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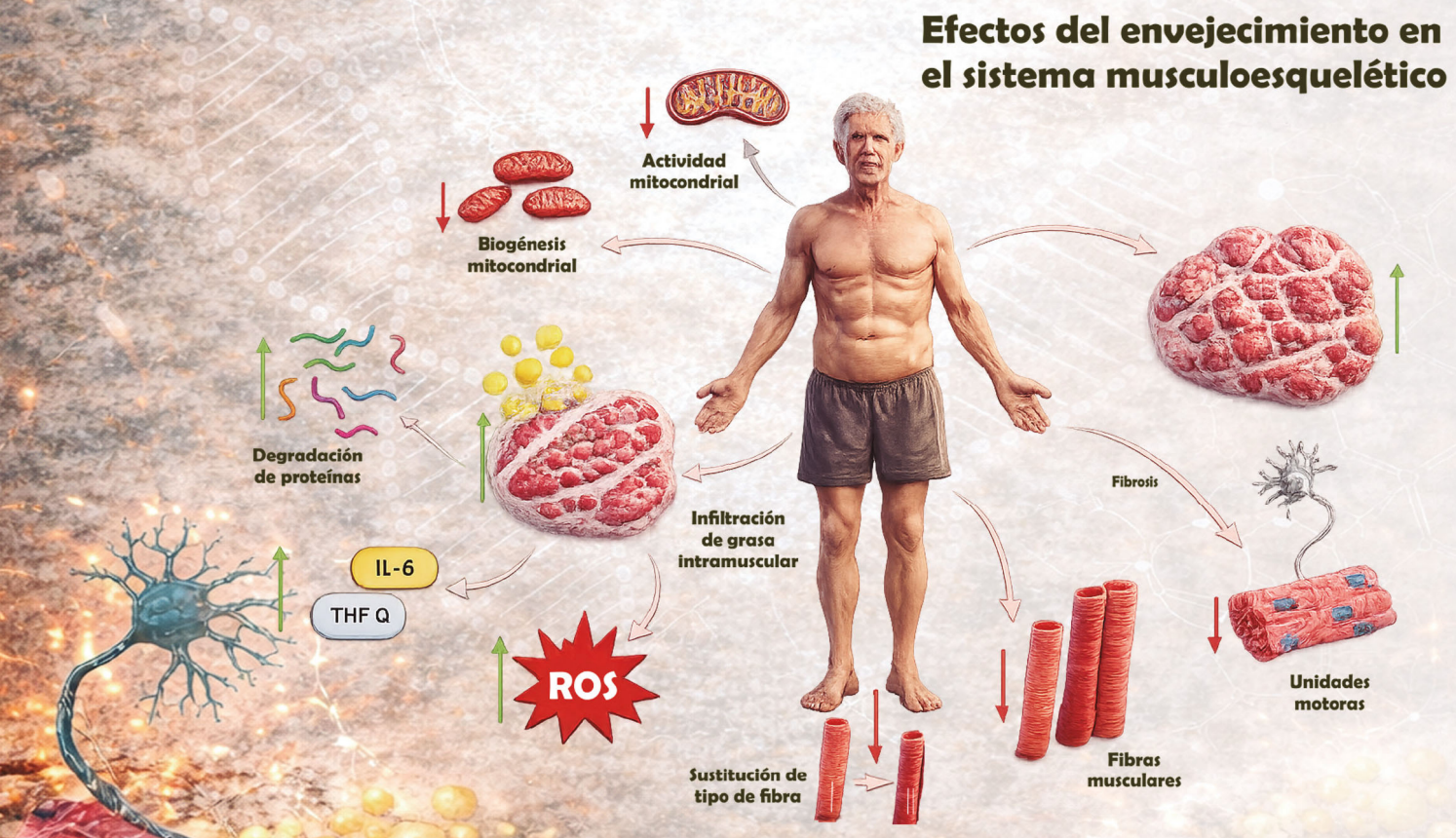

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INVESTIGACIÓN en DISCAPACIDAD

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ORIGINAL ARTICLE

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Analysis of the giant cell tumor cell line of bone TIB 223 on the effect of quercetin

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Abstract

The uncontrolled and inappropriate growth of cells in the body is known as cancer. Giant Cell Tumor of Bone (GCTB) is a neoplasm with an aggressive behavior that, when it metastasizes, particularly manifests in the lungs. This study aimed to conduct a preliminary assessment of the activation of apoptosis as a cell death mechanism induced by quercetin TIB 223 cells. For this purpose, messenger RNA levels and the expression of proteins related to this pathway were analyzed. The TIB 223 cells were treated with two different concentrations of quercetin (91.1 µM and 220 µM). A flow cytometry analysis was performed to evaluate the expression of caspase-3 and Proliferating Cell Nuclear Antigen (PCNA) proteins. Quantitative Polymerase Chain Reaction (qPCR) analysis was performed to evaluate changes in the expression of genes regulating apoptosis (caspase-3) and proliferation (PCNA) after treatment. Flow cytometry analysis revealed a decrease in PCNA levels, indicating increased apoptosis and reduced proliferation, suggesting that quercetin effectively induces apoptotic pathways in GCTB cells. These results provide insight into the molecular mechanisms behind the anticancer activity of quercetin, highlighting its potential as a therapeutic agent for metastatic GCTB cells. We conclude that quercetin has the potential to be used in the future as a concomitant therapy alongside standard treatments to prevent the recurrence of GCTH tumors, either at the primary tumor site or in metastatic lesions.

Abbreviations:
CIPN = Chemotherapy-Induced Peripheral Neuropathy
GCTB = Giant Cell Tumor of Bone
PCNA = Proliferating Cell Nuclear Antigen
PSB = Phosphate Buffered Saline
qPCR = Quantitative Polymerase Chain Reaction

INTRODUCTION

The uncontrolled and inappropriate growth of cells in a tissue of the body is known as cancer. These cells threaten the normal function of organs and other cells. In more advanced cases, they travel through the bloodstream to reach different areas of the human body.[1]

A bone tumor is a proliferation of cells within the bones. This proliferation is abnormal and can be cancerous, either malignant or benign. Its cause is

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unknown; however, it is associated with various factors such as hereditary genetic abnormalities, radiation, and injuries.[2]

Giant Cell Tumors of Bone (GCTB) are aggressive neoplasms that arises from osteoclasts. They exhibit abundant vascularization with giant cells, are rare and develop when benign cells cluster together to form a large mass. These giant cells can spread to different parts of the body and become aggressively proliferating tumors.[3]

Beyond its biological aggressiveness, GCTB imposes a substantial disability burden that is increasingly recognized in clinical and epidemiological studies. Giant cell tumors frequently compromise structural bone integrity, leading to pain, functional limitations, and motor disability, largely due to cortical bone destruction and a high incidence of pathological fractures. Skeletal complications such as fractures, spinal cord compression and the need for orthopedic surgery are among the major sources of disability in bone tumors and bone metastases, often resulting in long-term mobility impairment and reduced independence in activities of daily living.[4,5]

Epidemiological analyses show that patients with bone tumors or skeletal metastatic disease experience significantly higher rates of mobility restriction, need for assistive devices, reduced quality of life, and greater dependence on healthcare resources compared with cancer patients without bone involvement.[6] In addition, conventional treatments used for GCTB such as repeated curettage, aggressive bone resections, radiotherapy, and systemic therapies can lead to persistent sequelae including chronic pain, neuropathy, fatigue, and limited joint function, all of which contribute to long-term disability.[7,8] Consequently, there is a growing interest in therapeutic strategies that may reduce both tumor burden and treatment-related morbidity, ultimately improving functional outcomes and reducing disability in affected patients.[8]

Metastasis originates when cells from the primary tumor travel through the body and begin to form a new tumor, either in the organs or tissues. Pulmonary metastasis is a neoplasm of various localizations that metastasize to the lungs. Generally, it does not cause symptoms, and when symptoms do occur, they are usually seen in advanced stages. There are several potential pathways through which neoplastic cells settle in the pulmonary parenchyma, including venous circulation, lymphatic circulation, direct extension, and bronchogenic dissemination.[9]

The most common oncological treatment for metastatic giant cell tumors is complete pulmonary resection with systematic lymph node dissection, which involves the anatomical resection of the lobes affected by the tumor. Other treatment modalities include chemotherapy, aimed at reducing or eliminating tumors through the use of pharmacological agents, and radiation therapy, which involves the administration of high-intensity radiation to eradicate tumors. Additionally, targeted therapy, which involves the use of specific medications to inhibit the growth of cancerous cells is employed. However, the side effects of these treatments may include peripheral neuropathy, arrhythmias, pulmonary inflammation or inflammation in other parts of the body, and hepatic damage.[3]

Currently, there are various alternative therapies, including combination therapies such as chemotherapy combined with hormone therapy. Hormone therapy involves the addition, blockade, or removal of hormones that are responsible for the initiation of certain types of cancer. Quercetin, a flavonoid found in various plant-based foods, is currently used in the treatment of certain allergies, asthma, and various types of cancer, including pancreatic, breast, ovarian, liver, glioblastoma, prostate, and lung cancers (primarily in experimental animal models). The described mechanism of action of quercetin in cancer involves inhibiting the growth of cancer cells both *in vitro* and in animal models, with its effects being implicated in apoptosis.[10,11]

To date, the cytotoxic activity of quercetin on isolated GCTB cells (TIB 223) derived from pulmonary metastases has not been described in depth. Therefore, the aim of this study was to conduct a preliminary assessment through messenger RNA analysis, as well as the expression of proteins related to cellular apoptosis, to determine if it is activated as a cell death mechanism in TIB 223 cells after being exposed to quercetin. Thus, the results generated will allow for further deepening the knowledge regarding the cell death model we are studying.

MATERIAL AND METHODS

Cell culture

The TIB 223 cell line of giant cell tumor was isolated from the lung of a male patient with fibrous histiocytoma, they were obtained from the *American Type Culture Collection* (Rockville, MD, USA). The cells

were cultured with culture medium (Corning McCoy's 5A [Iwakata & Grace modification]), the cells were cultured with 10% fetal bovine serum and 1% antibiotic-antimycotic in controlled humidity and temperature conditions. They were expanded in 150 cm² flasks, and once expanded, the cells were detached and aliquots of one million cells were frozen in cryovials in liquid nitrogen until further use. In a previous study conducted by our research group, it was established that quercetin-induced cell death was observed at 24 hours with an IC_{50} of 91.1 μM of quercetin.[12]

Flow Cytometry analysis

For this experiment, the previously established IC_{50} of 91.1 μM of quercetin was used. A slightly higher dose, more than twice the IC_{50}, corresponding to 220 μM, was also used.[12] The cells were cultured for approximately two months, the culture mean was changed every second day during those two months, after this period of time, quercetin was added and the cells were cultured again, once the time had passed to see the effect the culture mean was removed, all the plates were washed whit phosphate buffered saline (PBS). The phosphate buffered saline was removed and the cells, following aspiration of PBS, cells were mechanically detached using a cell scraper in fresh PBS. The cell suspension was transferred to a 1.5 mL microcentrifuge tube and centrifuged at 1,500 rpm for 20 minutes at 4 ºC. Upon completion of centrifugation, the PBS supernatant was removed while preserving the cell pellet, which was subsequently stored in frozen conditions.

After 24 hours of exposure to TIB 223 cells, 2 mL of medium was extracted from each dish to initiate trypsinization. One milliliter of trypsin was added to each dish, and they were immediately placed in an orbital incubator to detach the cells. This process was carried out for five minutes at 150 rpm at 38 ºC. Upon completion, the remaining medium from each dish was added, and the samples were centrifuged. Subsequently, 1 mL of the permeabilizing agent obtained from BD Biosciences (Cat: 554722, San José, CA, USA), was added to each dish, followed by 20 minutes of refrigeration. After the incubation period, the supernatant was decanted, and 600 μL of the washing solution was added. Following this step, 1 μL of each antibody, 1 μL of caspase-3 for the corresponding dishes, and 1 μL of Proliferating Cell Nuclear Antigen (PCNA) for the corresponding dishes were added, and the samples were refrigerated.

For flow cytometry analysis, 1 μL of washing with PBS were added to each sample before being placed in the cytometer for analysis.

Quantitative Polymerase Chain Reaction (qPCR) Analysis

Following treatment with two different concentrations of quercetin (91.1 and 220 μM), incubation was conducted for 24 hours. For relative qPCR, previously collected cells stored at -80 ºC were thawed, and total RNA extraction was performed using Trizol reagent (Invitrogen, Carlsbad, California, USA). Subsequently, cDNA was synthesized using 1 μg of total RNA and kit reagents. For qPCR implementation, the reagents listed in *(Table 1)* were utilized.

The equipment was then programmed through four stages: the first stage consisted of one cycle at 42 ºC for 15 minutes, followed by a second stage comprising another cycle at 95 ºC for 3 minutes. The third stage included 40 cycles with the following temperatures: 15 seconds at 95 ºC, 30 seconds at 57 and/or 60 ºC, and the final stage consisted of the Melting analysis. All samples were analyzed in triplicate to ensure reproducibility of results. Finally, relative mRNA

Table 1: Genes used in quantitative polymerase chain reaction, considering the RPL27 gene as constitutive.

Gen	Forward	Reverse
HRPL27	CTGGGAAGGTGGTGCTTGTC	TAGCGGTCAATTCCAGCCAC
Caspase 8	ATTTGCCTGTATGCCCGAGC	CCTGAGTGAGTCTGATCCACAC
Caspase 3	AGAGGGATCGTTGTAGAAGTC	ACAGTCCAGTTCTGTACCACG
PCNA	CCTGCTGGGATATTTAGCTCCA	CAGCGGTAGGTGTCGAAAGC
RIP1K	TGGGGCTCATCATAGAGGAAG	TGGCCTTGGTGAGGTTTGATCC
VEGFA	ATGAACTTTCTGCTGTCTTGGGT	TGGCCTTGGTGAGGTTTGATCC
SNHG6	CTCTGCCGAGGTGCAAGAAAG	AATACATGCCGCGTGATCCT

quantification was determined using the ΔΔCT (delta delta CT) method.

Statistical analysis

All experiments were performed in biological triplicates, and each analytical technique was carried out under identical experimental conditions to ensure reproducibility. Statistical analyses were performed using GraphPad Prism version 9.5.0 (GraphPad Software, San Diego, CA, USA).

For the flow cytometry assays, the percentage of positive cells for each marker (caspase-3 and PCNA) was quantified for the control, 91.1 μM quercetin, and 220 μM quercetin conditions. Because the three experimental groups consisted of independent samples, comparisons between groups were conducted using an unpaired two-tailed t-test. Each treatment concentration was compared independently against the control group to determine whether quercetin induced statistically significant changes in marker expression. In addition, a direct comparison was performed between the 91.1 and 220 μM groups to evaluate whether increasing the concentration produced additional significant effects.

For qPCR analysis, relative gene expression levels were calculated using the 2-ΔΔCT method, using RPL27 as the reference housekeeping gene. Each gene was analyzed in triplicate reactions, and the resulting fold-change values were compared across the three conditions. As with the flow cytometry data, unpaired two-tailed t-tests were used to identify significant differences in expression between the control and each quercetin concentration. Genes analyzed included caspase-3, caspase-8, PCNA, RIPK1, SNHG6, and VEGFA. Only genes with statistically significant differential expression in at least one of the treatment groups were considered biologically relevant. For all analyses, p-values < 0.05 were considered statistically significant.

RESULTS

The following are observations of morphological changes after 24 hours of treatment. These cells exhibit a morphology similar to that of fibroblasts *(Figure 1A-C)*.

Flow cytometry analysis at 24 hours of treatment

Flow cytometry analysis at 24 hours showed that the control had a mean expression of positive cells for the caspase 3 marker of 0.42 ± 0.11%, while for the 91.1 μM concentration, the mean expression for the marker was 93.77 ± 2.61%, and finally for the 220 μM concentration was 95.40 ± 2.75% *(Figure 1 D-E)*. Upon analysis, statistically significant differences were found between both conditions and the control ($p \leq 0.0001$ for 91.1 μM and $p \leq 0.0001$ for 220 μM); however, no significant difference was found between the two treatment concentrations ($p = 0.47$) *(Figure 1F)*.

On the other hand, for PCNA, flow cytometry analysis at 24 hours showed that the control had a mean expression of positive cells for the caspase 3 marker of 23.48 ± 4.14%, while for the 91.1 μM concentration, the mean expression for the marker was 1.56 ± 1.37%, and finally for the 220 μM concentration was 6.17 ± 0.06% *(Figure 1G-H)*. Upon analysis, statistically significant differences were found between both conditions and the control ($p \leq 0.0010$ for 91.1 μM and $p \leq 0.0006$ for 220 μM); however, no significant difference was found between the two treatment concentrations ($p = 0.15$) *(Figure 1I)*.

qPCR analysis

The control yielded an average RNA of 1.6, the 91.1 μM concentration yielded an average of 2.1, and the 220 μM concentration yielded an average of 12.92. The average RNA was adjusted from 1.4 to 10 μL. Similarly, we can observe the quantities used in the mix for performing qPCR. Notably, the same quantities of the mix were used throughout, while the RNA varied for each concentration and control. In the following figure, we can observe the different genes used in qPCR at 24 hours of treatment with 91.1 and 220 μM concentrations.

From these graphs, we can observe that PCNA, caspase 3, and the SNHG6 gene proved to be significant. However, we can observe that there was an increase for caspase 8, although it did not reach significance, and for the remaining genes, RIPK1 and VEGFA, we can observe that there was no significance whatsoever *(Figure 2)*.

DISCUSSION

This study demonstrated the effect of quercetin on cell death and proliferation in the giant cell tumor line TIB 223. Several in vitro studies have shown that quercetin can inhibit proliferation and induce apoptosis in different types of cancer cells, such as breast, lung, colon, prostate cancer, and leukemia.[13]

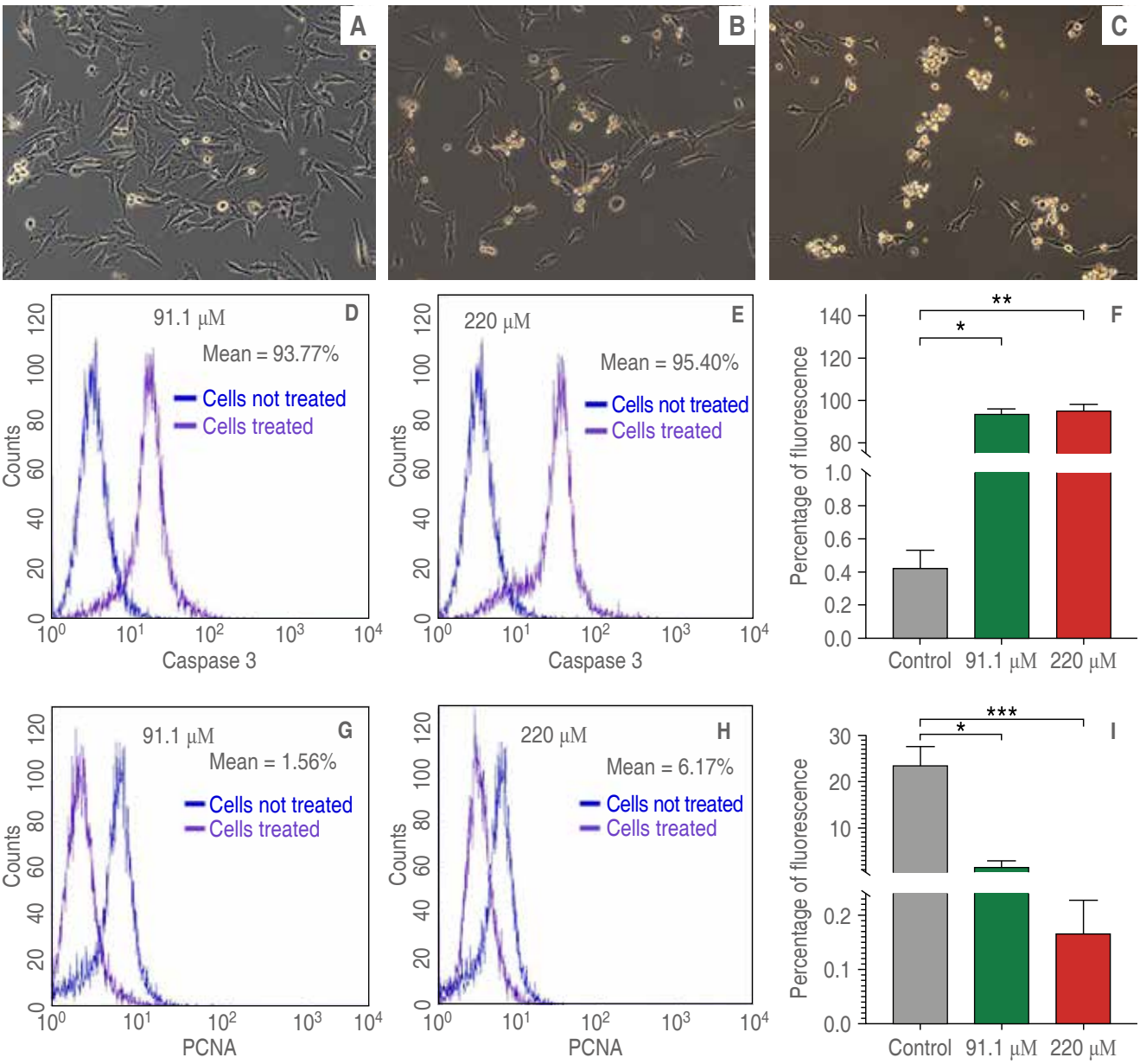

Figure 1: Morphological and flow cytometry analysis of TIB-223 cells after 24 hours of quercetin treatment. **A-C)** Bright-field micrographs showing morphological changes of TIB-223 cells after 24 hours. **(A)** Untreated control cells display an elongated, fibroblast-like morphology. **(B)** Cells treated with 91.1 µM quercetin show early signs of rounding and loss of adherence. **(C)** Cells treated with 220 µM quercetin exhibit marked cytoplasmic retraction, clustering, and increased detachment, consistent with apoptotic morphology. **(D-F)** Caspase-3 expression assessed by flow cytometry. In the histograms **(D-E)**, the lilac line represents untreated control cells, whereas the blue line represents quercetin-treated cells. A strong shift in fluorescence intensity indicates increased caspase-3 activation. Treatment with 91.1 µM resulted in 93.77% ± 2.61 caspase-3-positive cells, while 220 µM produced 95.40% ± 2.75, compared with only 0.42% ± 0.11 in the control. Statistical analysis **(F)** showed both concentrations were significantly different from control ($p < 0.0001$), with no significant difference between doses ($p = 0.47$). **(G-I)** PCNA expression assessed by flow cytometry. As in the previous panels, lilac = control and blue = treated cells. Treatment with quercetin markedly decreased PCNA-positive cells: 23.48% ± 4.14 in control vs 1.56% ± 1.37 at 91.1 µM and 6.17% ± 0.06 at 220 µM. Statistical comparison **(I)** confirmed significant reductions relative to control ($p = 0.0010$ and $p = 0.0006$, respectively) but no significant difference between the two quercetin concentrations ($p = 0.15$).

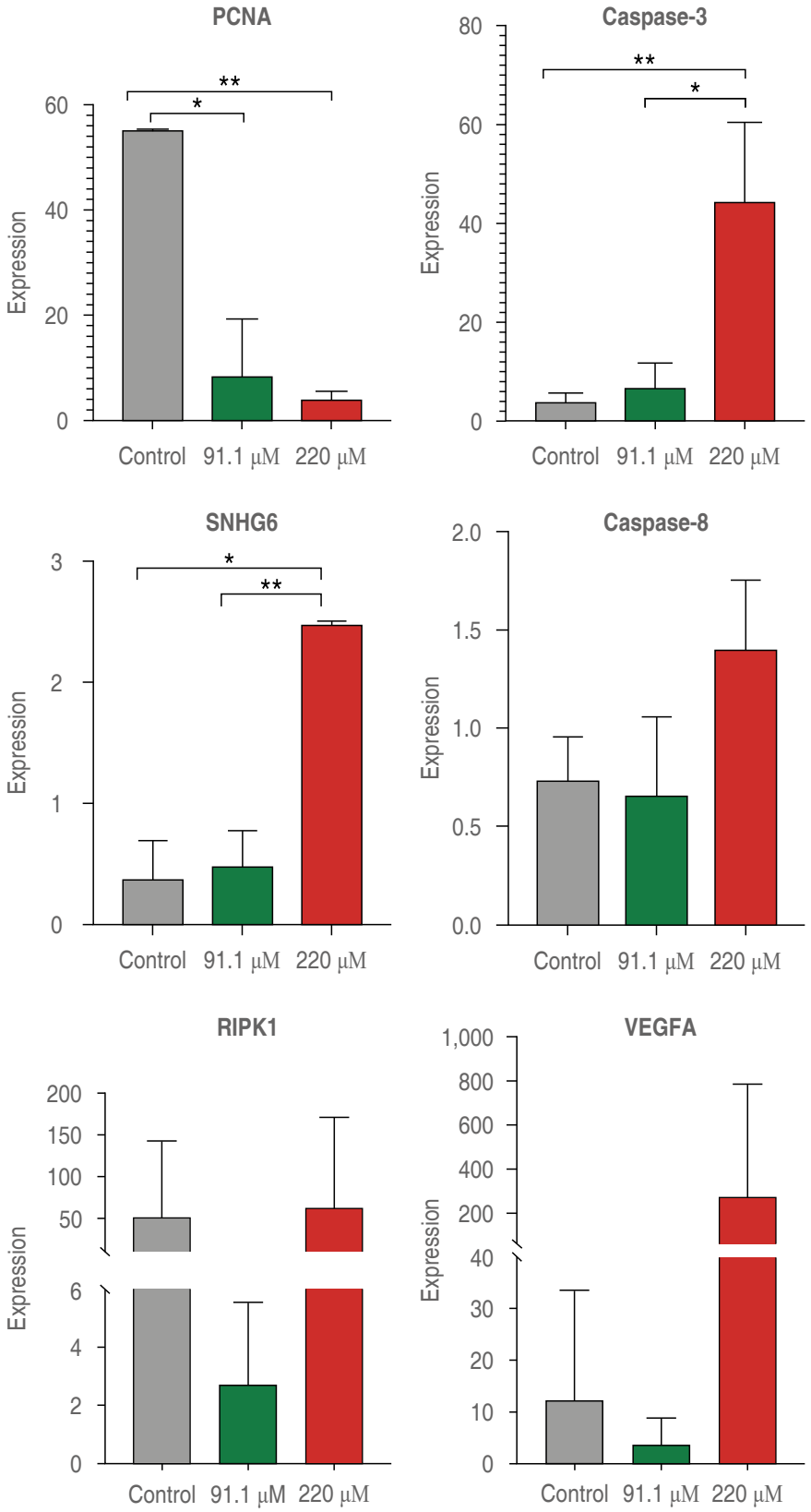

Figure 2:

The Quantitative Polymerase Chain Reaction (qPCR) results analyzing changes in gene expression within TIB 223 giant cell tumor of bone cells after a 24-hour exposure to quercetin. The data clearly illustrates the compound's potent and dose-dependent molecular effects. The figure is organized into distinct panels for key genes. In the panel showing Proliferating Cell Nuclear Antigen (PCNA), a critical marker for cell proliferation, a dramatic reduction in mRNA levels is evident. Expression decreases significantly at the 91.1 µM dose and falls even further at the higher 220 µM concentration. This demonstrates quercetin's powerful ability to halt the uncontrolled growth characteristic of these cancer cells. Conversely, the panel for Caspase 3, a central executioner enzyme in apoptosis, shows a striking opposite trend. Its mRNA expression is strongly upregulated upon treatment. The increase is moderate at 91.1 µM but becomes exceptionally pronounced at 220 µM, where expression rises to a level many times higher than the control. This confirms the direct activation of the cell's intrinsic suicide machinery. Furthermore, the panel for the long non-coding RNA SNHG6, a regulator often involved in cancer progression, also shows a statistically significant change in its expression profile following quercetin treatment, indicating a broader impact on the tumor's regulatory network. Collectively, these transcriptional results provide a coherent molecular narrative. They show that quercetin simultaneously downregulates a major proliferation driver (PCNA) and upregulates a key death promoter (caspase-3), effectively switching the cellular program from survival to apoptosis. This dual action, which intensifies with higher doses, offers a clear genetic explanation for quercetin's observed anticancer activity against these aggressive bone tumor cells.

The proposed mechanisms for these effects include the regulation of cell signaling pathways involved in cell proliferation and survival, the induction of oxidative stress, the modulation of gene expression related to apoptosis, and the inhibition of key enzymes in cellular metabolism.[14]

Scientific evidence indicates that quercetin, a flavonoid present in many fruits and vegetables, can exert anticancer effects through the negative regulation of the expression and function of PCNA, a key protein in cell proliferation.[15] The decrease in PCNA induced by quercetin contributes to inhibiting the uncontrolled proliferation of cancer cells, arresting the cell cycle, and sensitizing these cells to chemotherapy.[16]

In this study, PCNA was found to show significant inhibition after treatment. This protein, which is encoded by the PCNA gene, plays a crucial role in DNA replication and cell proliferation.[17] In cancer cells, quercetin can decrease PCNA levels, thus inhibiting the uncontrolled proliferation of these cells.[18] Previous work has shown that in many types of cancer, PCNA levels are significantly elevated compared to normal tissues.[19] Numerous *in vitro* studies have reported that quercetin treatment significantly reduces PCNA levels in different cancer cell lines, such as breast cancer, lung cancer, and colon cancer, among others.[20] Our results are consistent with the literature: untreated cells showed high PCNA expression, whereas treatment significantly reduced it.

On the other hand, caspases 8 and 3, which encode enzymes that participate in the process of apoptosis or programmed cell death,[21] were also evaluated. Quercetin has been reported as a major inducer of apoptosis in cancer cells by activating these caspases, leading to DNA fragmentation and cell death.[22] The activation of these caspases is described as a crucial mechanism by which quercetin exerts pro-apoptotic effects in various cancer cell lines, including TIB 223, suggesting its potential as an antitumor agent.[23]

Regarding RIPK1, it is important to note that this gene encodes a serine/threonine kinase that functions as a central regulator of cell survival, apoptosis, and necroptosis.[24] RIPK1 is subject to regulation by a variety of enzymes and modifications, including ubiquitination and phosphorylation. Under normal conditions, RIPK1 participates in the early cell-death checkpoint, where its ubiquitination within TNFR1 complex I promotes NF-κB activation and the transcription of pro-survival genes, thereby suppressing its cytotoxic activity.[25] When these regulatory ubiquitin modifications are lost, RIPK1 is redirected toward cytosolic complexes (complex IIa or IIb), where it can activate caspase-8 to induce apoptosis or interact with RIPK3 to promote necroptosis through MLKL activation.[26] As highlighted by DeRoo et al,[27] RIPK1 functions as a molecular switch determining whether cells activate apoptosis or necroptosis depending on caspase-8 availability and RIPK3 recruitment. Furthermore, pharmacological studies have demonstrated that the kinase activity of RIPK1 is essential for initiating necroptosis, and selective inhibition such as with Necrostatin-1 can block this pathway without impairing apoptosis, underscoring its clinical relevance in inflammatory and degenerative diseases.[28] In our study, RIPK1 expression did not show significant modulation following quercetin treatment, which may be explained by the fact that RIPK1 function is primarily regulated by post-translational modifications rather than changes in mRNA abundance. Thus, although quercetin may influence pathways associated with RIPK1, the interactions among these pathways are complex, and the activation of one can exert regulatory effects on the signaling of the others; therefore, a direct transcriptional effect on RIPK1 is not necessarily expected in the TIB 223 *in vitro* model.

Previous studies have also reported that VEGFA is a gene that encodes the Vascular Endothelial Growth Factor A protein, a key mediator of angiogenesis and tumor vascularization.[29] Quercetin has demonstrated anti-angiogenic and anticancer properties, and in several cancer models it can negatively regulate VEGFA expression, inhibiting angiogenesis and tumor growth.[30] In our study, however, VEGFA expression did not show significant differences after treatment, suggesting that quercetin's effects on angiogenesis may depend on cell type, tumor microenvironment, or longer exposure times.

Our *in vitro* observations indicate that quercetin reduces PCNA expression and increases caspase-3 activation. These results suggest that quercetin can limit tumor cell proliferation and promote apoptotic clearance. In the clinical setting of bone tumors and skeletal metastases, reduced tumor burden within bone is mechanistically linked to decreased osteolytic activity, lower risk of pathological fracture, and preservation of structural integrity-outcomes that directly influence mobility and motor function. Authors reviewing bone metastasis and skeletal complications highlight that tumor progression in bone promotes pain, cortical destruction and fractures, all major drivers of functional decline and disability in cancer patients. Therefore, therapies that reduce proliferation and

increase apoptosis in bone-infiltrating tumor cells may translate into decreased bone destruction and reduced motor disability.[4,31,32]

Regarding the use of less toxic adjuvant treatments (such as quercetin), it is important to note that the conventional systemic therapies for metastatic bone disease (chemotherapy, radiation) can cause persistent, disabling adverse effects notably Chemotherapy-Induced Peripheral Neuropathy (CIPN), chronic fatigue and mobility decline which independently worsen disability and quality of life among survivors. A less toxic adjunct such as quercetin (if shown effective and safe in vivo and clinically) could potentially reduce the cumulative exposure to more neurotoxic or myelosuppressive agents, thereby lowering the incidence or severity of treatment-related disability (for example CIPN-related falls, long-term gait impairment, or chronic fatigue limiting activities of daily living). These links between toxic treatment effects and long-term disability are well documented in survivorship literature.[7,33,34]

On the other hand, we can mention that the functional impairment and disability are frequent consequences of bone metastases and pulmonary metastatic disease. Large observational and registry studies report elevated rates of mobility limitation, increased short-term disability use, and greater health-care burden in patients with skeletal metastases compared with non-metastatic patients. Pulmonary metastases causing reduced respiratory reserve and systemic morbidity can further compound disability. When positioning the present *in vitro* results in a clinical context, it is therefore important to cite these epidemiologic data and to state explicitly that translation to reduced disability requires in vivo demonstration of tumor control, preservation of bone strength, and assessment of patient-centred functional outcomes.[6,35,36]

As a first approach to understanding the mechanisms by which quercetin induces cell death in the TIB 223 cell line, we can say that quercetin demonstrated potent pro-apoptotic and antiproliferative effects in TIB 223 cells *in vitro*, supporting its potential as an adjuvant therapeutic strategy for giant cell tumor of bone and metastatic lesions. Considering the above, we can hypothesize the following clinical applications: translation of these findings could include 1) evaluation of quercetin as an adjuvant to standard therapy to reduce tumor burden in bone metastases; 2) investigation of combination regimens that allow dose reduction of cytotoxic agents; and 3) assessment of functional outcomes (fracture incidence, mobility scores, activities of daily living) as clinical endpoints.

Likewise, the strengths we identified in the work are the following: the study reports both protein (flow cytometry) and gene expression (qPCR) evidence supporting apoptosis and reduced proliferation, and used a previously determined IC_{50} to select biologically relevant doses. The limitations of the study include the restriction to *in vitro* conditions quercetin bioavailability, metabolism, and pharmacokinetics in vivo may alter potency; the study does not assess effects on bone-resorbing osteoclast activity or biomechanical bone strength; sample size is modest (triplicates) and functional/behavioural outcomes were not measured.

Finally, continuing with this line of work, future studies should include: 1) *in vivo* studies using orthotopic or bone-metastasis models to assess tumor control, bone integrity and fracture risk; 2) pharmacokinetic and toxicology profiling to define tolerable systemic exposures; 3) combination studies to evaluate synergy with existing therapies and potential to reduce toxic agent doses; and 4) inclusion of functional/ disability-oriented endpoints (e.g., gait analysis, fracture incidence, validated patient-reported outcomes) in preclinical and clinical phases. These steps will be crucial to determine whether the molecular effects observed in vitro can meaningfully reduce bone destruction and disability in patients.

CONCLUSIONS

The results obtained in this study revealed that quercetin, a natural flavonoid, exhibits a potent pro-apoptotic effect in the TIB 233 giant cell tumor cell line. This observation is supported by the significant increase in caspase 3 activity and decrease in PCNA, which are key enzymes in the apoptotic pathway, following quercetin treatment.

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Complications after spinal cord injury in a specialty hospital in Mexico

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complications, spinal cord injury, pressure ulcers, pain, spasticity.

Abstract

Introduction: there is a severe scarcity of data related to complications in people with spinal cord injury (SCI) in Latin America. Those complications are frequent causes of morbidity and mortality, leading to increased hospitalization rates, employability loss, and decreased quality of life. Objective: to describe the main complications that occur in people with SCI at the National Rehabilitation Institute (INR-LGII). **Material and methods:** an observational, cross-sectional, descriptive clinical study was carried out on patients attended at a tertiary-level hospital in Mexico City with SCI. **Results:** 1,284 individuals were studied, 54.51% of them had complications. The most common complications by frequency of occurrence were: pressure ulcers, spasticity, pain, respiratory complications, and infections. Regarding the degree of independence and life satisfaction, individuals with complications had a lower mean score in the following scales: the Spinal Cord Independence Measure version III (SCIM-III) and the Life Satisfaction Questionnaire-9 (LSAT-9). An association was found between having complications and traumatic etiology, a more severe injury and sex. **Conclusions:** this study is clinically relevant because complications after a SCI are frequent and impact individuals, their families, and the whole society. Moreover, knowledge about these complications may reinforce the security of the patient, diminish costs and design treatment strategies to avoid those complications.

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Abbreviations:
95%CI = 95% confidence interval
AIS = ASIA Impairment Scale
ASIA = American Spinal Injury Association
ISNCSCI = International Standards for Neurological Classification of SCI
LISAT-9 = Life Satisfaction Questionnaire-9
PU = pressure ulcers
SCI = spinal cord injury
SCIM-III = Spinal Cord Independence Measure version III

INTRODUCTION

Spinal cord injury (SCI) is a critical condition that has functional, psychological and socio-economic impacts;[1] and therefore, affects quality of life.[2] The medical complications may lead to frequent causes of morbidity and mortality which may generate a larger rate of re-hospitalization, loss of employment, and a poor quality of life.[1]

It is estimated that in the United States, the incidence of people with SCI from traumatic etiology is 54 per million people per year, approximately 282,000 survivors that may lead to complications and require medical attention and re-hospitalizations.[3] In the Spinal Cord Injury Systems Database Model, re-hospitalizations occurred in 55% of participants during the first year after SCI and

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continued at an approximate rate of 37% per year for the next 20 years. The main causes of hospitalization are: urinary complications, respiratory complications and pressure ulcers (PU).[4]

Although more than 80% of the world population lives in more than 100 developing countries, there is no study that has reviewed the global mortality nor the main complications that people with SCI in Latin America present.[5]

Investigations into demographic and clinical characteristics give a better understanding of risk factors, clinical consequences and complications originating from SCI, which leads to better preventive strategies.[6] Thus, this study aims to describe the main complications as well as their association with sociodemographic and clinical variables of people with SCI who attended a tertiary-level hospital from 2015 to 2021 (level 3 in Mexico is a Specialty Hospital and is the equivalent to the level 1 Trauma Centers, defined as somewhere able to provide «definitive care for every aspect of injury»).

SCI is evaluated by using the International Standards for Neurological Classification of SCI (ISNCSCI) Worksheet, which identifies: by completeness (ASIA Impairment Scale)

Complete (grade A): no sensory or motor function is preserved in the sacral segments (S4-S5).

Incomplete (grade B): sensory function is preserved below the neurological level, but motor function is not.

Incomplete (grade C): motor function is preserved below the neurological level, but more than half of the key muscles have a muscle grade of less than 3 (out of 5). This means the person cannot move their limbs against gravity.

Incomplete (grade D): motor function is preserved below the neurological level, and more than half of the key muscles have a muscle grade of 3 or greater. This means the person can move their limbs against gravity.

Normal (grade E): motor and sensory function are normal for all parts of the body, though some reflexes may be abnormal.[7]

Moreover, we used the Life Satisfaction Questionnaire-9 (LISAT-9) is a standardized tool designed to assess an individual's overall life satisfaction and satisfaction within specific life domains. Its classification is associated with the score obtained: the higher scores indicate greater satisfaction. There is no total sum score; instead, each item is analyzed individually, and median or mean scores may be reported for group comparisons. This provides meaningful information on quality of life for clinical and research purposes in the field of SCI (for analytical purposes, responses are often dichotomized: Satisfied = scores 5-6 VS not satisfied = scores 1-4).[8,9]

Objective

To describe the main complications of individuals with SCI in a specialty hospital in Mexico City from 2015 to 2021 and to identify associations between complications and clinical and sociodemographic variables.

MATERIAL AND METHODS

Study design

An observational, cross-sectional, comparative and descriptive clinical study was carried out on people admitted with SCI from 2015 to 2021 at the SCI service in the National Rehabilitation Institute «Luis Guillermo Ibarra Ibarra» (INR-LGII), a specialty hospital in Mexico City. A database was elaborated to manage the information. The study was approved by an Investigative Committee.

Description of the participants

Persons with SCI, attended the SCI service. We based our measurements on the last note of the record; it was eliminated if the medical record was completed with less than 80% of the variables and excluded if SCI was rejected. We included all the adults with SCI from any etiology, severity and neurological level according to the International Standards of Neurological Classification of Spinal Cord Injury (ISNCSCI). ISNCSCI standardizes the physical examination that assesses the severity and impairment of motor and sensory function, and it is considered the gold standard for evaluating and documenting SCIs. It also identifies the Impairment Scale (AIS), based on the Frankel scale, which is a clinician-administered scale used to classify the severity (completeness) of injury in individuals with SCI.[10]

Outcomes

Complications were defined as «an unanticipated problem that arises following, and is a result of, the SCI». We specifically looked in the first note of the clinical record for pain, pressure ulcers, spasticity and spasms,

respiratory complications, infections, deep venous thrombosis, osteopenia, orthostatic hypotension and dysreflexia and urinary lithiasis.[2] Information about complications was directly asked during medical visits and recorded in the medical records.

To address potential biases, the information was collected exclusively by two trained SCI experts.

Proposed statistical analysis

Descriptive statistics were performed with measures of central tendency for the quantitative variables and frequencies and proportions for the qualitative variables. To estimate the relationship between the qualitative variables, χ^2 test of independence was used. To determine the relationship between qualitative and quantitative variables, means of groups defined by the qualitative variables were compared with Student t or ANOVA. We considered a confidentiality index of 95% and a significance level $p < 0.05$. The SPSS 21 program was used.

Also, a log-binomial regression analysis was conducted to derive prevalence ratios[11] estimating the presence of different complications according to demographic and clinical variables.

RESULTS

1,284 persons were included, most of them were men (66.2%, n = 1,940), with an average age of 42.23 years old (ranging from 18 to 88).

Table 1: Complications in patients attended at the INR-LGII 2015-2021.

Complication	n (%)
Pressure ulcers	429 (33.4)
Spasticity	108 (8.4)
Pain	98 (7.6)
Respiratory	48 (3.7)
Infection	39 (3.0)
Deep venous thrombosis	23 (1.8)
Spasms	14 (1.1)
Osteopenia	11 (0.9)
Orthostatic hypotension	6 (0.5)
Urinary lithiasis	5 (0.4)
Dysreflexia	4 (0.3)
Other	128 (10.0)

INR-LGII = National Rehabilitation Institute «Luis Guillermo Ibarra Ibarra».

Table 2: Comparison of means of quantitative variables.

Variables	Mean ± DS	p
Life satisfaction		< 0.001
With complications	37.2 ± 8.49	
Without complications	39.58 ± 7.69	
SCIM-III		< 0.001
With complications	71.4 ± 29.26	
Without complications	82.98 ± 26.95	
Age		0.54
With complications	41.94 ± 16.01	
Without complications	42.54 ± 16.57	

SCIM-III = spinal cord independence measure version III.
Statistics estimated from database of patients with SCI of INR-LGII.

Regarding the clinical characteristics of SCI, most individuals had a complete injury classified with the ISNCSCI using the ASIA Impairment Scale (AIS). Its distribution in this study was: AIS A in 42.7% of patients, followed by D (28.9%), C (14.5%), B (11.1%), and E (2.8%).

The most frequent neurological level was low thoracic (T7-T12) (29.8%), followed by high thoracic (T1-T6 (26.9%), low cervical (C5-C8) (16.9%), high cervical (C1-C4) (15.8%), lumbar (10.3%) and sacral (0.2%). The most common etiology was traumatic injury (64.8%).

Most participants presented complications, 54.51% (n = 699), of which the most frequent, in descending order, were: pressure ulcers in 33.4% (n = 429), spasticity in 8.4% (108) and pain in 7.6% (n = 98), see *Table 1*.

The means' comparison of the quantitative variables between groups defined by the presence of complications were examined, as shown in *Table 2* below.

The table shows that the group of participants with complications had a lower Life Satisfaction Questionnaire-9 (LISAT-9) score compared to the group without complications, and this difference was statistically significant ($p < 0.001$). Also, subjects with complications had a SCIM-III score significantly lower than the group of subjects without complications. No significant differences were observed in terms of age.

Complications were more frequent in men than in women. 502 men had complications (39%) in comparison to 198 women who developed complications (15.42%) (χ^2 test $p > 0.001$). Complications were more frequent in individuals with traumatic injury etiology

than with non-traumatic injury (784 subjects [61%] vs 500 [38.94%]; χ^2 test $p < 0.001$). Distribution according to IISNCSCI is presented in *Figure 1*.

A logistic regression analysis was performed to determine the effects of age, sex, satisfaction with life, independence, AIS, and neurologic level on the likelihood that participants presented complications.

The logistic regression model was statistically significant, p = 0.037. The model had a Nagelkerke R2 = 0.164 and correctly classified 66.2% of cases *(Table 3)*.

Men were 1.51 times more likely to present complications than women; people with motor complete SCI (AIS A and B) were 2.403 times more likely to have complications than those with motor incomplete SCI; people with tetraplegia (C1-C8) were 1.08 times more likely to have complications than those with paraplegia (≤ T1); and people with traumatic SCI were 1.87 times more likely to have complications than those with non-traumatic SCI. Increasing age and independence were associated with a higher likelihood of complications. Satisfaction with life and neurologic level did not show a statistically significant effect on the presence of complications.

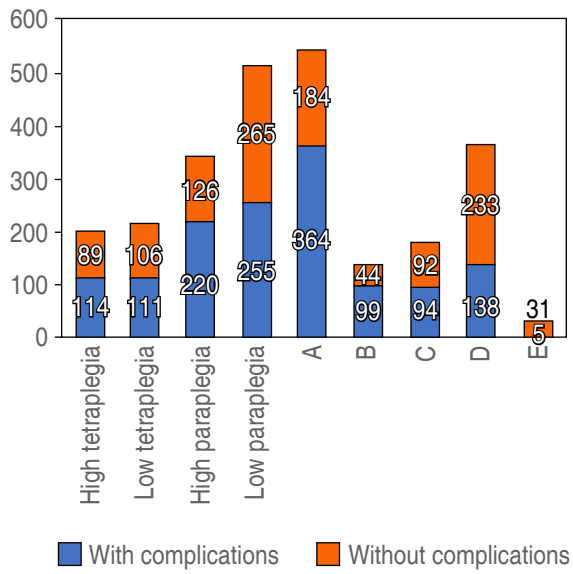

Figure 1: Complications according to spinal cord injury severity.

For particular complications, a logistic regression analysis was performed to determine the effects of age, sex, satisfaction with life, independence, AIS, and neurologic level on the likelihood that participants presented the complications.

Pressure ulcers

The logistic regression model was statistically significant, p = 0.047. The model had a Nagelkerke R2 = 0.263 and correctly classified 70.9% of cases.

Men were 2.1 times more likely to present pressure ulcers than women. People with motor complete SCI (AIS A and B) were 4.55 times more likely to have pressure ulcers than those with motor incomplete SCI. Increasing age and independence were associated with an increased likelihood of presenting pressure ulcers, but increasing satisfaction with life was associated with a reduction in the probability of exhibiting pressure ulcers. Etiology and neurologic level did not show a statistically significant effect on the presence of pressure ulcers.

Table 3: Regression analysis components.

Variable	B	SE	Wald	Sig	Exp(B)	95%CI for Exp(B)	
						Lower	Upper
Etiology (traumatic)	0.626	0.147		0.000	1.869	1.4	2.496
Sex (men)	0.411	0.134		0.002	1.508	1.160	1.960
SCIM-III	0.010	0.003	14.953	0.000	1.010	1.005	1.016
LISAT-9	0.013	0.008	2.358	0.125	1.013	0.996	1.030
Age	−0.012	0.004	8.032	0.005	0.988	0.980	0.996
AIS (motor complete)	0.877	0.143	37.368	0.000	2.403	1.814	3.182
Neurological level (tetraplegia)	0.081	0.140	0.336	0.562	1.084	0.824	1.427
Constant	−1.761	0.377	21.825	0.000	0.172		

95%CI = 95% confidence interval. AIS = ASIA Impairment Scale. LISAT-9 = Life Satisfaction Questionnaire-9. SCIM-III = Spinal Cord Independence Measure version III. SE = standard error. Sig = significance.

Pain

The logistic regression model was statistically significant, p = 0.012. The model had a Nagelkerke R2 = 0.10 and correctly classified 92.4% of cases.

Females were 1.7 times more likely to present pain than males, and people with traumatic SCI were 1.76 times more likely to present pain than those with non-traumatic etiology. Increasing age and more independence were associated with an increased likelihood of exhibiting pain, but increasing satisfaction with life was associated with a reduction in the probability of exhibiting pain. AIS and neurologic level did not show a statistically significant effect on the presence of pain.

Respiratory complications

The logistic regression model was statistically significant, p = 0.032. The model had a Nagelkerke R2 = 0.105 and correctly classified 96.2% of cases.

Subjects with traumatic SCI were 2.92 times more likely to present respiratory complications than persons with non-traumatic SCI. Individuals with motor complete SCI were 1.69 times more likely to present respiratory complications than individuals with motor incomplete SCI. Persons with tetraplegia had 1.75 times more probability of having respiratory complications than people with paraplegia. Increasing independence was associated with a reduction in the likelihood of presenting respiratory complications. Age and satisfaction with life did not show a statistically significant effect on the presence of pressure ulcers.

DISCUSSION

In the present study, SCI complications were described, along with the association between these complications and the clinical and sociodemographic variables in a single hospital in Mexico City.

Most of the participants were male (66.2%), with complete paraplegia, and the majority presented complications (54.5%). The reported frequency varies worldwide, with the highest prevalence of up to 56% reported in Europe, while as low as 11% in the United States. In the meta-analysis by Shiferaw et al.,[12] they referred to 32.36%, being more common in those with SCI AIS A, with upper thoracic injury, and males.

We found a statistically significant association between people with complications and a lower satisfaction with life than those without complications. This is similar to other authors,[13] who mentioned that a reduction in life satisfaction is observed more frequently in those patients with intestinal-related issues and those who present moderate or severe nociceptive pain. Another study reported that 73.5% of people had at least one episode of a urinary tract infection, and their overall quality of life worsened.[14]

Considering the frequency of specific complications, the results of this study were similar to international data,[15] according to which PU is the most common complication. Shiferaw et al in 2020 in «The global burden of pressure ulcers among patients with spinal cord injury: a systematic review and meta-analysis» revealed that about one in three patients as the global pooled magnitude of pressure ulcers among patients with SCI; and on the subgroup analysis, the highest magnitude in Africa 41.19%. Therefore, policy makers and other concerned bodies should design country context-specific preventive strategies to reduce the burden of pressure ulcers in patients with spinal cord injury.[12] Chen et al in 2020 study findings «Incidence of pressure injury in individuals with spinal cord injury: a systematic review and meta-analysis» indicate that more than one in five individuals with SCI will develop a pressure injury and its high risk of developing them, especially in community settings or low- and middle-income developing countries.[16] Moreover, Lessing et al in 2020 in «Pressure ulcers after traumatic spinal injury in East Africa: risk factors, illustrative case, and low-cost protocol for prevention and treatment» report high-risk patients were those with delayed presentation, complete neurologic injuries, and thoracic injuries.[17] Pérez et al in «Frequency of ulcers for pressure in the patient with spinal cord injury, its correlation with the neurologic level and scale of ASIA» also found that the ulcers for pressure are the most frequent chronic complication that is presented in the patient with spinal cord injury being observed for up of 60%, considering more than 87% with a low socioeconomic level in Mexico. However, no association was found between having PU and sociodemographic variables.[18]

In the literature, urinary tract infection is the second most frequent complication. Golestani et al.[19] compared the results of developing and developed countries, showing that pressure ulcers and urinary tract infections are major secondary complications in all regions. In our study, infections were the fifth most frequent complication. The cross-sectional nature of the study might be the reason for that finding, since patients might not report complications that were treated successfully in the past.

Spasticity and pain were reported in 70 and 80% respectively by Gatti et al.[20] However, we found a lower rate of these complications. Furthermore, we encountered an association of pain with the female sex, also reported by Werhagen et al.[21] We did not find an association between pain and SCI severity (AIS, nor neurologic level). Conversely, Jorgensen et. al.[13] showed that veterans with AIS D reported more pain, less vitality, and lower overall health compared with those with a different SCI type. There are several plausible explanations for these findings, such as fatigue related to walking, the frustration of being slow to multitask and feeling misunderstood due to less visible deficits (such as pain, sexual problems, and those related to the bowel and bladder). Margot-Duclot A et al[22] report that cervical and thoracic SCI levels, as well as cauda equina injuries, seem to have a greater association with neuropathic pain.

Spasticity was the second most frequent complication in this study. DeForest et al reported spasms in muscles innervated at or below the injury level close to 80%.[23] Also, we observed that spasms are more frequently reported by male individuals.

We found respiratory complications in 3.7% and a higher frequency of them was observed in persons with SCI AIS A and B, as well as in those whose neurological level was a cervical level (tetraplegia). According to the study reported by Vieri Failli et al.,[24] their data are similar to ours in terms of severity of the injury; they also observed high rates of pneumonia in individuals with AIS A and B. Regarding the neurological level, in our study a higher risk was found in those persons with SCI at the cervical level, which is not surprising because of the weakness of respiratory muscles at those levels.[1]

Due to people with SCI's life expectancy increasing, more research worldwide is required to improve information related to long-term complications in this group of people.

This study is clinically relevant because the high rates of complications should alarm the authorities to establish political statements. In our Specialty Hospital, the SCI medical specialist takes care of complex SCI inpatients and outpatients with or without medical complications. So, from the very start, it is a challenge to care for this type of individual and we face different scenarios to whom we adapt in the best way, since in Mexico we don't have long-term acute care hospitals or skilled nursing facilities. Medical doctors should emphasize the awareness and prevention of these complications from the first meeting with the patient. This would improve preventive management, diminish costs, and help design strategies to manage complications in people with SCI.

Limitations

Since this was a cross-sectional study, it was not possible to retrieve data that had not been previously documented in the medical record. In addition, this study investigated medical complications, while SCI also has psychosocial complications beyond the scope of this investigation and these may influence the patient's prognosis as much as medical complications.

At the time of data collection, it was not possible to find specific information that could have been important. It was not possible to collect data on the recurrence of complications and then to describe if these lead to more hospital admissions and consequently a greater propensity to suffer more complications.

The results should be interpreted with caution, as they only reflect the reality of a high-complexity hospital in Mexico. Therefore, the conclusions derived should be exclusively for public health policies or resource allocation in that region.

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Data available on request due to privacy/ethical restrictions.

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NGS panel for non-syndromic hearing loss: diagnostic yield and genotype-phenotype correlation in a Mexican population

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hearing loss, sensorineural, next-generation sequencing, connexin 26, genotype-phenotype correlation.

Abstract

Introduction: hearing loss is defined as the total or partial loss of auditory function, constituting a major cause of disability worldwide. It is the most common sensory disorder in humans, affecting approximately 1 in 3,000 newborns. Current molecular genetic studies report a diagnostic rate of around 50%. **Material and methods:** eleven patients with hearing loss were studied using a panel of 224 related genes. Sequencing (≥ 50 ×) was performed with Illumina technology, aligned to the GRCh37 human reference genome. Variants were reported according to the Human Genome Variation Society (HGVS) guidelines and confirmed through validated methods (Invitae). Results were correlated with patient phenotype and family history. **Results:** of the 11 cases (three males and eight females), one had a positive family history. Seven patients (63.6%) had a positive genetic result, three (27.3%) presented Variants of Uncertain Significance (VUS), and one had a negative result. Pathogenic variants (PV) were identified in the *GJB2* gene (three heterozygous and one compound heterozygous case). Compound heterozygous variants were found in *USH2A* and *ADGRV1*. Two patients showed inner ear malformations. **Conclusions:** the hearing loss gene panel (224 genes) demonstrated acceptable diagnostic yield, identifying PV in 63.6% of cases. *GJB2* was the most frequently involved gene, although not in the same proportion as observed in other populations, and often in heterozygous form. No direct correlation was found between the degree of hearing loss and the presence of PV; however, in some cases, there was an association with heterozygous or homozygous status. VUS may potentially contribute to Non-Syndromic Sensorineural Hearing Loss (NSHL), possibly modifying the phenotype. Segregation studies are necessary to improve diagnostic precision and support genetic counseling.

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Abbreviations:
ACMG = American College of Medical Genetics and Genomics
HGVS = Human Genome Variation Society
NGS = Next-Generation Sequencing
NSHL = Non-Syndromic Sensorineural Hearing Loss
VUS = Variants of Uncertain Significance

INTRODUCTION

The World Health Organization (WHO) defines hearing loss as a threshold exceeding 20 dB. It is a leading cause of global disability and the most common sensory disorder at birth, affecting 2-3 per 1,000 live births. Hearing loss is classified by type (conductive, sensorineural, mixed), origin (genetic, non-genetic), and onset (congenital, prelingual, postlingual). Up to 80% of prelingual cases are genetic, mostly non-syndromic (70%).[1]

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Contents

Non-Syndromic Sensorineural Hearing Loss (NSHL) lacks external abnormalities but may involve inner ear alterations. Unlike syndromic forms, NSHL is typically autosomal recessive (77%), though dominant (19-22%), mitochondrial, or X-linked inheritance occur. Autosomal dominant *GJB2* variants usually present as postlingual, progressive high-frequency loss with variable penetrance. Specific variants like *c.109G>A* (*p.Val37Ile*) and *c.101T>C* (*p.Met34Thr*) show variable clinical presentations and controversial classifications.[1-4]

The *c.101T>C* (*p.Met34Thr*) variant was initially reported to be associated with reduced penetrance dominant hearing loss and its classification has been controversial. One study identified it as a point mutation in a caucasian family with autosomal dominant deafness and palmoplantar keratoderma.[5]

The advent of Next-Generation Sequencing (NGS) has significantly advanced the identification of candidate genes implicated in disorders characterized by high genetic heterogeneity. Exome sequencing, in particular, has proven instrumental in detecting DNA variants associated with Mendelian conditions, such as NSHL. To date, over 80 genes and more than 1,000 pathogenic mutations have been implicated in NSHL, positioning it as an exemplary model for illustrating the diagnostic power of NGS technologies.[2] However, the diagnostic yield varies significantly based on clinical and genetic factors, including the severity of hearing loss, age of onset, family history, patient ethnicity, and the scope of the genetic panel employed. In general, higher diagnostic rates have been observed in individuals with a family history or when hearing loss is congenital and bilaterally symmetrical. Several studies have evaluated targeted gene panels for hereditary diseases, reporting limited diagnostic performance and complex interpretation; therefore, their use as screening tools in patients with low clinical probability is not recommended. Although targeted gene panels are widely used in clinical practice, they present important limitations, including variable diagnostic yield, challenges in variant interpretation (particularly Variants of Uncertain Significance [VUS]) and discrepancies in variant detection and filtering across laboratories. These limitations highlight the need to define population-specific mutational spectra to improve the accuracy and clinical utility of molecular diagnosis in hearing loss.[6]

OBJECTIVE

The aim of this study was to identify genetic variants associated with NSHL in a sample of the National Institute of Rehabilitation (INR LGII Instituto Nacional de Rehabilitación «Luis Guillermo Ibarra Ibarra» for its Spanish meaning) patients using a panel of 224 hearing loss-related genes (Invitae) and to evaluate their diagnostic performance. NGS enabled the assessment of genotype–phenotype correlations, allowing the analysis of genetic factors contributing to hearing loss in this population.

MATERIAL AND METHODS

Eleven Mexican patients with a clinical diagnosis of sensorineural hearing loss, under follow-up at the National Institute of Rehabilitation were included. All patients were referred by the Audiology or Speech-Language Pathology services, and selected by clinical geneticists due to the suspicion of genetic hearing loss, mostly bilateral and without other identifiable cause that could better explain the hearing loss. Molecular analysis was performed by NGS, using a targeted panel of 224 genes associated with syndromic and NSHL. Biological samples consisted of peripheral blood collected in EDTA tubes. Genomic DNA extraction was performed by Invitae Corporation, followed by enrichment by hybrid capture and sequencing with Illumina technology. All target regions were sequenced with an average minimum depth of coverage of $\geq$ 50×, or supplemented with additional analysis when necessary. Prior to the performance of genetic studies, written informed consent was obtained from all patients or, if applicable, from their legal representatives.

During processing, reads were aligned to the *GRCh37/hg19* reference genome, and variants in coding regions, 20 flanking intronic base pairs, and other regions previously associated with disease were evaluated. No promoter or coding regions were analyzed, except for clinically relevant regions known at the time of panel design. The interpretation of the identified variants was performed according to the Human Genome Variation Society (HGVS) nomenclature, and they were classified according to the guidelines of the American College of Medical Genetics and Genomics (ACMG). Validated in-house algorithms were used for the detection of copy number variants (CNVs). Clinically relevant variants were confirmed by orthogonal methods such as Multiplex Ligation-dependent Probe Amplification (MLPA), MLPA-seq or Single-Molecule Real-Time sequencing (SMRT) long read sequencing (PacBio), as appropriate. The technical protocol followed by Invitae is described in its institutional documentation (Invitae Corporation,

2021). All variants were again cross-checked by the researchers in different databases. The genotype-phenotype correlation was performed by integrating molecular findings with family history, clinical history and available paraclinical studies, including audiometry and computed tomography (CT). The classification of the degree of hearing loss was established according to the criteria of the World Health Organization (WHO, 2021), which allowed a more accurate clinical interpretation of the variants identified.

RESULTS

Eleven patients with sensorineural hearing loss were studied. No relevant perinatal history or exposure to ototoxic drugs was found. The mean age was 24.3 years (range: 6-48 years), five were minors. The sex ratio was three males and eight females. One of the cases was familial. Pathogenic variants (PV) or likely pathogenic (LP) variants were identified in seven of the 11 patients analyzed, representing a diagnostic yield of 63.6%. Three patients (27.3%) had VUS and one had a negative result *(Table 1)*. Moreover, structural malformations of the inner ear were observed in two patients: one with a variant in *GJB2*, who presented absence of the cisternal and intracanalicular portions of the cochlear nerve (right CN VIII), along with hypodevelopment of the internal auditory canal; and another patient with a variant in *MYO7A* showed bilateral cochlear nerve agenesis on Magnetic Resonance Imaging (MRI), as well as a history of cochlear implantation in the left ear. *Table 1* summarizes the demographic characteristics, degree of hearing loss, imaging findings, and genetic results for each patient, including variant classification and zygosity, and their correlation with the expected phenotype described in the literature. The most frequently found gene with PV was *GJB2*, in four patients (three heterozygotes and one compound heterozygote). Variants in *USH2A* and *ADGRV1* (both in compound heterozygous state) were also identified. Of the two patients with variants in *USH2A*, only one had retinitis pigmentosa on ophthalmologic evaluation. In patients with PV, most of them presented bilateral moderate to profound hearing loss. The other genes we found are described in *Table 1*. During the analysis, no clinically relevant CNVs were identified in the patients analyzed.

DISCUSSION

Previous studies in the Mexican population have reported that although variants in the *GJB2* gene are less frequent compared to other populations (with proportions ranging between 10 and 30%), they continue to be the most prevalent in this population.[1,7,8]

We identified one patient with compound heterozygosity —a common finding— but also three cases with heterozygosity alone, a pattern that is increasingly reported. This was the case for patients 2, 3, and 4, who carried the following PV, respectively: *c.109G>A* (*p.Val37Ile*), *c.101T>C* (*p.Met34Thr*) and *c.34G>T* (*p.Gly12Cys*).[3-5] However, there is no clear correlation between heterozygosity and homozygosity or compound heterozygosity with the degree of hearing loss found.

In these patients, whose variants are found in heterozygosity (homozygosity is generally considered necessary for the pathological phenotype to manifest), we cannot fully explain it nor confirm that these heterozygous variants are the cause, and there is controversy in the literature. However, phenotypic expression in heterozygotes is plausible given the increasing prevalence of symptomatic carriers, or potentially due to unidentified modifier genes. Notably, we did not identify other variants (PV, VUS) to suggest digenic inheritance in these cases.[3-5]

The PV *c.109G>A* (*p.Val37Ile*) in the *GJB2* is frequently found in heterozygosity in normal-hearing populations, particularly in China.[3,4] Although initially classified as a benign polymorphism, it has been reevaluated due to its significant overrepresentation in hearing loss cohorts. Liang et al. reported marked phenotypic variability associated with this variant in both homozygous and heterozygous states, with most patients presenting mild-to-moderate hearing loss.[3,4,9]

In the case of patient 3, the variant *c.101T>C* (*p.Met34Thr*) can indeed cause hearing loss in heterozygosity, but there may also be an influence of some other genes. It has also been observed, that carriers of the *c.35delG* mutation in *GJB2* have significant hearing loss, and that in heterozygous women, hearing impairment may be more severe than in men.[10] Familial cases of heterozygous mutations in the *GJB2* gene have been reported with a high prevalence in individuals with the *1555A->G* mitochondrial mutation, suggesting it as an aggravating factor in the phenotypic expression of NSHL. Similarly, the combination of a heterozygous mutation in *GJB2* with deletions in the *GJB6* gene can cause severe hearing loss, demonstrating a di-genic inheritance pattern in some cases.[11]

Several case studies have documented the presence of atypical heterozygous variants of the *GJB2*

Table 1: Demographic and molecular characterization of the study cohort.

Patient	1		2	3	4	5	6
Gender and age Gene/Locus	Female, 48 years USH2A / 1q41		Female, 45 years GJB2 / 13q12.11	Female, 36 years GJB2 / 13q12.11	Female, 15 years GJB2 / 13q12.11	Male, 6 years MITF / 3p13	Female, 10 years MYO7A / 11q13.5
ClinVar/ACMG criteria	Deletion (Exons 22-50)	c.5278del (p.Asp1760Metfs*10) Frameshift; Stop codon	c.109G>A (p.Val37Ile) Missense	c.101T>C (p.Met34Thr) SNV; Missense	c.34G>T (p.Gly12Cys) SNV; Missense	Deletion (complete coding sequence)	c.4117C>T (p.Arg1373*) SNV; Nonsense Stop codon
Classification	PV	PV	PV (Low penetrance)	PV	PV	PV	PV
Zygosity (Patient)	Compound Heterozygous		Heterozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous
Associated Inheritance Pattern	AR pattern	AR pattern	• AR pattern • AD pattern	• AR pattern • AD pattern	AD pattern	AD pattern	AR pattern
Findings in Present Cohort	Bilateral RE Moderate (47.5 dB) LE moderately severe (61.25 dB) No imaging studies Ophthalmologic evaluation: Pigmentary retinosis, severe myopia and astigmatism (R 20/80; L 20/100)		Bilateral sensorineural RE complete loss (120 dB) LE moderately severe (51.25 dB) CT: The absence of the cisternal and intracanalicular portions of the right VIII cranial nerve + hypodevelopment of the internal auditory canal	Bilateral sensorineural RE Moderate (47.5 dB) LE moderate (41.25 dB) No imaging studies	Bilateral RE Deep (82.5 dB) LE severe (76.25 dB) CT scan without evidence of structural ear pathology	Bilateral sensorineural RE complete loss (111.25 dB) LE complete loss (106.25 dB) CT scan without evidence of structural ear pathology	Bilateral sensorineural RE complete loss (120 dB) LE complete loss (120 dB) CT: Hypoplasia and/or agenesis of the cochlear nerve, left cochlear implant. MRI: In the right ear, no presence of the cochlear nerve is shown, but the inferior vestibular nerve is present. In the left ear, the cochlear nerve is not identified
Reported Phenotypes in literature	Exons 22-50 usually result in more severe phenotypes, with earlier visual impairment and more pronounced hearing impairment. (Varsome)	Exon 26, Truncating mutation. Reported as pathogenic in Usher syndrome cohorts. Causes loss of protein function[17]	Biallelic: Associated with progressive NSHL. Monoallelic: Associated with DFNA3A or syndromic forms (skin disorders)[5]	Mild, progressive HL; low penetrance. Highly controversial variant. May act as a hypomorphic allele in compound heterozygosity. Normal hearing was also reported[18]	NSHL, characterized by moderate to profound hearing loss. With a high frequency in the heterozygous state among Hispanic/ Mexican patients[19]	Congenital sensorineural deafness, usually bilateral, extensive depigmentation, similar to Waardenburg type 2A and Tietz syndrome. Susceptibility to malignant melanoma.[20] (OMIM)	Pathogenic variants in the MYO7A gene, responsible for Usher syndrome type 1B, may also manifest as NSHL with both AD and AR inheritance patterns[15]

ACMG = American College of Medical Genetics and Genomics. AD = autosomal dominant. AR = autosomal recessive. Cx26 = Connexin 26. HL = hearing loss. LE = left ear. LP = like pathogenic. NSHL = non-syndromic hearing loss. PV = pathogenic variant. RE = right ear. SNV = Single Nucleotide Variant. VUS = Variant of Uncertain Significance. ZSD = Zellweger spectrum disorder.
Demographic characteristics and study findings of the patient cohort.
* Stop codon.

Continue Table 1: Demographic and molecular characterization of the study cohort.

7		8			9			10	11
Male, 8 years		Female, 37 years			Female, 30 years			Male, 12 years	Female, 21 years
ADGRV1 / 5q14.3		GJB2 / 13q12.11		PEX5 / 12p13.31	BSND / 1p32.3	CEACAM16 / 19q13.31	USH2A / 1q41	SLC26A4 / 7q22.3	Negative
Deletion (Exons 53-54)	c.15736C>T (p.Arg5246*)	c.516G>A (p.Trp172*) nonsense Stop codon	c.34G>T (p.Gly12Cys) SNV; Missense	c.317-2A>G (Splice acceptor)	c.859G>T (p.Glu287*) SNV; Nonsense Stop codon	c.631C>T (p.Arg211Cys) SNV; Missense	c.10993G>A (p.Gly3665Arg) SNV; Missense	c.1061T>C (p.Phe354Ser) Missense	Negative
PV	PV	PV	PV	LP	LP	VUS	VUS	VUS	Negative
Compound Heterozygous		Compound Heterozygous		Heterozygous		Probably Trigenic inheritance		Heterozygous	Negative
AR pattern	AR pattern	AR pattern	AD pattern	AR pattern	AR pattern	AD pattern	AR pattern	AR pattern	Negative
Bilateral sensorineural RE Severe (67.5 dB) LE moderately severe (58.75 dB) CT scan without evidence of structural ear pathology		Bilateral RE moderately severe (56.25 dB) LE severe (75 dB) CT: Subluxation of left hammer-anvil joint			Bilateral RE Severe (66 dB) LE Normal (7.5 dB) CT: Left labyrinthitis, vascular finding Ophthalmologic evaluation: No alterations			Bilateral RE Deep (86.25 dB) LE deep (81.25 dB) CT scan without evidence of structural ear pathology	Bilateral RE complete loss (120 dB) LE complete loss (120 dB) CT: Right tympanic glomus, probable adenoma at the pituitary level
The ADGRV1 gene is associated with autosomal recessive Usher syndrome type 2C, retinitis pigmentosa and nonsyndromic deafness. No specific clinical manifestations have been described in the literature about this variant (Varsome)	The c.15736C>T variant causes a loss of function by introducing a premature stop codon. In the homozygous state, this mutation is known to suggest Usher syndrome type 2C, which includes sensorineural hearing loss (Varsome)	Severe-to-profound congenital hearing loss[21]	NSHL, characterized by moderate to profound hearing loss. With a high frequency in the heterozygous state among Hispanic/ Mexican patients[19]	The PEX5 gene causes autosomal recessive ZSD, a syndromic disorder that involves deafness[22]	BSND is the causative gene for DFNB73 (NSHL), but mutations are also known to cause Bartter syndrome type IV. The HL phenotype may be accompanied by subclinical renal metabolic changes[23]	Bilateral NSHL with early onset and progressive course[24]	The available evidence is currently insufficient to determine the role of this variant in disease (Varsome)	Associated with NSHL and Pendred's syndrome, also reported in autoimmune thyroid diseases[25]	Negative

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* Stop codon.

gene associated with specific and complex deafness phenotypes, challenging the purely recessive inheritance model. In one study, whole exome sequencing (WES) identified a pathogenic de novo variant *c.223C>T* (*p.Arg75Trp*) in *GJB2*, linked to autosomal dominant deafness and palmoplantar keratoderma. Similarly, another study described the heterozygous missense variant *c.370C>T* (*p.Gln124*)[I] in a patient with late-onset deafness and preserved speech. The latter variant showed extremely low allele frequencies (< 0.02%) in population genomic databases, supporting its likely pathogenicity. Finally, one study reported the heterozygous variant *p.Gly45Glu* in a patient with a lethal form of KID syndrome, a variant inherited from his mother, who in turn also carried it along with another nonsense variant, *p.Tyr136X*. These findings suggest that heterozygous variants of *GJB2* may manifest pathogenic effects through complex inheritance mechanisms, including de novo dominant inheritance and interaction with other genetic variants.[5,12,13] Other *GJB2* variants reported in heterozygosity have been: *c.224G>A* (*p.Arg75Gln*), *c.617A>G* (*p.Asn206Ser*).[3,4] These results confirm the clinical utility of the panel of genes for hearing loss and demonstrate the relevance of the *GJB2* gene in our population, despite the previously reported differences in frequency between different regions.

Of the remaining variants, very frequently in different studies, USHER-related genes such as *USH2A, USH1C, ADGRV1, MYO7A* and *CDH23* have been found to cause hearing loss. In general, no other manifestations were found that would allow considering that these were syndromic hearing losses and it is something very common that has been found in the different series of patients.[14] We identified three PV in *USH2A*, consistent with previous reports. As well as two cases of PV in *ADGRV1*, in a compound heterozygote, one of these variants associated with Usher syndrome type 2C. More than 200 mutations have been identified in *MYO7A* causing Usher type 1B, we describe a case in heterozygote in the *MYO7A* gene, but other unknown or undetected genes could be the responsible or acting together with *MYO7A*, since the pattern proposed is recessive.[13,15] Mutations in *MITF* have been associated with Waardenburg syndrome type 2A and with isolated hearing loss. In this study, we report a heterozygous case with a pathogenic complete coding sequence deletion presenting without syndromic features. While the hearing loss can be explained by this variant, it is also important to highlight the increased susceptibility to malignant melanoma associated with alterations in the same gene. This finding illustrates how exome sequencing may reveal clinically relevant information beyond the primary indication for testing, which should be considered during genetic counseling.[4]

Some mutations were reported in VUS, in the *BSND* gene, certain variants have been associated with Bartter syndrome type IV, in our case this association has not been described. In the same case a variant of the *CEACAM16* gene was reported in VUS, in the literature there is still not enough evidence to associate it directly with autosomal dominant NSHL. A mutation in the *SLC26A4* gene in VUS was reported in one case; this has been associated with Pendred syndrome and inner ear malformations.[16]

These results confirm the clinical usefulness of the panel of genes for hearing loss and not the single study of the *GJB2* gene. Overall, our results support the use of multigene panels as an effective diagnostic tool in patients with sensorineural hearing loss, and demonstrate the relevance of the *GJB2* gene and other genes such as those related to USHER syndrome in our population. The exome could even give us other important findings for patients. Likewise, it is necessary to highlight the need for segregation and clinical follow-up studies to clarify the phenotypic impact of VUS, as well as the genotype-phenotype correlation and to be able to provide adequate genetic counseling.

CONCLUSIONS

The 224-gene hearing loss panel demonstrated robust diagnostic performance, identifying PV in 63.6% of analyzed cases. The *GJB2* gene was the most frequently implicated, although at a lower proportion than reported in other populations and predominantly in the heterozygous state, which poses interpretative challenges regarding penetrance, inheritance patterns, and the possible presence of undetected variants in non-covered regions.

VUS may contribute to the phenotype of NSHL, particularly in the presence of family history or subtle clinical findings, as well as through the potential influence of epistatic interactions or modifier genes in certain cases.

The identification of PV in genes associated with Usher syndrome, such as *USH2A*, highlights the

[I] Stop codon.

importance of considering syndromic etiologies in the differential diagnosis, even in the absence of systemic features at initial evaluation. Similarly, in genes such as *CDH23*, the specific variant type may determine whether retinitis pigmentosa develops, underscoring the complexity of genotype–phenotype correlations.

Our findings, consistent with previous reports in Mexican patients, indicate that *SLC26A4* is a relevant contributor to sensorineural hearing loss after *GJB2*. The detection of diverse *SLC26A4* variants, without a recurrent mutation, reinforces the high genetic heterogeneity of hearing loss in this population.

These results support the clinical utility of comprehensive multigene panels in patients with hearing loss, while emphasizing the need for family segregation studies, longitudinal follow-up, and population-specific databases to refine variant interpretation, establish stronger genotype–phenotype associations, and improve genetic counseling. Notably, a subset of patients remained without a molecular diagnosis, underscoring the need for broader genomic approaches, including non-coding regions and novel genes, in future research.

Unexpected or secondary findings, although not directly related to the primary genotype, may provide clinically relevant information by enabling preventive or anticipatory actions for other conditions. The identification of incidental or non-pathogenic variants can contribute to a more comprehensive genetic counseling approach, particularly when interpreted within an appropriate clinical and familial context.

Finally, this study provides population-specific insights into the genetic landscape of hearing loss in Mexican patients, contributing to the development of precision medicine, early diagnosis, and personalized management strategies, with potential implications for public health policies in hearing impairment.

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Odisea diagnóstica de una enfermedad rara en un programa de rehabilitación pediátrica: a propósito del caso clínico más longevo reportado de encefalopatía etilmalónica

Diagnostic odyssey of a rare disease in a pediatric rehabilitation program: the longest-living reported case of ethylmalonic encephalopathy

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Palabras clave:
enfermedades raras, enfermedades mitocondriales, rehabilitación, longevidad, genética.

Keywords:
rare diseases, mitochondrial diseases, rehabilitation, longevity, genetics.

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Resumen

Introducción: la encefalopatía etilmalónica (EEM) es una enfermedad metabólica rara, autosómica recesiva, caracterizada por alteraciones mitocondriales que producen acumulación de sulfuro de hidrógeno y metabolitos tóxicos. Sus manifestaciones clínicas incluyen retraso global del desarrollo, crisis convulsivas, hipotonía y síntomas multisistémicos que pueden simular parálisis cerebral, lo que dificulta el diagnóstico temprano. **Objetivo:** describir el caso clínico de un paciente con EEM, enfatizando el desafío diagnóstico, el abordaje terapéutico y la importancia del soporte rehabilitador multidisciplinario. **Caso clínico:** hombre de 25 años diagnosticado inicialmente con parálisis cerebral espástica y discapacidad intelectual moderada. Presentó diarrea crónica, petequias, acrocianosis, espasticidad, poliposis intestinal y vejiga neurogénica. Tras múltiples valoraciones médicas, el diagnóstico de EEM se confirmó a los 22 años mediante secuenciación genética (ETHE1 c.488G>A, homocigoto). El tratamiento farmacológico específico se inició de manera tardía; sin embargo, el paciente alcanzó una longevidad sin precedentes gracias al acompañamiento familiar y un programa de rehabilitación pediátrica integral durante casi dos décadas. La literatura describe una supervivencia máxima cercana a los 11 años en la mayoría de los casos de EEM. Este reporte constituye el caso más longevo documentado hasta la fecha, lo que resalta el impacto positivo del manejo rehabilitador y la red de apoyo. **Conclusiones:** la EEM debe considerarse en diagnósticos diferenciales de parálisis cerebral, especialmente ante síntomas como diarrea crónica, acrocianosis y manifestaciones hemorrágicas. Este caso subraya la relevancia de la rehabilitación multidisciplinaria y el soporte crónico como factores determinantes en la calidad de vida y supervivencia de personas con discapacidad por enfermedades metabólicas raras.

Abstract

Introduction: *ethylmalonic encephalopathy (EE) is a rare autosomal recessive metabolic disorder caused by mitochondrial dysfunction and accumulation of hydrogen sulfide and toxic metabolites. Clinical features include global developmental delay, seizures, hypotonia, and multisystem involvement*

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that may mimic cerebral palsy, leading to delayed diagnosis. ***Objective:*** *to present a clinical case of EE, emphasizing diagnostic challenges, therapeutic strategies, and the critical role of multidisciplinary rehabilitation.* ***Case report:*** *a 25-year-old male was initially diagnosed with spastic cerebral palsy and moderate intellectual disability. He exhibited chronic diarrhea, petechiae, acrocyanosis, spasticity, intestinal polyposis, and neurogenic bladder. After multiple evaluations, EE was confirmed at age 22 by genetic sequencing (ETHE1 c.488G>A, homozygous). Although specific pharmacological therapy began late, the patient achieved the longest survival ever reported, primarily due to long-term family support and an intensive pediatric rehabilitation program spanning nearly two decades.* ***Results:*** *published literature reports a maximum survival of approximately 11 years in most EE cases. This report documents the oldest patient with EE, highlighting the decisive impact of rehabilitation and sustained supportive care.* ***Conclusions:*** *EE should be considered in the differential diagnosis of atypical cerebral palsy, particularly when chronic diarrhea, acrocyanosis, or hemorrhagic manifestations are present. This case emphasizes the essential role of multidisciplinary rehabilitation and chronic care in improving quality of life and extending survival in individuals with disability due to rare metabolic disorders.*

Abreviaturas:
EEM = encefalopatía etilmalónica
PC = parálisis cerebral

INTRODUCCIÓN

La encefalopatía etilmalónica (EEM) es una enfermedad metabólica rara, caracterizada por la acumulación de etilmalonato, un metabolito que resulta de la disfunción en el metabolismo de los ácidos orgánicos. Esta condición se manifiesta clínicamente a través de una variedad de síntomas neurológicos, que pueden incluir retraso en el desarrollo, crisis convulsivas y alteraciones del comportamiento que pueden mimetizar a la parálisis cerebral (PC).

El objetivo de esta presentación de caso clínico es describir la historia clínica de un paciente diagnosticado con EEM, analizando los síntomas, las pruebas diagnósticas realizadas, el enfoque terapéutico y rehabilitatorio y el seguimiento a largo plazo. A través de este caso, se busca aumentar la comprensión sobre esta enfermedad poco frecuente, destacar el interés de contemplar la importancia dentro de los diagnósticos diferenciales para facilitar la detección temprana y, principalmente, subrayar las implicaciones del manejo de rehabilitación y soporte crónico como factores determinantes en la excepcional longevidad de este paciente.

MATERIAL Y MÉTODOS

Se han seguido los protocolos sobre la publicación de datos de pacientes, respetando la privacidad y contamos con la autorización de los padres del paciente bajo firma de consentimiento informado para su publicación.

CASO CLÍNICO

Hombre de 25 años de edad, hijo de padres aparentemente no consanguíneos. En los antecedentes familiares destaca madre con diabetes mellitus tipo 2 e hipertensión arterial esencial, hermana con crisis convulsivas desde los 15 días de vida y hermano con hemivértebra no especificada, infecciones recurrentes óticas con hipoacusia bilateral y *pectus excavatum (Figura 1)*. Es importante señalar que, al momento de la publicación, estos familiares no han sido estudiados genéticamente para la variante ETHE1 (Material complementario 1).

El paciente es producto de una tercera gesta, embarazo normoevolutivo, obtenido por cesárea, de 39 semanas de gestación, con un peso al nacimiento de 4,280 g (p97), talla 50 cm (p50), no se cuenta con datos de perímetro cefálico. No requirió ningún tipo de apoyo ventilatorio y fue dado de alta con su madre. Se le detectó luxación congénita de cadera y comenzó con evacuaciones líquidas persistentes, así como irritabilidad, presentando equimosis o petequias al mínimo contacto en la piel.

Se diagnosticó con retraso global del desarrollo e hipotonía de origen central a los ocho meses de edad, logrando deambulación claudicante y de puntillas a un año y seis meses, consigue decir frases, para comunicarse señala los objetos.

A los 18 meses de edad, se estableció el diagnóstico de PC, lo que marcó el inicio de un programa de rehabilitación pediátrico con manejo multidisciplinario con los objetivos de mejorar estado general, facilitar movilidad, reforzar alineación de segmentos, prevención y corrección de contracturas, reforzar control de cuello y tronco, movilidad asistida con silla de ruedas por medio de terapia física, ocupacional y de lenguaje,

así como orientación nutricional y manejo emocional reforzando redes de apoyo y acompañamiento psicológico con manejo por psicología, trabajo social y médico por rehabilitación pediátrica, pediatría, neuropediatría, audiología, genética, nutrición y ortopedia pediátrica. Se realizan estudios de audición reportados como normales. A pesar de la intervención, persistieron síntomas atípicos para la PC, como periodos de evacuaciones diarreicas (hasta 4-5 deposiciones al día) e irritabilidad. A los cuatro años se refiere estrabismo divergente con sacadas del ojo izquierdo, sin ptosis palpebral.

Según reporta la madre, el paciente ha presentado periódicamente episodios de hipoglucemia asociados a eventos de estrés metabólico como enfermedades infecciosas (al menos un episodio cada dos meses), ayunos prolongados y durante el sueño. A los cinco años, la madre comienza a notar acrocianosis ortostática en zonas de declive acompañadas de petequias y equimosis, gingivorragia durante el cepillado de dientes, epistaxis y fragilidad capilar. A esta edad, se agregó el diagnóstico de discapacidad intelectual moderada.

Figura 1:

Se observa postura de paciente con escoliosis severa en silla de ruedas de traslado.

Se realizó tenotomía de isquiotibiales, después de la cual el paciente no pudo recuperar la marcha, dejando la silla de ruedas como principal método de movilidad. Asimismo, se observó progresión de la hipotrofia muscular desde los nueve años y complicaciones relacionadas con la espasticidad como coxalgia y *clonus* en tobillo que limitaba posicionamiento en silla de ruedas, las cuáles fueron manejadas con toxina botulínica. Se realiza interconsulta por genética médica sin integrar diagnóstico. En investigación por gastroenterología debido a diarrea crónica, una colonoscopia evidenció poliposis crónica. Se deriva a urología, realizando ultrasonido renal con datos de sedimentos indicativos de cistitis crónica, el uretrocistograma confirma retención urinaria, con manejo con cateterismo intermitente o por periodos por sonda urinaria a permanencia. A los 17 años se procede a valoración urodinámica evidenciándose vejiga neurogénica con presencia y litiasis renal, se inicia oxibutinina. Presenta también problemas de deglución con derrame anterior descartando disfagia a líquidos. Sólo se ha referido una crisis convulsiva a los 19 años durante el sueño, generalizada, tónico-clónica con una duración de 10 minutos, alcanzando el estatus epiléptico, sin perder el control de esfínteres con estado postictal, se realizó EEG normal, pero posterior a dicho evento continuaron crisis parciales con espasmos en cabeza, de una duración de 3 minutos; la actividad epiléptica fue tratada con valproato de magnesio, actualmente suspendido y debido a irritabilidad por neuropediatría se inició risperidona 2 mg cada 12 horas. Se da de alta de rehabilitación pediátrica después de siete años a los 17 años seis meses, tras haber tomado 696 servicios, egresa con evaluación final de *Gross Motor Function Measure 88* con total de 27.11%, a) decúbito y volteo 74.51%, b) sentado 53.33%, c) gateo y posición de rodillas 0%, d) bipedestación 7.69%, y e) caminar, correr y saltar 0%, con WeeFIM inicial de 36, final de 64 de 126. Fue graduado de escolarización en educación especial en centro de atención múltiple en secundaria. Se ajusta con la familia un plan de manejo para casa con programa de terapia física, tratamiento electroanalgésico por coxalgia con equipo de TENS y medios físicos, e integración en actividades de inclusión en comunidad (equinoterapia), se integró a un programa de capacitación laboral, se adecuó dispositivo de asistencias tecnológicas con silla de ruedas (no fue candidato a andadera con soporte), se remodeló baño en su casa para facilitar traslados

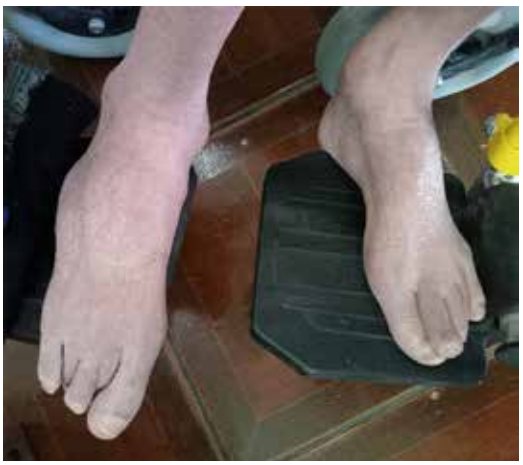

Figura 2:

Detalle del brazo del paciente, evidenciando petequias tras contacto mínimo y pies con acrocianosis ortostática.

e higiene y acompañamiento psicológico. Egresa con diagnóstico de parálisis cerebral espástica bilateral, nivel del sistema de la clasificación de la función motora gruesa IV, luxación de caderas bilateral, escoliosis, coxalgia, discapacidad intelectual moderada con trastorno de conducta asociado, diarrea crónica, poliposis intestinal, vejiga neurogénica, enfermedad ácido péptica y posible vasculitis (fenómeno de Reynaud, xerodermia, petequias y dermografismo).

Después de cinco años del alta de centro de rehabilitación pediátrico tras una actualización médica en metabolopatías que afectan el sistema nervioso central, el rehabilitador pediátrico a cargo vuelve a contactar a la familia por sospecha diagnóstica ya dirigida ante posible encefalopatía etilmalónica, derivando a interconsulta con médico especialista en genética en medio privado a los 22 años de edad.

El soporte nutricional reportado por la madre se basa en un régimen de comidas cocidas y caldos, con una variedad de proteínas (pollo, pescado a la plancha y carne guisada) y carbohidratos complejos como arroz con verduras (chayote, zanahoria y brócoli). Se incluyen jugos de guayaba, manzana, licuados nutritivos, «licuado de plátano con nueces» y preparaciones tradicionales. Destaca el uso de agua de arroz con canela, empleada específicamente para el manejo de los episodios recurrentes de diarrea crónica, lo que demuestra la continuidad y el meticuloso cuidado sintomático provisto por la red familiar.

En la exploración física se describen facies estrecha y alargada, ojos de apariencia hundida, cejas pobladas, puente nasal estrecho y alto, fisuras palpebrales oblicuas hacia arriba, lipodistrofia generalizada, narinas cortas, columela colgante, macrostomia aparente, *filtrum* corto, pabellón auricular derecho con rotación posterior, hélices desdoblados e hipoplásicos bilaterales, petequias en región periférica a pabellones, incisivos grandes, sobremordida superior, escoliosis en región lumbar severa, *pectus excavatum*, equimosis y petequias generalizadas en tórax y extremidades, xerodermia generalizada con zonas de descamación, manos de apariencia larga, uñas cóncavas en manos y pies, línea Sidney bilateral, hipoplasia tenar bilateral, acrocianosis en lechos ungueales y en ambos pies, pulsos pedios presentes pero débiles, *hallux valgus* bilateral, reflejos osteotendinosos rotulianos aumentados y signo Babinski positivo de predominio en pie izquierdo. Campos pulmonares hipoventilados, precordio sin soplo *(Figura 2)*.

No se cuenta con análisis bioquímico actual. Se comentó a los padres la sospecha y se realizó secuenciación Sanger de panel multigenes con el siguiente resultado: variante en gen *ETHE1* c.488G>A (p.Arg163Gln) en estado homocigoto, el cual se encuentra asociado a encefalopatía etilmalónica, cuyo cuadro clínico es correspondiente al de nuestro paciente. El tratamiento específico para EEM se implementó después del diagnóstico genético, lo que suma un periodo de tres años hasta diciembre de 2025, e incluyó: rivoflavina 100 mg/día, L-carnitina 500 mg/tres veces al día, coenzima Q10 100 mg/dos veces al día, N-acetilcisteína 20 mg/kg/día y vitamina E 400 IU por día, reportando mejoría parcial de la sintomatología.

DISCUSIÓN

La EEM es una enfermedad rara, autosómica recesiva, causada por variantes patogénicas en el gen ***ETHE1***,

que codifica la proteína mitocondrial Ethe1. Su deficiencia provoca acumulación de sulfuro de hidrógeno y tiosulfato, con manifestaciones neurológicas y multisistémicas graves.[1,2]

Nuestro paciente presentó desde la infancia signos expuestos con frecuencia en la literatura: retraso global del desarrollo, discapacidad intelectual, petequias, diarrea crónica, hipotonía, convulsiones, acrocianosis ortostática y espasticidad, además de hallazgos menos descritos como poliposis intestinal y vejiga neurogénica. En la revisión de 64 casos publicados, los síntomas más comunes fueron retraso del desarrollo/discapacidad intelectual (89%), hipotonía (82.8%), petequias (78.1%), diarrea crónica (75%) y acrocianosis (65.6%).[2-5]

La longevidad de 25 años en este caso es excepcional, ya que la mayoría de pacientes reportados fallecen en la primera década. El genotipo c.488G>A (p.Arg163Gln) ha sido descrito previamente con un fenotipo comparable, aunque en uno de esos reportes la paciente falleció a los seis años. Otras series documentan supervivencia prolongada únicamente en casos con trasplante hepático exitoso.[6-10]

En nuestro paciente, el tratamiento farmacológico específico se inició de manera tardía, por lo que el factor más relevante en su supervivencia parece ser el programa integral de rehabilitación y soporte crónico de su familia, que incluyó fisioterapia, terapia ocupacional, manejo de espasticidad y apoyos tecnológicos. Esto subraya que la atención no farmacológica de calidad puede influir decisivamente en la evolución clínica.

CONCLUSIONES

Este caso clínico representa la supervivencia más prolongada reportada en EEM y enfatiza la importancia del abordaje rehabilitador multidisciplinario como modulador de la calidad de vida y la longevidad. La experiencia destaca la necesidad de considerar la EEM en pacientes con parálisis cerebral atípica y síntomas de alarma como diarrea crónica, acrocianosis o manifestaciones hemorrágicas. Asimismo, refuerza la relevancia del diagnóstico temprano, la integración de cuidados de rehabilitación y la importancia del manejo familiar.

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Efectos del envejecimiento en el músculo esquelético e impacto del ejercicio en la salud muscular de adultos mayores

Effects of aging on skeletal muscle and the impact of exercise on muscle health in older adults

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Resumen

Uno de los fenómenos más comunes durante el envejecimiento es la sarcopenia, caracterizada por la pérdida de masa, fuerza y función del músculo esquelético. En este trabajo se revisan los principales mecanismos moleculares y celulares implicados en el deterioro progresivo del músculo asociado a la edad, tales como la sustitución del tipo de fibras (tipo II a tipo I), la infiltración de tejido fibroadiposo, la fibrosis, la disfunción del metabolismo mitocondrial y la senescencia de las células satélite. Así mismo, se abordan los efectos benéficos del ejercicio físico en procesos como la biogénesis mitocondrial, la expresión de miocinas, la vascularización del tejido muscular y las diferentes regulaciones a nivel epigenéticos en pro de la mejora de la función muscular.

Abstract

One of the most common phenomena during aging is sarcopenia, characterized by the loss of skeletal muscle mass, strength, and function. This work reviews the main molecular and cellular mechanisms involved in the progressive deterioration of aging muscle, such as the shift from type II to type I muscle fibers, infiltration of fibroadipose tissue, fibrosis, mitochondrial metabolic dysfunction, and satellite cell senescence. Additionally, the beneficial effects of physical exercise will be addressed, including its role in promoting mitochondrial biogenesis, myokine expression, muscle tissue vascularization, and various epigenetic regulations that support the improvement of muscle function.

INTRODUCCIÓN

Durante el envejecimiento se presentan distintos cambios fisiológicos que impactan de forma directa en la calidad de vida. Dentro de estos cambios, el más notorio es el deterioro de la función del músculo. Esto afecta tanto la movilidad y la independencia corporal como procesos metabólicos.

El ejercicio físico ha demostrado ser una herramienta útil para combatir los efectos negativos que produce el envejecimiento en el músculo. Existen numerosas investigaciones que demuestran la capacidad de la actividad física para mejorar la función mitocondrial, reducir procesos inflamatorios, promover la síntesis de proteínas y conservar la fuerza del músculo.

Este trabajo abarca los principales efectos del envejecimiento sobre el músculo y los beneficios del ejercicio para disminuirlos, proponiendo el ejercicio físico como una estrategia efectiva para mantener la salud muscular durante la vejez.

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MÚSCULO ESQUELÉTICO

El músculo esquelético (ME) es un tejido plástico y dinámico que se encuentra unido a los huesos del cuerpo. Representa aproximadamente el 40% del peso total del cuerpo humano. Se constituye por una red de células tubulares, fusionadas y multinucleadas denominadas fibras musculares, organizadas en grupos más grandes llamados fascículos.[1-3] Esta red de fibras se encuentra altamente inervada y vascularizada debido a que las fibras poseen la propiedad de contraerse y relajarse, lo que provoca a su vez una alta demanda de energía. Estas propiedades permiten al ME llevar a cabo su función principal desde una perspectiva mecánica: convertir energía química en energía mecánica para permitir el mantenimiento de la postura y el movimiento del cuerpo y así posibilitar la realización de las actividades diarias. Para llevar a cabo estas actividades, el cuerpo humano cuenta con alrededor de 599 músculos, cada uno con diferentes propiedades contráctiles.[2-4]

IMPORTANCIA DEL MÚSCULO ESQUELÉTICO EN LA SALUD

Más allá de sus propiedades mecánicas y estructurales, el ME es un órgano metabólicamente activo que lleva a cabo funciones primordiales en la homeostasis energética, la inmunorregulación y la prevención de enfermedades crónicas.[1,3] Su deterioro durante el envejecimiento tiene un impacto negativo en la calidad de vida y la funcionalidad del organismo.

El ME es el principal reservorio de aminoácidos del organismo.[2,3] Se ha estudiado que las proteínas musculares pueden degradarse en aminoácidos esenciales que funcionan como precursores en la síntesis proteica y en rutas metabólicas como la gluconeogénesis, cuando los niveles séricos de éstos disminuyen en situaciones de estrés fisiológico como el ayuno o en enfermedades críticas.[5-7] En condiciones de estrés como traumatismo, sepsis o quemaduras la demanda de aminoácidos producto de la degradación muscular se incrementa y toma un rol primordial para los procesos como la síntesis de enzimas, proteínas inmunológicas y otros factores reparadores.[8]

El ME también desempeña un papel importante en la regulación del metabolismo de la glucosa, ya que es el principal sitio de captación de glucosa inducida por insulina, volviéndose esencial para el control glucémico y la prevención de enfermedades como la diabetes tipo 2. La reducción de la masa muscular se ha asociado a una mayor resistencia a la insulina y a un mayor riesgo de padecer enfermedades cardiometabólicas.[9]

Además, el ME actúa como un órgano endocrino al secretar miocinas tales como IL-6, irisina y factor neutrófico derivado del cerebro (BDNF). Estas sustancias tienen un efecto antiinflamatorio y modulador sobre otros tejidos y participan en otros procesos como la plasticidad sináptica, la modulación del metabolismo sistémico y la remodelación ósea. Estudios han afirmado que la pérdida muscular afecta negativamente la densidad ósea y la biomecánica corporal, lo que aumenta el riesgo de fracturas y caídas.[10,11]

INFLUENCIA DEL ENVEJECIMIENTO SOBRE EL MÚSCULO ESQUELÉTICO

Al envejecer, el ME sufre diferentes cambios, tanto morfológicos como fisiológicos, que afectan su integridad y desempeño. El principal fenómeno que aparece durante el envejecimiento es la pérdida de la fuerza, la función y la masa muscular, fenómeno conocido como sarcopenia *(Tabla 1)*.[12]

En el adulto mayor, la sarcopenia es catalogada como un síndrome musculoesquelético asociado a la edad, caracterizado por la disminución del tejido muscular, así como por alteraciones en su calidad, cambios en la composición de las fibras musculares y disminución de la capacidad contráctil del ME.[13,14] Incluso desde antes de llegar a la tercera edad, el ME empieza a perder masa y volumen; se sabe que después de los 30 años el ser humano empieza a perder alrededor del 0.1 al 1% de la masa muscular y, al llegar a los 74 años, esta pérdida avanza a una tasa anual del 0.8%.[15-17] A nivel motor, este desgaste se ve acompañado por la disminución del número de unidades motoras en los músculos de las piernas, como lo es el tibial anterior.[18,19] Aunado a esto, la sarcopenia tiene como consecuencia una mayor fragilidad corporal y mayor riesgo de caídas y, por ende, cierta pérdida de autonomía e independencia física.[17]

A nivel tisular, en procesos de sarcopenia, existe una disminución en el número y el tamaño de las fibras musculares. Este proceso suele ser selectivo, debido a que las fibras de tipo II, de mecanismo glucolítico y de contracción rápida, son las más afectadas durante este fenómeno.[20,21] Por el contrario, las fibras de tipo I, de metabolismo oxidativo y contracción lenta, suelen verse menos afectadas durante la sarcopenia. Se conoce que, durante el envejecimiento, hay un aumento en la expresión de enzimas glucolíticas como PKM, PGK1

y GADPH en las fibras de tipo I,[22,23] así como una disminución de proteínas chaperonas como UNC45B, HSP90AA1, CRYAB en las fibras de tipo II.[23,24]

Además, se ha observado que, en procesos de sarcopenia en adultos mayores, existen cambios en la arquitectura fascicular y una mayor infiltración de tejido adiposo intramuscular.[25,26] Durante el envejecimiento se presentan modificaciones en la matriz extracelular como una mayor acumulación de colágeno relacionada con la pérdida de plasticidad en las fibras, lo que conlleva una acumulación excesiva de tejido conectivo, fenómeno conocido como fibrosis endomisial.[27-29] Aunado a esto, investigaciones recientes afirman que, durante el envejecimiento, los progenitores fibroadipogénicos se diferencian a un estado profibrótico[27] que, a su vez, se acompaña de una acumulación de células senescentes y de productos de desecho.[30] Estos procesos conducen a un reemplazo progresivo de las fibras musculares funcionales, provocando la ya mencionada pérdida de la función muscular característica de la sarcopenia.

Los cambios mencionados no sólo modifican negativamente la calidad del músculo a nivel tisular, sino que también causan un deterioro a nivel metabólico, incrementando la resistencia anabólica a los aminoácidos y a la síntesis de proteínas de la ingesta proteica.[31,32] A nivel proteico, los cambios en el músculo están mediados por las vías catabólicas como la vía de degradación ubiquitina-proteasoma, reguladas a su vez por vías de señalización como la vía IGF-1/Akt/mTOR, las cuales se ven modificadas en el músculo envejecido.[33,34] Por otro lado, la infiltración de tejido adiposo en las fibras del ME conlleva el aumento de especies reactivas de oxígeno y el incremento de citocinas proinflamatorias tales como IL-6 y TNF-α, favoreciendo un microambiente inflamatorio que promueve la degradación proteica.[35-38]

En consonancia con el deterioro metabólico e inflamatorio, existen estudios que han señalado que el envejecimiento se asocia a un declive en la función mitocondrial en el ME. Se ha estudiado que, con la edad, el contenido mitocondrial disminuye en ambos tipos de fibra del ME.[39] A su vez, durante el envejecimiento se incrementa la expresión de proteínas relacionadas con la mitofagia tales como BNIP3 y SQSTM1, y disminuye la expresión de proteínas reguladoras de la fusión mitocondrial como OPA1 y MFN2, especialmente en fibras de tipo II.[40]

Recientemente, un estudio señaló que entre adultos jóvenes y adultos mayores existen diferencias

Tabla 1: Influencia del envejecimiento sobre el músculo esquelético.

Estudio, año de publicación	Población	Tipo de estudio	Resultados
Piasecki et al. 2016	Hombres 26 ± 5 y 71 ± 4 años	Transversal	Pérdida de unidades motoras y remodelación neuromuscular con la edad
Engelke et al. 2022	Hombres 20-70 años	Transversal	Aumento de grasa intramuscular con la edad
Grevendonk et al. 2021	20-70 años	Transversal	Reducción de capacidad oxidativa mitocondrial y función física con la edad
Murgia et al. 2017	Adultos jóvenes y mayores	Transversal	Cambios proteómicos específicos por tipo de fibra en el envejecimiento

Tabla 2: Efectos del ejercicio en el músculo esquelético de adultos mayores.

Estudio, año de publicación	Tipo de ejercicio	Protocolo	Resultados
Hurley et al. 2019	Aeróbico	12 semanas, 4 días/semana, 40 minutos a 70% de la frecuencia cardiaca de reserva	↑ función microvascular y perfusión muscular
Singh et al. 1999	Resistencia	Programa progresivo 72-98 años	↑ fuerza, ↑ IGF-I intramuscular, ↑ fibras tipo II
Macedo Santiago et al. 2018	Resistencia	Ocho semanas, tres sesiones/semana	↓ IL-6, TNF-α; ↓ inflamación sistémica
Grevendonk et al. 2021	Entrenamiento habitual (crónico)	Grupos entrenados versus no entrenados	↑ capacidad mitocondrial en mayores entrenados

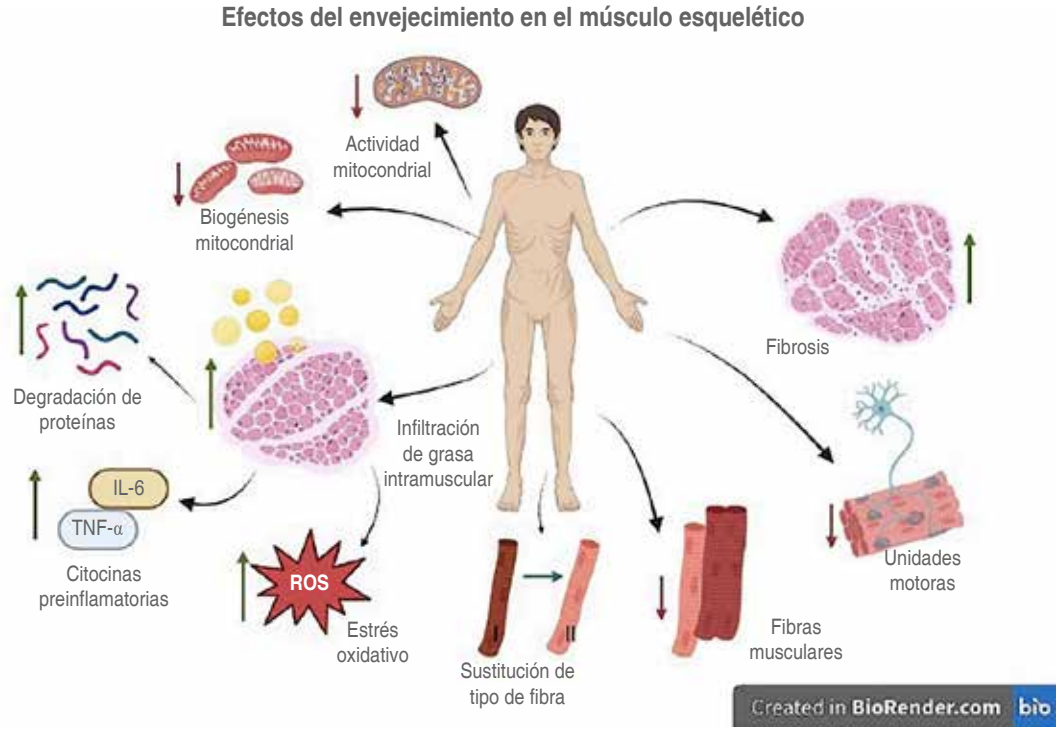

Figura 1: Influencia del envejecimiento sobre procesos involucrados en el músculo esquelético: disminuye la actividad y la biogénesis mitocondrial, el número de unidades motoras y de fibras musculares, las cuales presentan una sustitución de fibras tipo I por fibras tipo II; además, aumenta la infiltración de tejido fibroadiposo muscular, lo que conduce a un incremento en la degradación de proteínas, en la expresión de citocinas preinflamatorias y a un ambiente favorable para la degradación de proteínas. Imagen creada utilizando el programa BioRender (www.biorender.com)
ROS = especies reactivas de oxígeno.

notables en cuanto a la respuesta al ejercicio.[41] En este estudio se demostró que los adultos mayores mostraron tener una menor capacidad oxidativa mitocondrial y que existe una correlación entre esta capacidad y la función muscular. Esto sugiere que la disminución de la eficiencia mitocondrial puede contribuir al deterioro de la función del ME asociado con el envejecimiento. De manera conjunta, estos hallazgos refuerzan la idea de que la salud muscular durante el envejecimiento no sólo es esencial para la locomoción, sino que constituye un eje importante para la salud metabólica, inmunológica y funcional; asimismo, la preservación del ME resulta clave para mantener dichas funciones *(Figura 1)*.

BENEFICIOS DEL EJERCICIO EN EL MÚSCULO ESQUELÉTICO DE ADULTOS MAYORES

La disminución de la actividad mitocondrial, asociada a la edad, está relacionada con la falta de actividad física.[42] Por otra parte, trabajos de investigación han revelado que la actividad física es beneficiosa para el metabolismo mitocondrial, el aumento de la proteína total y el incremento de la biogénesis mitocondrial a través de la activación de PGC-1α, que regula la expresión de factores como NRF1 y TFAM, esenciales para la replicación y transcripción del DNA mitocondrial. Esta activación mejora la eficiencia energética del ME y reduce el estrés oxidativo, factores clave en el deterioro muscular asociado a la edad.[43-46] En conjunto, estas adaptaciones mitocondriales mejoran la capacidad oxidativa del músculo y la eficiencia en la producción de trifosfato de adenosina (ATP), lo cual contribuye a una mayor resistencia a la fatiga muscular en la vejez.

En el ámbito molecular, se sabe que el ejercicio estimula la activación de células satélite y de las vías promotoras de síntesis de proteínas que conducen a la hipertrofia de las fibras musculares.[31] El ejercicio disminuye la expresión de proteínas que participan

en vías de señalización de degradación muscular como TNF-α e IL-6.[32,47,48] Se sabe también que el ejercicio aeróbico y anaeróbico en adultos mayores puede incrementar la expresión de miocinas antiinflamatorias como irisina, BDNF, decorina, IGF-1, ácido β-aminoisobutírico, IL-15 y SDF-1 que influyen en distintos procesos metabólicos del organismo.[49-53] Otras miocinas como apelina (aeróbico), BMP-7 y SPARC (aeróbico), y sestrina, involucradas directamente en proceso de formación, irrigación y crecimiento del ME, también se ven incrementadas con el ejercicio aeróbico de resistencia.[54-58]

El ejercicio optimiza el uso de la glucosa en el ME induciendo así un mayor transporte de GLUT4, lo que permite mantener niveles adecuados de glucosa sérica, disminuyendo el riesgo de resistencia a la insulina;[59] esto podría compensar también la disminución de fibras glucolíticas.

Otros estudios indican que el ejercicio regular puede reducir la acumulación de células envejecidas en el ME e inducir la activación de rutas antioxidantes como las controladas por enzimas como SOD2 y GPx, que participan en vías que atenúan el estrés oxidativo producido por el envejecimiento, donde hay un aumento del metabolismo de las fibras oxidativas.[60,61]

MODIFICACIONES EPIGENÉTICAS

En las últimas décadas, estudios han mostrado que el ejercicio físico estimula diferentes mecanismos postranscripcionales en el ME. Se conoce que estos mecanismos pueden mediar modificaciones epigenéticas como son las metilaciones en las histonas, lo que regula la transcripción de distintos genes como *Rbm10* y *Timm8a1,* los cuales participan en procesos como la actividad mitocondrial y el *splicing* alternativo.[24,62] En el ME el ejercicio induce mecanismos como la metilación m6a del mRNA que modula vías de proliferación y diferenciación celular, atrofia e hipertrofia.[63-68]

MODIFICACIONES ESTRUCTURALES

El ejercicio puede estimular adaptaciones en la estructura del ME que son observables en adultos mayores. A nivel de circulación, se ha estudiado que la actividad física incrementa la expresión de VEGF (factor de crecimiento endotelial vascular, por sus siglas en inglés), incrementando así la angiogénesis y la vascularización del tejido muscular, mejorando así la irrigación sanguínea.[69] Además, se ha señalado que el ejercicio aeróbico mejora la función micro- y macrovascular en el ME. Esto puede compensar la pérdida de unidades motoras que ocurre en el envejecimiento, ayudando a preservar la integridad y la función muscular.[19,69-72] El ejercicio contribuye también a disminuir la infiltración de tejido fibroadiposo en las fibras musculares, contribuyendo a un correcto funcionamiento del ME *(Tabla 2)*.[73,74]

Estos hallazgos refuerzan que el ejercicio es una actividad importante para conservar el funcionamiento del músculo a lo largo del proceso de envejecimiento.

CONCLUSIONES

El envejecimiento conlleva una serie de cambios morfológicos, funcionales y moleculares que afectan de forma negativa la estructura y el desempeño del ME, incrementando el riesgo de sarcopenia y enfermedades metabólicas. Sin embargo, la evidencia científica demuestra que el ejercicio físico no es sólo una herramienta preventiva, sino que también es una estrategia terapéutica capaz de contrarrestar los diferente aspectos del deterioro muscular, desde la mejora en la biogénesis mitocondrial y la sensibilidad a los aminoácidos, hasta la activación de rutas anabólicas, antiinflamatorias y antioxidantes. La actividad física regular impacta positivamente en la salud muscular, metabólica y sistémica de las personas mayores.

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Los beneficios de tratar la discapacidad visual relacionada con catarata

The benefits of treating cataract-related visual disability

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Resumen

El objetivo principal de la cirugía de catarata es mejorar la visión, aunque tiene otros efectos sobre la salud en general como aumentar la capacidad de desplazamiento y facilitar la relación interpersonal del paciente. La catarata en adultos mayores puede coexistir con otras causas de discapacidad; su abordaje puede verse limitado debido a la restricción visual. La cirugía de catarata puede facilitar atender otras discapacidades, lo que amplifica su beneficio, aunque la agudeza visual se limite por comorbilidades. En esta revisión narrativa se aborda la discapacidad visual en pacientes con dos enfermedades extraoculares y cuatro oculares. Se destaca el beneficio que puede obtenerse al reducirla mediante la cirugía de catarata.

Abstract

The main objective of cataract surgery is improving vision, and it has other effects over general health such as increasing mobility and making the patient's interpersonal relations easier, which improve quality of life. Cataracts in elder people may coexist with other ocular and extraocular diseases that cause disability, whose approach can be limited by the visual restriction that cataract causes. Since cataracts are a reversible cause of disability, treating it surgically can make easier to deal with other disabilities, so this intervention amplifies the benefit, even when comorbidities could limit visual acuity results. This narrative revision work deals with visual disability in patients with two extraocular and four ocular diseases, and outlines the benefit that could be achieved by reducing it with cataract surgery.

INTRODUCCIÓN

La catarata es una opacidad de cristalino que limita la visión del paciente y puede causar discapacidad desde etapas tempranas, dependiendo de las necesidades visuales de cada individuo. En nuestro país, como en otros países de la región, el acceso a cirugía para tratar la catarata puede restringirse por la ubicación de las unidades médicas que la realizan o por el costo que debe cubrir el paciente. Retrasar la cirugía de catarata puede aumentar la discapacidad, sobre todo cuando coexisten otras causas de ésta; ante la presencia de varias causas de discapacidad, tratar una causa recuperable puede facilitar el manejo de las restantes.

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El tratamiento de la catarata se basa en su remoción quirúrgica y la sustitución del cristalino opaco con una lente intraocular. Se trata de un procedimiento que se realiza en forma ambulatoria, bajo anestesia local, que ofrece una rehabilitación temprana, con un periodo de recuperación corto; en nuestro país, un estudio de Nuevo León reportó una cobertura efectiva de cirugía de catarata de 54.1%.[1]

Esta revisión narrativa busca identificar y sintetizar la información existente sobre la interacción entre la discapacidad visual por catarata y otras condiciones discapacitantes, con el propósito de delinear el beneficio que aporta la cirugía de catarata, más allá de la restitución de la agudeza visual.

DISCAPACIDAD VISUAL POR CATARATA Y SU IMPACTO EN LA CALIDAD DE VIDA DEL PACIENTE

Para el año 2020, la catarata era aún una de las principales causas de ceguera en el mundo y ocupaba el segundo lugar como causa de discapacidad visual moderada y severa.[2] Aunque la discapacidad que causa la catarata es reversible,[1] altera la calidad y la expectativa de vida de las personas,[3,4] independientemente del tipo de opacidad del cristalino.[5]

La Organización Mundial de la Salud (OMS) define la calidad de vida como la percepción individual de la posición en la vida, en el contexto de la cultura y los sistemas en los que se vive, en relación con los objetivos, expectativas, estándares y preocupaciones personales; en resumen, se refiere al bienestar físico, emocional y social. Medir la calidad de vida permite evaluar el éxito de un tratamiento y la satisfacción del paciente con la vida en general; la calidad de vida es difícil de medir debido a la subjetividad y experiencias individuales.[3,6]

Diversos cuestionarios miden la calidad de visión y la calidad de vida de los pacientes; en el contexto de cirugía de catarata, el más comúnmente usado es el *Visual Function Index 14* (VF-14), que contiene 14 apartados en relación con actividades de la vida diaria como leer, escribir, ver los pasos, las escaleras y manejar un vehículo. Los estudios que han usado este instrumento y otros de segunda generación (*Rasch-validated IVI*, una nueva versión del VF-14, y el Catquest-9SF) han demostrado una mejoría en la calidad visual y de vida en los pacientes después de la cirugía,[6] aunque no se ha medido en pacientes con catarata ni con otras causas de discapacidad.

La catarata es una causa independiente de discapacidad visual, que puede deteriorar la discapacidad asociada a otras enfermedades, oculares o extraoculares; la coexistencia de otras enfermedades oculares que causan discapacidad puede limitar el resultado funcional de la cirugía de catarata. Se realizó una revisión narrativa para abordar dos enfermedades extraoculares y cuatro oculares asociadas con la discapacidad causada por catarata, cuyo manejo y pronóstico puede mejorar el tratamiendo de esta enfermedad.

Las causas extraoculares de discapacidad se seleccionaron en función del potencial preventivo que tiene una mejor orientación visuoespacial, que se alcanza después de la cirugía de catarata. Como causas oculares de discapacidad se seleccionaron las enfermedades crónicas, cuya mayor repercusión se presenta en pacientes cuya edad favorece la aparición de cataratas. Para las seis enfermedades: la catarata agrega riesgo (fracturas), acentúa la deprivación sensorial (demencia), limita el seguimiento (retinopatía diabética, glaucoma, degeneración macular) o puede agravarse con el tratamiento (uveítis). En una población vulnerable, poder reducir la discapacidad eficazmente y a corto plazo es una ventaja que conviene otorgar al paciente.

El objetivo del trabajo fue identificar la experiencia disponible sobre el manejo conjunto de la catarata y las otras causas de discapacidad, mediante una búsqueda en PubMed y Scopus, que incluyó estudios clínicos, epidemiológicos y revisiones, tanto sistemáticas como no sistemáticas, para poder estimar el beneficio de la cirugía de catarata, ya que no se dispone de estadísticas nacionales donde se reporte ese abordaje simultáneo.

DISCAPACIDAD VISUAL POR CATARATA EN PACIENTES MAYORES DE 60 AÑOS QUE PRESENTAN FRACTURAS ASOCIADAS A CAÍDAS

Las cataratas aparecen típicamente en la edad adulta, comúnmente como un desorden relacionado con la edad; en 2020, la catarata afectó a más de 15 millones de adultos mayores de 50 años y representó aproximadamente 45% de los casos de ceguera a nivel mundial.

Las fracturas en adultos mayores son frecuentes debido, en parte, a que en esta población disminuye la movilidad y densidad ósea, lo cual aumenta el riesgo de osteoporosis y fracturas en los huesos de soporte como la cadera y la columna vertebral. Una fractura puede requerir una rehabilitación prolongada, lo que aumenta la dependencia del paciente a otras personas; también disminuye la confianza, lo que limita aún más la actividad física y exacerba el riesgo de futuras fracturas. En pacientes mayores, la rehabilitación después de una fractura puede ser más prolongada que en otros grupos etarios; el impacto psicológico de las fracturas genera aislamiento social, debido a la pérdida de confianza de los pacientes en sí mismos; en conjunto con los otros factores mencionados, disminuye la calidad de vida y aumenta la mortalidad.

La etiología de las fracturas en adultos mayores es multifactorial; el déficit motor y sensorial juegan papeles trascendentales; en particular, el deterioro visual es crítico, pues impide al individuo conducirse de manera segura dentro de su medio por la limitación en la agudeza visual, alteraciones en la percepción de profundidad, baja sensibilidad al contraste y pérdida del campo visual.[7]

Algunos estudios reportan que las caídas ocurren al menos una vez al año en 30% de los pacientes mayores de 65 años y en 50% de mayores de 80; muchas terminan en fracturas graves, principalmente de cadera; las fracturas en el adulto mayor son un problema grave para el individuo y generan altos costos que impactan a los sistemas de salud, al requerir hospitalización y tratamientos de alta especialidad. Un factor de riesgo asociado con frecuencia es el deterioro visual secundario a catarata, seguido de los errores refractivos no corregidos; una estrategia para reducir los riesgos de caídas y consecuentes fracturas es mejorar la visión de los pacientes con catarata mediante una cirugía temprana.[8]

Resulta entonces relevante, en primer lugar, realizar estudios para conocer el estado de salud visual en la población de adultos mayores y, en segundo lugar, generar estrategias de rehabilitación visual temprana y prevención de la ceguera. Si bien existen guías internacionales de prevención de caídas como las del *National Institute for Health and Care Excellence,* que incluyen la detección de problemas visuales, no se aplican debidamente ni de manera estandarizada en la mayoría de las instituciones de salud; un reporte del *Royal College of Physicians* de 2011 sobre caídas y fracturas secundarias en adultos mayores refería que sólo 17% de los pacientes con fractura de cadera secundaria habían tenido un examen visual formal previo al incidente.[9,10]

Una estrategia para reducir el riesgo de caídas en los pacientes con catarata es su extracción mediante facoemulsificación y la colocación de una lente intraocular.[11] En un metaanálisis de 2025, los pacientes postoperados de catarata tuvieron una reducción del riesgo de fractura de 26% frente a los pacientes con catarata no operada.[7]

DISCAPACIDAD VISUAL POR CATARATA EN PACIENTES CON DEMENCIA

La demencia afecta a casi 50 millones de personas en el mundo. Aún no existen tratamientos efectivos para esta enfermedad, por lo que son importantes los esfuerzos para reducir o retrasar su aparición.[12] Una proporción de los adultos mayores de 65 años presenta deterioros sensoriales significativos como pérdida visual o auditiva, que constituyen riesgos para desarrollar demencia; manejar estas pérdidas sensoriales puede modificar potencialmente ese riesgo.[13]

En la demencia senil hay degeneración progresiva del tejido cerebral; el mecanismo depende de la etiología (enfermedad de Alzheimer, demencia vascular, agregados anómalos de proteínas: cuerpos de Lewy en demencia por Parkinson, etc.); otras demencias pueden involucrar isquemia crónica (infartos cerebrales múltiples en la demencia vascular). Clínicamente, la demencia se manifiesta por pérdida de la memoria, alteraciones del lenguaje, desorientación, dificultades en las funciones ejecutivas y cambios de personalidad

o comportamiento. Estos cambios son irreversibles y progresivos, lo que lleva a una dependencia total; además de las lesiones neurales específicas, suele haber atrofia cortical generalizada.

La visión es fundamental para interactuar socialmente, reconocer rostros, mantener contacto visual, leer expresiones faciales y el lenguaje corporal; la catarata en adultos mayores puede provocar dificultades psicosociales, aislamiento y reducción de la actividad o el ejercicio, todo ello asociado con el deterioro cognitivo.[13]

En el paciente con demencia que padece cataratas, pueden agravarse los síntomas neuropsiquiátricos, incluyendo alucinaciones visuales, ilusiones, ideas paranoides, depresión, apatía o agitación. Una visión baja puede exacerbar estos síntomas: al no ver adecuadamente, pueden malinterpretarse estímulos visuales ambiguos, lo cual podría coincidir con la identificación errónea de personas y objetos, aparición de alucinaciones visuales o delirios paranoides. En pacientes con demencia, la disminución de agudeza visual se ha asociado con alucinaciones (razón de momios [RM] ~10), síntomas psicóticos (RM ~6) y manía (RM ~5), mientras que la pérdida de visión se correlaciona con más depresión y agitación.[13]

La disminución del riesgo para desarrollar demencia tras retirar las cataratas también podría asociarse con una mayor cantidad y calidad de luz percibida. Se ha demostrado que las células ganglionares de la retina, intrínsecamente fotosensibles (ipRGC) y en extremo sensibles a la luz de onda corta (azul), están asociadas con la función cognitiva, el ritmo circadiano y la enfermedad del Alzheimer. Las ipRGC se proyectan a múltiples áreas del cerebro y su excitación puede desencadenar una actividad cortical generalizada; se ha propuesto que, al extraer las cataratas, el retiro del tono amarillo del cristalino que bloquea la luz azul facilitaría la estimulación de las ipRGC y podría reducir el riesgo de demencia.[14]

Lee y su equipo evaluaron 3,038 adultos de 65 años o más con cataratas; existió un menor riesgo de desarrollar demencia (razón de riesgos 0.71; intervalos de confianza [IC] del 95%, 0.62-0.83; $p < 0.001$) en quienes se retiró la catarata que en quienes no se operaron;[14] las cataratas también se asocian con síndrome de fragilidad, riesgo de caídas, fracturas, accidentes automovilísticos, depresión y deterioro cognitivo. La asociación entre discapacidad visual y depresión se explica por la menor frecuencia de actividades como la lectura, pérdida de autonomía, interacción social disminuida y pérdida de autoestima;[15] el beneficio de retirar la catarata para reducir el riesgo de depresión es independiente de la edad y el sexo.[16]

La cirugía de catarata suele ser segura y efectiva en pacientes con demencia; no se ha encontrado un riesgo mayor de complicaciones quirúrgicas u hospitalizaciones postoperatorias en pacientes con demencia que en pacientes sin ella. Los riesgos se centran en el manejo anestésico y la adherencia a los cuidados postoperatorios; con planificación adecuada (por ejemplo, decidir tempranamente usar anestesia general para evitar estrés intraoperatorio en un paciente no cooperador) y con el apoyo cercano de los cuidadores, la cirugía de catarata suele ser segura y efectiva también en esta población.[17]

La cirugía de catarata en los adultos mayores es un procedimiento altamente costo-efectivo por los beneficios sobre la salud, independientemente de su impacto en la esfera cognitiva;[18] tratar las cataratas en pacientes con demencia requiere un enfoque ético centrado en la persona y compartido con la familia. Como la cirugía de catarata se asocia con un riesgo menor para desarrollar demencia en los adultos mayores y su efecto persiste más de 10 años, la mejora en la calidad de vida de las personas afectadas y sus familias es considerable, con un impacto favorable sobre la dignidad del paciente y su dinámica de cuidado.

DISCAPACIDAD VISUAL POR CATARATA EN PACIENTES CON DEGENERACIÓN MACULAR

La degeneración macular relacionada con la edad es una enfermedad en que el área de la retina con la mejor resolución (mácula) presenta cambios que pueden llevar a la atrofia o a la formación de neovasos; en ambos casos, los pacientes pueden presentar una pérdida de la visión central. El tratamiento para la forma neovascular se basa en la inyección intraocular de fármacos antiangiogénicos, mientras que, para la atrofia, no existe aún un tratamiento eficaz. Las cataratas pueden acentuar la discapacidad visual en pacientes con degeneración macular; alrededor de 74% de las personas mayores de 65 años con pérdida visual tienen simultáneamente cataratas y degeneración macular relacionada con la edad.[19]

La cirugía de cataratas facilita el seguimiento de la degeneración macular relacionada con la edad;[19-21] la mayoría de los estudios no ha identificado una asociación significativa entre la cirugía de catarata y un mayor riesgo de progresión y desarrollo de la degeneración macular relacionada con la edad.[19] Tanto los pacientes con degeneración macular neovascular

como los que tienen degeneración macular atrófica mejoran su agudeza visual después de la cirugía de catarata; aunque el grosor macular puede aumentar después de la cirugía, regresa al nivel preoperatorio seis meses después de ella. En pacientes con degeneración macular neovascular, la necesidad de terapia antiangiogénica no cambia en el postoperatorio.[22]

La literatura sugiere programar la cirugía de catarata al menos seis meses después del inicio de la terapia antiangiogénica, cuando la actividad neovascular macular podría estar suficientemente controlada. Las inyecciones intravítreas con antiangiogénicos en las semanas previas e incluso durante la cirugía de catarata reducen el riesgo de que se reactiven las lesiones neovasculares coroideas.[20]

Es importante elegir el momento adecuado, ya que no se justifica retrasar la cirugía de cataratas en pacientes que la requieran y tengan la variedad atrófica de degeneración macular.[23]

DISCAPACIDAD VISUAL POR CATARATA EN PACIENTES CON GLAUCOMA

La coexistencia de catarata y glaucoma representa un desafío clínico debido a que ambas condiciones afectan la visión, en forma distinta, pero complementaria; la pérdida visual inducida por catarata suele revertirse mediante la cirugía, pero el daño visual que causa el glaucoma es irreversible. La catarata, como opacidad del cristalino, produce una disminución progresiva de la agudeza visual, visión borrosa, fotofobia, deslumbramiento y reducción en la sensibilidad al contraste y a los colores; en cambio, el glaucoma es una neuropatía óptica progresiva, frecuentemente asociada con hipertensión ocular, que se manifiesta inicialmente por pérdida del campo visual paracentral y, en estadios avanzados, afecta la visión central hasta llegar a la ceguera.

La discapacidad visual en estos pacientes combina la pérdida de agudeza visual secundaria a la catarata y la restricción del campo visual ocasionada por el glaucoma; esta afección conjunta puede reducir de forma considerable la funcionalidad visual, incluso si la agudeza visual central no parece estar alterada gravemente. En estadios avanzados, esta combinación puede generar una discapacidad visual importante, con repercusión directa en la autonomía y calidad de vida del paciente.

La coexistencia de catarata y glaucoma también implica un reto diagnóstico, ya que la primera puede limitar la evaluación clínica del nervio óptico. Además, la reducción de la sensibilidad al contraste espacial y temporal que induce la catarata puede interferir con la detección de un glaucoma que debuta o que progresa.[24]

El manejo quirúrgico de estos pacientes representa un desafío terapéutico: la presencia de glaucoma aumenta el riesgo de complicaciones transoperatorias (ruptura de la cápsula posterior, necesidad de implantar el lente intraocular en el surco ciliar o realizar una vitrectomía anterior) y postoperatorias (inflamación intraocular más intensa, hipertensión ocular prolongada y la posible necesidad de una segunda cirugía).

Los resultados visuales, tanto de agudeza como de calidad visual, suelen ser más limitados en pacientes con glaucoma que en pacientes sin él.[25] No obstante, a pesar de los mayores riesgos quirúrgicos y de resultados visuales más modestos, la cirugía de catarata puede mejorar significativamente la calidad de vida de los pacientes con glaucoma.[25-27]

La cirugía de catarata también puede tener un efecto benéfico sobre ciertos índices del campo visual en pacientes con glaucoma, aunque esto depende del tipo de opacidad lenticular y del estadio del daño glaucomatoso. Por ejemplo, se ha observado que las cataratas nucleares interfieren menos con los parámetros campimétricos que las corticales o subcapsulares.[28,29]

La coexistencia de catarata y glaucoma exige un abordaje individualizado, con una evaluación minuciosa de los riesgos y beneficios, con el objetivo de optimizar la función visual y mejorar la calidad de vida del paciente. En resumen, aunque el glaucoma limita la recuperación total, la cirugía sigue siendo costo-efectiva.

DISCAPACIDAD VISUAL POR CATARATA EN PACIENTES CON RETINOPATÍA DIABÉTICA

La causa más frecuente de pérdida visual en personas que padecen diabetes es la catarata; sin embargo, la retinopatía diabética, complicación crónica y específica de la enfermedad metabólica, puede causar una pérdida visual irreversible. En la retinopatía diabética, el cierre capilar que induce la diabetes causa isquemia de la retina y, en algunos casos, hemorragia vítrea, cicatrización glial o desprendimiento de la retina; como el descontrol metabólico contribuye a la formación de catarata, los ojos con daño retiniano tienen también posibilidad de desarrollarla, incluso a una edad menor a la habitual.[30]

En el estudio de Das y su equipo, de un total de 11,182 de pacientes con diabetes tipo 2, 6,407 (57.3%) presentaban opacidad del cristalino y 3,611 (32.3%)

tenían cualquier grado de retinopatía diabética;[31] en el estudio de Wen y colaboradores, la catarata causó visión corregida baja más comúnmente que la retinopatía diabética (46.2% vs 26.9%).[32] En estudios de nuestro país, en un análisis multivariado, la probabilidad de deficiencia visual ocasionada por catarata (RM ajustada 1.78, IC95% 0.62-5.11) fue menor que la de la retinopatía que amenaza la visión (RM ajustada 9.89, IC95% 3.34-293);[33] sin embargo, en un estudio de población abierta (n = 5,935), la catarata fue una causa más frecuente de ceguera (29.8%) que la retinopatía diabética (17.5%).[34]

En nuestro país, los años de vida vividos con discapacidad relacionados con catarata, ajustados por edad, son 77 por 100,000 habitantes (intervalos de incertidumbre [II] 53-107), mientras que por retinopatía diabética son 19 (II 12-26).[35]

Además de buscar recuperar la visión, la cirugía de catarata en el paciente diabético es necesaria para vigilar la progresión de la retinopatía diabética.[36] La cirugía de catarata beneficia a la mayoría de los pacientes con retinopatía diabética sin enfermedad macular grave; la agudeza visual preoperatoria y el grado de la retinopatía pueden limitar el resultado visual postoperatorio.[37]

En el estudio de Lee y su equipo, los pacientes con retinopatía diabética severa o proliferativa tuvieron un promedio de agudeza visual postoperatoria menor a la preoperatoria, pero la muestra fue muy pequeña.[38] Aunque la probabilidad de alcanzar una agudeza visual corregida después de la cirugía aumenta ≤ 20/25 con la gravedad de retinopatía, Liu y colaboradores encontraron que los pacientes con cualquier grado de retinopatía diabética mejoraban en promedio cuatro líneas de visión después de la cirugía de catarata.[39]

DISCAPACIDAD VISUAL POR CATARATA EN PACIENTES CON UVEÍTIS

La uveítis es un grupo raro y heterogéneo de enfermedades, de etiología principalmente infecciosa y autoinmune, caracterizadas por inflamación que afecta el tracto uveal; es una causa potencial de ceguera (constituye 10 a 15% de todos los casos de ceguera y el 20% de los casos de ceguera legal en Estados Unidos). En países en vías de desarrollo causa 25% de los casos de ceguera; más de 50% de los pacientes desarrolla complicaciones relacionadas con uveítis y 35% desarrollan discapacidad visual.[40]

Tabla 1: Beneficios esperados de la cirugía de cataratas en personas con otras discapacidades.

Enfermedad	Restricción agregada por la catarata	Beneficio esperado con la cirugía de catarata
Fracturas	La deficiencia visual puede limitar la marcha y el equilibrio. Disminuyen la percepción de la profundidad, afectan la capacidad de mantener el equilibrio, la coordinación y los reflejos.	Mejoría visual, aumento de referencias para la deambulación, mejoría del equilibrio.
Demencia	Interacción social limitada por mala visión, deambulación restringida. La mala visión puede llevar al aislamiento social, la falta de ejercicio físico y la disminución de la participación en actividades intelectuales, factores vinculados con un mayor riesgo de demencia.	La mejoría visual aumenta la capacidad para reconocer personas, objetos y lugares. Podría mejorar la interacción social.
Degeneración macular relacionada con la edad	La catarata puede causar más deficiencia visual que la enfermedad macular.	Mejoría de la visión periférica, lo cual ayuda a la deambulación y las actividades que no requieren la visión fina.
Glaucoma	La catarata puede limitar el seguimiento y restringe la función del campo visual residual.	Facilita la valoración del nervio óptico y el campo visual; promueve la rehabilitación con el campo visual residual.
Retinopatía diabética Uveítis	La catarata puede limitar el seguimiento y el tratamiento, y limitar más que la retinopatía en fases iniciales. Las adherencias más comunes del iris son hacia el cristalino. Limita la evaluación de inflamación en la coroides y la retina.	Facilita el seguimiento y tratamiento de la retinopatía en todos sus grados. Puede permitir mayor movilidad pupilar y facilitar la evaluación de inflamación de la coroides y la retina.

Las complicaciones asociadas con pérdida visual en pacientes con uveítis son glaucoma, catarata, desprendimiento de retina y cicatrices maculares. Un 30 a 50% de los pacientes con uveítis desarrollan catarata, dependiendo de la patología, principalmente por la inflamación intraocular y el uso crónico de esteroide.[40]

El edema macular es una complicación común en los pacientes con uveítis causada por el daño a la barrera hematorretiniana seguida de la acumulación de líquido intra- y extracelular en la mácula; puede persistir aún con un control adecuado de la uveítis y llevar al daño de los fotorreceptores y pérdida de la visión central. El edema macular ocasiona pérdida visual severa en 41% de los pacientes con uveítis y ceguera en 29%;[41] una catarata puede dificultar su seguimiento; puede limitar la visión después de la cirugía de catarata.

Con respecto a la cirugía, los pacientes cuya uveítis está inactiva por lo menos 30 días antes de la cirugía de catarata tienen una menor probabilidad de recurrencia de la inflamación.[42] En el estudio de Shekhar y su equipo, 13.5% de los casos no tuvo una mejoría significativa de la agudeza visual;[43] los mejores resultados se obtienen en pacientes con uveítis anterior.[44,45]

Los beneficios esperados con la cirugía de catarata en pacientes con otras discapacidades se presentan en la *Tabla 1*.

LIMITACIONES DEL ESTUDIO

La revisión de literatura realizada es narrativa, ya que los estudios que evalúan la combinación del efecto de discapacidades son escasos. Idealmente, esta evaluación debería incluir instrumentos de calidad de vida estandarizados para cada discapacidad, con la finalidad de permitir reproducir las mediciones.

Los estudios evaluados en su mayoría fueron descriptivos o revisiones sobre grupos particulares, por lo que la información obtenida no puede generalizarse; sin embargo, permiten delinear un espectro de discapacidad combinada que permite el desarrollo prospectivo de la investigación. Las ventajas de realizar la cirugía de catarata que se plantean en este trabajo requieren confirmarse prospectivamente; señalan una necesidad no cubierta de evaluar simultáneamente la discapacidad visual y otras discapacidades en población mexicana.

CONCLUSIONES

Aún en los casos en que la función visual está limitada por otras enfermedades oculares, retirar la catarata permite mejorar la visión residual, lo que agrega valor para el seguimiento de enfermedades oculares y funcionalidad para la prevención de fracturas o demencia.

Cuando coexisten discapacidades, el impacto funcional resultante puede superar la suma de ellas; el tratamiento quirúrgico de la catarata ayuda a reducir ese impacto a corto plazo; la recuperación visual, aunque no sea la óptima, otorga al paciente una funcionalidad que no debe despreciarse. En algunos casos, la cirugía de catarata con comorbilidades que ocasionan discapacidad requiere procedimientos de alta especialidad, pero el resultado sobre la calidad de vida del paciente puede superar el uso de recursos.

Existen casos en que la cirugía de catarata no ofrece posibilidad de recuperación; cuando existe una probabilidad razonable de mejorar la visión, conviene reducir la discapacidad con este procedimiento quirúrgico.

Para los pacientes con riesgo de demencia o fracturas por caídas, la cirugía de catarata mejora la interacción espacial y social y potencia funciones que van más allá de obtener una visión más nítida. Por el contrario, retrasar una cirugía de catarata deteriora funciones extraoculares e incrementa el riesgo de una condición mórbida que limite progresivamente la calidad de vida del paciente.

Todas las discapacidades requieren atención; reducir la discapacidad visual con un procedimiento resolutivo a corto plazo ubica a la cirugía de catarata como un nicho con potencial para generar un beneficio que trasciende a la mejoría visual. Las iniciativas de salud dirigidas a tratar la catarata también amplían las oportunidades de rehabilitación en una población vulnerable, por lo cual es importante medir la agudeza visual en pacientes con otros tipos de discapacidad.

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