recent study performed in a Drosophila model focused on silencing specific miRNAs and regulating the expression of muscleblind and demonstrated that the silencing of miR-277 or miR-304 in muscle using sponge constructs achieved muscleblind upregulation, which was sufficient to rescue characteristic DM1 model phenotypes such as missplicing events, reduced lifespan, and muscle atrophy.[41] A summary of deregulated miRNAs in DM1 is showed in *Table 1*.

A study of transcriptome in an inducible glial cell model for DM1, the MIO-M1 $CTG_{(648)}$ cells, revealed for the first time a dysregulated levels of miRNAs and lncRNAs in central nervous system.[42] Except for miR-222 in muscle,[43] the deregulated miRNAs found in this study had not been previously reported in DM1. An analysis revealed an involvement of the altered miRNAs in processes with relevance to CNS function, specifically in nervous system development.

The deregulated expression of miR-4288, miR-222, miR103, miR-298 and miR-448 found in the DM1 model is shared with other neurodegenerative conditions such as Alzheimer's disease (AD) and Huntington's disease (HD).[44-47] CELF3 was identified as a miR-298 target, while CELF5 and CELF6 were both predicted as miR-448 targets. MBNL1 was revealed as one of the predicted miR-4288 targets. Considering the central role playing by MBNL and CELF proteins in the DM1 pathogenic mechanism, further studies are required to explore the functional consequences of the indicated dysregulated miRNAs. The ontological analysis also revealed a regulation of the immune/inflammatory response mediated by miRNAs in MIO-M1 $CTG_{(648)}$ cells.[42]

LncRNAs IN DM1

The deregulation of lncRNAs in DM1 has not yet been studied. Recent studies have demonstrated the importance of lncRNAs in various pathologies, including neuromuscular diseases.[25] However, a recent study classifies an antisense transcript from the DM1 locus as an lncRNA. A previous study performed by Tapscott and coworkers was the first to report that there is an antisense transcription emanating from the adjacent SIX5 regulatory region that extends into the insulator element and is converted into 21 nucleotides. The authors suggest that it is involved in local modifications of chromatin.[5]

However, a recent study by Gudde et al. shows that transcripts of this antisense (DM1-AS) occur as very low-abundance RNAs of different lengths.[18] This antisense transcript contains alternative polyadenylation sites, and alternative splicing may remove the (CAG)n repeat from the longer DM1-AS RNAs. The results of this study indicate that DM1-AS RNAs are produced extending downstream from the insulator element formed by the CTCF-binding sites. Bioinformatics analysis and RT-qPCR approaches have shown that DM1-AS transcripts are produced in essentially all cell types and tissues. Despite a mild increase in DM1-AS expression in patients, the findings indicate that DM1-AS transcripts occur roughly 5–50-fold less frequently than DMPK mRNA molecules, with variation in this ratio dependent on cell or tissue type.

The extremely low expression of these transcripts has important implications for the function of DM1-AS RNA and for its potential contribution to DM1 pathology. Presence of expanded DM1-AS RNA in the nucleus and in the cytoplasm would allow involvement in the formation of toxic nuclear RNP aggregates and in the generation of RAN translation products in the cytoplasm. RNP foci containing expanded (CAG)n RNA have indeed been reported for DM1 cells. Homopolymeric RAN peptides, which could be formed from DM1-AS RNA with expanded (CAG)n tracts, may exert proteotoxicity at a very low concentration, like formation of abnormally aggregated protein complexes around prion-protein cores in only some cells in a tissue population. This study also proposes that DM1-AS RNAs could engage in formation of dsRNA molecules by hybridization to complementary sequences in *DMPK* transcripts. Such an event might trigger toxic dsRNA-responsive kinase signaling with possible immune effects or abnormal effects of aberrant repeat-containing siRNA, formed after DICER processing of the dsRNA.

Another theory is that DM1-AS transcripts may play a structural role in local chromatin organization in the DM1 locus in the nucleus. Given the evidence from their previously mentioned work, Gudde et al. conclude that primary and processed DM1-AS transcripts belong to the heterogeneous class of lncRNAs, because they share many signatures with this type of RNA. lncRNAs, like mRNAs, may be subject to posttranscriptional

processing, including capping, polyadenylation and splicing. Despite their naming, it has now become clear that at least some lncRNAs still do encompass an ORF and can undergo translation.[18,48-51]

In an inducible glial cell model for DM1, the MIO-M1 $CTG_{(648)}$ cells, previously mentioned they found dysregulated levels of lncRNAs. However, the role these ncRNAs play in the pathogenesis of DM1 is still unknown.[42]

siRNAs IN DM1

siRNA is derived from long double-stranded RNA molecules (including RNAs arising from virus replication, transposon activity or gene transcription), which can be cut by the DICER enzyme into RNA fragments of 19-24 nt, with the resulting RNA fragments exercising their functions when loaded onto Argonaute (AGO) proteins *(Figure 1)*. Recent studies showed that siRNA can lead to transcriptional gene silencing in cells by means of DNA methylation and histone modification in cells.[16,27,52-54]

The previously mentioned study by Cho, et al. found that the antisense transcription of the DM1 locus can be converted into 21 nucleotide fragments (siRNAs) that recruit histone methyltransferases, HP1, and DNA methyltransferases, with associated conversion of the region to heterochromatin. In a

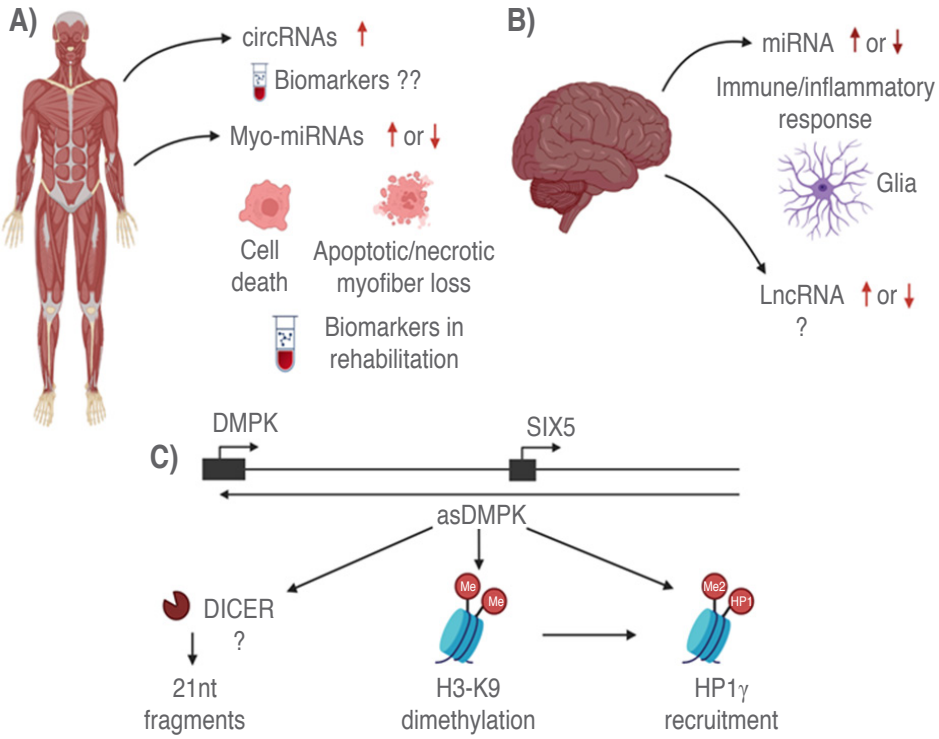

Figure 1: A) Interestingly, upregulated circRNAs have been reported in muscle from DM1 patients, however, require more comprehensive analyses in order to determine whether circRNAs are reliable biomarkers and could be used for prognosis and as therapeutic agents and targets in DM1. The dysregulation of muscle-specific miRNAs (Myo-miRNAs) in DM1, opens the possibility of using these ncRNAs as biomarkers of rehabilitation, or indicators of cell death, apoptotic/necrotic or myofiber loss. **B)** ncRNAs play a very important role at the CNS level. In a glia DM1 model, the dysregulation of miRNAs that may be involved in the immune/inflammatory response has been described. Dysregulation in the levels of lncRNAs was also reported, although the role of these lncRNAs in glia has not been described. **C)** Model described by Cho, et al. where in the WT allele is associated with bidirectional transcription (forming an antisense RNA, asDMPK), the formation of 21nt RNA fragments (possibly mediated by DICER), H3-K9 dimethylation and recruitment of HP1g in the region of CTG repeats. This mechanism suggests local modifications of chromatin, mediated by siRNAs.

Table 1: miRNAs and circRNAs deregulated in DM1.

Sample	Reporter changes	Method	Comments	References
Human muscle biopsies from the vastus lateralis	Up: miR-206	RT-qPCR	Seven unrelated patients, aged 30-50 years	Gambardella, et al. (2010)[61]
Human muscle biopsies from the vastus lateralis	Up: miR-206 Down: miR-1, miR-133a, miR-133b	RT-qPCR	Twelve unrelated patients, aged 19-52 years	Fritegotto, et al. (2017)[22]
Human muscle biopsies from biceps	Up: miR-1, miR-335 Down: miR-29b, miR-29c, miR-33	RT-qPCR	Fifteen unrelated patients, aged 38 ± 17 years	Perbellini, et al. (2011)[20]
Serum	Up: miR-1, miR-133a, miR-133b, miR-206	RT-qPCR	Twenty-three patients	Koutsoulidou, et al. (2015)[23]
Plasma (validation)	Up: miR-1, miR-133a, miR-133b, miR-206, miR-140-3p, miR-574, miR-454 Down: miR-27b	RT-qPCR	One hundred three patients, aged 44.1 ± 1.3 years	Perfetti, et al. (2016)[39]
Serum (validation)	None (validation)	RT-qPCR	Twenty-six patients, aged 26-61 years	Fernández-Costa, et al. (2016)[40]
Drosophila i(CTG)480 transgenic line Human skeletal muscle biopsies (biceps, vastus and deltoid)	Up: one miRNA Down: nineteen miRNAs Down: miR-1, miR-7, miR-10a	SOLiD™ 3 sequencing	Deregulation of miR-1, miR-7 (given their conservation in humans) Five patients, aged 47 ± 5 years	Fernández-Costa, et al. (2013)[13]
Mouse model (EpA960; MCM) Human heart tissues	Postnatal down: miR-23a, miR-23b Deregulated: 54 miRNAs Down: twenty miRNAs	RT-qPCR	Eight patients, aged 26-55 years	Kalsotra, et al. (2014)[12]
Human heart left ventricles samples	Down: miR-1	RT-qPCR	Eight adults	Rau, et al. (2011)[14]
Human muscle biopsies from the biceps brachii	Up: miR-208a, miR-381 Down: miR-193b-3p	Gene chip human exon 1.0 ST array (Affymetrix)	miRNAs validated in DM2 were also tested in an age-and sex-matched cohort of DM1 patients	Greco, et al. (2012)[62]
Myoblast cell lines, muscle biopsy and samples from the *HSA*^{LR} transgenic mouse model	Increase of circRNAs level	Next generation sequencing	Human cell lines three DM1 and controls. Human muscle biopsies five DM1 and six controls. Mouse muscles ten DM1 and ten controls	Czubak, et al. (2019)[59]
Muscle tissue biopsies, myogenic cell lines	Increased circular fraction: CDYL, HPK3, RTN4_03 and ZNF609	RNA seq	Muscle tissue biopsies from biceps brachii of 30 DM1 and 29 sex- and age-matched control individuals	Voellenkle, et al. (2019)[60]
Inducible glial cell model (MIO-M1-CTG(648) cells)	111 deregulated genes; 9.1% of ncRNAS	Clariom D Arrays for human samples	Four experimental groups, 3 biological replicates	Azotla-Vilchis CN, et al. (2021)[42]

more recent study that aimed to define the potential effects of bi-directional transcription, expanded CAG repeat transcripts were co-expressed with the DM1 CTG repeats. This resulted in dramatically enhanced toxicity concomitant with the generation of triplet repeat-derived siRNAs. Both CAG and CUG strands can be processed into ~21 nt small RNAs when co-expressed and small RNAs derived from both strands are methylated in a *Hen1*-dependent manner. These results suggest that both CAG and CUG small RNAs can be loaded into mature, holo-RISCs presumably due to the symmetrical thermodynamic properties of the repeat small RNA duplex. This study confirms that two CAG containing genes, *atx2* and *tbp* are targets of the triplet repeat-derived siRNAs. These results suggest that bi-directional transcription of the repeat region in diseases like DM1 may confer additional components of pathogenicity due to deleterious interactions between the two-overlapping repeat-containing transcripts through the generation and activity of triplet repeat-derived siRNAs. These effects may include downregulating the expression of other genes containing CAG repeats. This suggests that both expanded CAG and CTG are required for triplet repeat-derived siRNA generation and toxicity *in vivo*.[16,55]

circRNAs IN DM1

circRNAs are single stranded circularized molecules which are mainly generated from the precursor mRNA backsplicing process.[56] Recently, strict tissue, cell, developmental, and age expression specificity has been demonstrated for several circRNAs, supporting the hypothesis that these transcripts are of functional importance. The biology and function of most circRNAs are still poorly recognized, but it is becoming increasingly clear that specific circular RNAs function as sponges for miRNAs and proteins, affecting RNA splicing and regulating transcription.[57] A recent study tested the hypothesis of circRNAs downregulation in DM1, known to be a burden with functional deficiency of MBNL proteins and dysregulation of alternative splicing.[58] Czubak et al., selected 20 validated circRNAs and analyzed their expression levels in several experimental systems, including human myoblast cultures and skeletal muscle biopsy samples from patients and healthy individuals. In addition, they used muscles from the HAS transgenic mouse model of DM1. However, they found no downregulation of the analyzed circRNAs in DM1 samples compared with those in non-DM1 samples. Therefore, these results question the role of MBNL proteins in circRNA biogenesis in muscles. Interestingly they discovered a consistent increase in circRNA levels.[59] The obtained data in this study do not confirm the hypothesis regarding the link between MBNL sequestration and disrupted circRNA biogenesis in DM1, but do not exclude the possibility of the existence of individual circRNAs that are regulated by MBNLs. An increased level of circRNAs in DM1 skeletal muscle has also most recently been reported in another study by Voellenkle et al *(Table 1)*.[58-60]

The most recent studies, which identified upregulation of circRNAs in DM1 patients' skeletal muscles, require more comprehensive analyses in order to determine whether circRNAs are reliable biomarkers and could be used for prognosis and as therapeutic agents and targets in DM1.[58] However, the role of individual circRNAs altered in DM1 and their global function in DM1 pathogenesis remain to be determined.

CONCLUSIONS

ncRNAs play important roles in healthy and disease tissues. It has been found that ncRNAs, particularly miRNAs, participate in the development, differentiation, and regeneration of muscle tissue in DM1. The potential role of some miRNAs as DM1 biomarkers has been revealed from serum patient's studies. More recent studies have illuminated the more detailed role of the initially described antisense DM1 RNA, now classified as a lncRNA, with a potential role in the formation of siRNAs, chromatin modifying and RAN translation mechanisms.

Nonetheless, lncRNA have not been described in DM1, and it would therefore be interesting to investigate the role they play in this disease.

It is important to mention the importance that ncRNAs can have as therapeutic targets, as it has been observed that their modulation can reverse some phenotypic traits of the disease, and an understanding of the mechanisms that involve ncRNAs can provide more candidates for genic therapies.

It appears that ncRNAs play an important role in DM1, adding new elements to the previously described mechanisms, that improve our understanding of this complex disease, leaving much to still be discovered.

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Conflict of interests: It is declared that there is no conflict of interest with any of the authors.

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Vol. 8, Núm. 1
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- ☐ El título de las revistas periódicas debe ser abreviado de acuerdo al Catálogo de la National Library of Medicine (NLM): disponible en: http://www.ncbi.nlm.nih.gov/nlmcatalog/journals (accesado Dic/2021). Se debe contar con información completa de cada referencia, que incluye: título del artículo, título de la revista abreviado, año, volumen y páginas inicial y final. Cuando se trate de más de seis autores, deben enlistarse los seis primeros y agregar la abreviatura et al.

Ejemplos, artículo de publicaciones periódicas, hasta con seis autores:

Torres-Rodríguez ST, Herrera-Cruz D, López-Yepes L, Lainfiesta-Moncada E. Biopsia pulmonar por minitoracotomía. ¿Es necesario el drenaje pleural? Neumol Cir Torax 2019; 78 (2): 133-138.

Siete o más autores:

Flores-Ramírez R, Argüello-Bolaños J, González-Perales K, Gallardo-Soberanis JR, Medina-Viramontes ME, Pozos-Cortés KP et al. Neumonitis lúpica: manejo con oxigenoterapia de alto flujo y posición prono. Reporte de caso y revisión de la literatura. Neumol Cir Torax 2019; 78 (2): 146-151.

Libros, anotar edición cuando no sea la primera:

Broaddus VC, Mason RJ, Ernst JD, King TE Jr., Lazarus SC, Murray JF, Nadel JA, Slutsky AS (eds). Murray & Nadel's textbook of respiratory medicine. 6th ed. Philadelphia, PA: Saunders Elsevier; 2016.

Capítulos de libros:

Gutierrez CJ, Marom EM, Erasmus JJ, Patz EF Jr. Radiologic imaging of thoracic abnormalities. In: Sellke FW, Del Nido PJ, Swanson SJ. Sabiston & Spencer surgery of the chest. 8th ed. Philadelphia, PA: Saunders Elsevier; 2010. p 25-37.

Para más ejemplos de formatos de las referencias, los autores deben consultar:

https://www.nlm.nih.gov/bsd/policy/cit_format.html (accesado Dic/2021).

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- ☐ La información que contengan no se repite en el texto o en las figuras. Como máximo se aceptan 50 por ciento más uno del total de páginas del texto.
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☐ Cada una estará numerada de acuerdo con el número que se le asignó en el texto del artículo.

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