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Relationship Between Multiple Sclerosis and Osteoporosis in Postmenopausal Women; A Case Report and Brief Review of the Literature

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ABSTRACT

Multiple sclerosis and osteoporosis are diseases that its comorbidity usually affects on postmenopausal women, certain evidence shows share pathogenic ways, and inclusively it's been proved that peri-pathogenic situations with certain treatments can predisposed patients with this pathology neurodegenerative to imbalance the bone density system. In this article we stablished what the multiple sclerosis and osteoporosis are, we investigate if there's a relationship between them and tried to explain more than a "casual statistic of comorbids" , also we use as an example this situation with an archetypal case report that represent exactly this type of patients.

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INTRODUCTION

The relevance about this topic, eradicates on how daily postmenopausal women patients possessed multiple sclerosis and osteoporosis, the same that appears in gynecological consultation and internal medicine, and it's important to know both pathologies and how they can be related. As an important conceptual background we know that is not clear if it exists some kind of direct relation between diseases more than just how their treatments affect one or another, but in another hand, statistically it's been proven that there is some type of correlation, this has motivated to researchers to try to clarify this topic, but this has been hard for the investigation area due to the lack of understanding about the molecular mechanisms of human physiology.

In this manuscript, we will try to show relevant information through vanguard investigation to offer the reader a hypothesis about the complex relations that this neurodegenerative disease and imbalance of the bone metabolism.

The objectives about this work are: Offer an explanation to this case, prove if there is a causal relation between them and give the reader a clear image of how it looks an archetype patient of this comorbid.

MATERIAL AND METHODS

Along the gynecologic consultation of Drs. Susana, she interviews a patient that works as an example of the typical case of this comorbid in question and the recopilated data is presented by the clinic history.

It's done a brief bibliographic review none systematized of the literature about the correlation between multiple sclerosis and osteoporosis in the following data bank: academic google, national library of medicine from the national biotechnology information.

CLINIC CASE

Female of 45 years old, with family history along 4 aunts with osteoporosis and 3 cousins by her mom side with multiple sclerosis. Previews surgery's: Cesarean section due on December 8th of 2007 secondary to stretch pelvis, this one had no complications. Along her obstetric history: total

delivery=1, vaginal delivery=0, cesarean delivery=1, abortions =0. She is also diagnosed with arterial systemic hypertension, HPV infection without any treatment, multiple nodular sclerosis in 2003, treated con interferon beta of 8 millions since 2008, rituximab in 2019, prednisone 6 mg each 24 hrs (2003-2006); last menstrual period at her 39 years, postmenopausal without any hormonal treatment, osteoporosis on her column and osteopenia on her hip in 2018, diagnosed by densitometry on her column and hip:

- Column: L1 to L4 0.553gr/cm2 T-score-4.5, Z-score-4.1, EC55.
- Total Hip: Tot. 0.664gr/cm2 T-Score-2.2 Z-score-2.2 ec 69
- Femoral Neck: 0.500gr/cm2, T-score-3.2, Z-score-3.0
- Left total hip: 0.685gr/cm2 T-Zcore-2.1, Z-score-2.0 EC 72
- Femoral Neck: 0.527gr/cm2, T-score-2.9, Z-score-2.7, EC 62.

February 25 Th. 2019: She attends to an assessment, because of nighttime hot flashes, conciliation and continuity insomnia, also vaginal dryness and libido loss, this had been treated with certain improvement along 7 years, with clonazepam 4 drops of 2.5 mgs.

Vitals: BP: 122/66 mmHG, HR: 82 bpm, RR 16, T: 36.6 Weight 60.3 kgs
Breast examination: Both simetric, without any infiltrated changes on skin and nipple, when touching there is no hyperesthesia, nodulations or enlarged lymph nodes.
We solicited paraclinical tests, starting with cholecalciferol 1600 units 1 each 24 hrs, along drospirenone 2 mg / estradiol 1 mg
April 4th 2019 Osteoporosis profile:
Parathormone 38.9, osteocalcin 28.8 ng/mL, degradation product collagen type 1 b crosslaps (b-ctx): 0.748 ng, P 3.48, Ca 9.3 mg Vitamin D(oh)25 (da+d3) total 36.8 ng/ml

STH 1.35 mUI/L, glucose 82 mg/dL, HbA1c 5.7%, total cholesterol 164 HDL 66 mg/dl, LDL
105 mg/dL, triglycerides 69 mg/dl

DISCUSSION

Multiple sclerosis and osteoporosis are both clinical entities of high prevalence in the general population, inclusively it isn't rare to see this comorbid, specially in gynecologic consultation on postmenopausal patients.

The prevalence of osteoporosis on elderly Mexican females above 50 years old is about 17% in lumber column and 16% on hip in respect to the total population. (1)

In Mexico is estimated that between 11 and 20 of each 100k people suffer because of multiple sclerosis. (2)

WHAT IS MULTIPLE SCLEROSIS?

The multiple sclerosis is a chronic disease, inflammatory, demyelinating and neurodegenerative of the central nervous system, it's multifactorial, and immunomeasure, influenced by genetic factors and also environmental, both of them are related because of it's exposure during adolescence, the most relevant described had been Epstein-Barr virus infection, tobacco exposure, as an active smoker as non-smoker, low vitamin D levels and obesity. It affectspecially on young adults, between 20-40 years old and even more in women (3,5,6)

It's manifested con reversible episodes of neurologic deficits, known as relapses, that generally lasts days or weeks that whiles time passes by they become irreversible, they become very
variable and can include one or two multiple neurologic deficits that involves sensorial alterations, motor weakness, visual alterations, unbalance, fatigue and cognitive difficulty.

Symptoms are generally developed on a time lapse of hours and days, and then remit gradually (inclusive if it isn't treated) during the next weeks or months, but the remission could not be completed. (8)

It can be classified depending on the rate and relapse characteristics in four principal groups: clinically isolated, relapsing-remitting, secondary-progressive, primary-progressive.

It is characterized by multifocal areas of demyelination with loss of oligodendrocytes and astroglial scarring, in addition to axonal injury, it is relevant, especially in advanced stages, all due to infiltration of immune cells, including T, B and myeloid cells.

The diagnosis it's done on patients in which they present symptoms and characteristic aspects on a MRI and that have a series of relapses and remissions. In some patients, multiple sclerosis that is clinical defined can be diagnosed in the moment of a first attack, in which over some clinical aspect, MRI and cerebroespinal fluid, using McDonald's criteria. (11).

For the patients with an acute exacerbation of multiple sclerosis (relapse, attack) that produced neurologic symptoms and a major disability or vision impairment, force o cerebella function, we recommend a brief treatment with high dosis of glucocorticoids. The principal objetive of the treatment is to accelerate time recovery of the attack of the multiple sclerosis.

Modified therapy of the disease, vary depending of the clinical type that the patient has, and its principal base are monoclonal antibodies and fumurates. (9)

WHAT IS OSTEOPOROSIS?

Osteoporosis is defined as a metabolic bone disorder, characterized por its low bone mass, deteriorated because of the microarchitecture of the bone tissue and skeletal fragility, that provokes a less bone resistance and a major fracture risk.

Osteoporotic fractures are more frequent on proximal femur, vertebra and distal radio.

Estrogen deficiency gives as a result an improvement of bone replacement due to effect over all times of bones cells. The imbalance on the formation and bone resorption has effects on the trabecular bone (that losses connectivity) and cortical bone (cortical thinning and porosity).

Osteoporosis is diagnosed by a muscular bone integral evaluation DXA, same that includes bone density of the spinal cord, total hip and femoral neck; vertebral morphometry, including FRAX, to evaluate the risk of fractures and stratify the group of risk.

The preventive strategy to improve the bone's health include good nutritional food (rich diet on proteins, vitamin D and calcium); resistance exercise or high impact; improving habits like reducing drinking alcohol and smoking.

Bone mineral density (BMD) is a key tool to identify osteoporosis. The World Health Organization (WHO) has defined, osteoporosis with BMD that is 2,5 standard deviation below maximum bone mass of adult women, or inferior to 2.

The diagnosis can be clinic due to a fragility fracture, particularly in the spinal column, hip, wrist, humerus, rib and pelvis; it is also done as a diagnosis depending on the measure of the bone mineral density (BMD) of the spinal cord and proximal femur, with a punctuation of T <2,5, standard deviation, always that other causes of low BMD (such as osteomalacia) has been discarded.

The preventive strategies to improve bones health includes, diet, exercise and not smoking.

Fractures can be prevented reducing falls in a high risk population. Several drugs are allowed so they can reduce the risk of a fracture by reducing bone resorption (like bisphosphonates or denosumab) or stimulating the structure of the bone (by using an anabolic drug, like teriparatida).

When we diagnose osteoporosis in our daily practice is by using levels of bone mineral density, such as fractures, whether they were long time ago or if it was recent, due to fragile structure or the relation with osteoporosis; and the risk of fracture in 10 years.

Some pharmaceutical strategies to reduce risk fractures is by slowing down bone resorption (like bisphosphonates and denosumab) o stimulating bones resorption (like teriparatida). Also the bestform to improve the treatment of the disease is by comprehending its celular base, drugs withthis type of knowledge had been key, and in the future they will still be key. (15-16)

Osteoporosis is a treatable disease, but a lot of people with this condition are still not diagnosed and treated.

RELATION BETWEEN MULTIPLE SCLEROSIS AND OSTEOPOROSIS

In a meta-analysis of Dr. Zhongming Huang, he suggests that patients with multiple sclerosis have a total reduction on its bone mineral density in terms of a control group (healthy population);he's group of investigation associate that the duration of a disease higher than 7 years, a dosis of steroids higher than 15 grams and an expanded status scale of disability higher than 3 points, are the principles risk factor of having lower bone mineral density on patients with multiple sclerosis. (4)

Decreased postmenopausal ovarian estrogen production is correlated bone density loss. This is associated with decreased serum levels of 17b-estradiol, estrone, and testosterone compared to the premenopausal baseline.

The osteoclast progenitor cell line and osteoclasts have surface receptors called receptor- activator for nuclear factor κB ligand (RANKL) (10); same that at low concentrations of estrogen increases its expression. This phenomenon culminates in increased recruitment ofosteoclasts, activation of the same and postponement of their apoptosis; in other words, they condition a state of bone resorption. (13) RANKL is neutralized by osteoprotegerin. Osteoprotegerin is secreted by the osteoblastic cell lineage and competes for the activation of the receptor activator of nuclear factor kappa beta, inhibiting bone resorption. (12, 14)

An asymmetry between these two entities – RANKL and osteoprotegerin — can lead, in the first case, to osteoporosis, or to the opposite pole, generating osteopetrosis. (17) Menopause, due to the decrease in ovarian activity, generates an imbalance where it favors the osteoclastic pathway, generating bone demineralization; likewise, multiple sclerosis affects bone mineral density, not necessarily through the same pathway, but through distortions in vitamin D metabolism, the impact of therapy, forced sedentary lifestyle, and the tendency to fall.

EDDS AND BONE DENSITY

The Kurtzke Expanded Disability Status Scale (EDDS) is a scale that assesses the functional status of patients with multiple sclerosis.

Although the length of time that the disease has been suffered is not synonymous with the severity of a disease, most patients with this neurodegenerative pathology do tend to have a higher degree of acquired disability, that is, multiple sclerosis, as well as its treatment and implications

in general, leads the body to physiological stress by testing certain physiological mechanisms involved in the subsequent lines.

VITAMIN D AND LOSS OF BONE DENSITY

There are two biologically inactive forms of vitamin D in humans, which undergo enzymatic transformation in the liver to 25(OH) D (calcidiol). Stimulated by the parathyroid hormone, 25 (OH) D undergoes a second hydroxylation in the kidney or other tissues to 1,25 (OH) 2VD (also known as calcitriol derived from vitamin D3), which is the active metabolite. 1,25 (OH)2 VD has a half-life of several hours, while 25 (OH) D has a relatively long half life (20 to 60 hours), and thus more accurately exemplifies general reserves of vitamin D in the body. And this is why serum 25 (OH) D is often measured for an integrated measure of vitamin D derived from both UVB exposure and diet (24).

Vitamin D deficiency also causes increased parathormone secretion due to low serum concentration of 1,25 (OH) 2D and low serum calcium, resulting in high bone turnover and increased bone resorption. This causes bone loss, mainly cortical bone, and this may contributeto the pathogenesis of osteoporosis. (18)

When vitamin D deficiency is severe, it causes rickets or osteomalacia, where the new bone, the osteoid, does not mineralize; and when the deficiency is less severe, it causes an increase in parathormone serum that leads to bone resorption, which leads to osteoporosis and even fractures. (18)

1,25 dihydroxyvitamin D3, and other forms of vitamin D, also regulate osteoclastogenesis through the RANK/RANKL/OPG axis.

High levels of vitamin D are associated with a reduced risk of developing multiple sclerosis, or, reducing clinical activity in established multiple sclerosis, as well as a decreased risk of relapse and reduced activity of the disease in a brain MRI. (19,20)

1,25 dihydroxyvitamin D3 and other forms of vitamin D, also regulate osteoclastogenesis through the RANK/RANKL/OPG axis. (21)

It is a fact that a correlation has been seen between low levels of vitamin D and multiple sclerosis (and that correlation does not necessarily mean causality), a mechanism that provides a sufficient explanation has not been elucidated. However, it is believed that errors in mechanisms of vitamin D immunomodulation may contribute to multiple sclerosis, as systemic 1,25(OH)2VD3 affects various types of immune cells, including macrophages, dendritic cells (DC), T and B cells. Macrophages and DCs constantly express the vitamin D receptor (VDR), whereas VDR expression in T cells only increases after activation. (25)

In short, imbalances in immunomodulatory capacity appear to be the cornerstone in the pathophysiology of experimental and human autoimmune encephalomyelitis. This action on the peripheral immune system is currently the main known mechanism through which vitamin D might influence MS, but other types of actions might be involved within the central nervous system.

Higher vitamin D levels are associated with a reduced risk of developing multiple sclerosis (MS) and with reduced clinical activity in established MS, including reduced risk of relapse and reduced disease activity on MRI brain (23)

So, we can conclude that more than a causal correlation between these two diseases, where the unifying force is vitamin D, rather this comorbidity is a phenomenon of statistically frequent incidence that vitamin D has in common, in osteoporosis as causal factor and sclerosis as an ingravescent factor.

HOW DO STEROIDS AFFECT BONE DENSITY LOSS?

One of the mainstays in the treatment of multiple sclerosis are steroids, but when serum levels of glucocorticoids increase, bone cells are directly affected, altering bone and mineral metabolism; this carrying out a decrease in bone formation also favoring bone resorption; there is loss of bonemass and alteration of bone quality.

Histomorphometric studies had shown reduced formation, decreased bone mineral position and a prolonged mineralization time, which causes a reduction in the amount of bone replaced in each remodeling cycle by up to 30%. Glucocorticoids inhibit the production, proliferation, maturation, and activity of osteoblast while increasing apoptosis of mature osteoblasts and osteocytes.

The explanation for this inhibition is due to the decrease in the production and action of different growth factors, sex hormones and various cytokines, such as the GH-IGF-I axis, such as a decrease in IGF-I axis, which mediates osteoblasts function, and of IGF-I binding proteins which have stimulatory effects on bone formation. Another mechanism of inhibition is the over expression of proteins such as BMP-2 and Cbfa1, necessary for the differentiation of osteoblast precursor cells.

The high risk of fracture when starting the consumption of glucocorticoids is explained by the apoptosis of the osteocytes, which affects the functions they exert in the regulation of bone quality; up to 25% of users of systemic glucocorticoids develop osteonecrosis, which could be a consequence of alterations in bone resistance due to a thinning of their trabecular and possibly a loss of connectivity between them, which may vary depending on the dose.

These drugs also affect the formation of the bone matrix by

inhibiting the expression of the type I collagen gene and by stimulating the expression of collagenase-3 by osteoblasts and chondrocytes; Collagenase-3 degrades type I and type II collagen, the main constituents of the bone and cartilage matrix.

Glucocorticoids produce a suppression of the synthesis of OPG (osteoprotegerin), in addition to an increase in the expression of RANKL, and therefore a stimulation of osteoclastogenesis. Remembering, the main intracellular signal pathway that governs bone remodeling is mediated by the factor tumor necrosis factor (TNF) and its receptor: RANK (receptor activator of nuclear factor kappa-B), which is an osteoclast membrane receptor that initiates osteoclastic bone resorption after binding to its ligand (RANKL), which is the major osteoclast-stimulating factor (also known as osteoprotegerin ligand [OPGL]); and OPG, the key inhibitor of bone resorption, by functioning as a soluble receptor for RANKL, without triggering signals. In this way, bone resorption will be regulated by the balance, at the local level, between OPG and RANKL. (22)

Glucocorticoids can alter calcium metabolism. Statistically, there is evidence of an incidence of osteoporosis after 15 grams of steroid treatment. This, depending on the dose, causes a decrease in the intestinal absorption of calcium or, also, an increase in its renal excretion, due to the mobilization of calcium from the bone and also by direct action at the renal level. It is important to take into account that these drugs do not reduce serum concentrations of calcidiol or calcitriol,nor do they alter the binding protein to vitamin D or affect the sensitivity of the intestinal epithelium to its action.

The decrease in the production of sex hormones, through multiple mechanisms, plays an important role in the bone loss produced by glucocorticoids, contributing to the increase in bone resorption, both in men and women and at any age. Glucocorticoids cause an acute and chronic decrease in testosterone in men and, at high doses, can cause oligomenorrhea in women. (22)

CONCLUSION

Multiple sclerosis and osteoporosis are highly prevalent diseases in Mexico that are common in postmenopausal women, and it is even common to find this comorbidity in this group of patients.

There is insufficient evidence to ensure a causal relationship between osteoporosis and multiple sclerosis, or vice versa. However, it is a fact that steps in the pathophysiological cascade of one can serve as ingravescent factors in the pathophysiology of the other; Likewise, each one has therapies that can contribute to their effects with damage mechanisms of these pathological entities.

Treating the postmenopausal patient's disease as a synergistic unit instead of isolated pathologiesthat coexist in the same body can lead us to guarantee the best possible quality of life for a patient.

despite the fact that cutting-edge research is advancing by leaps and bounds, our understanding of the molecular mechanisms of our body is insufficient to elucidate this issue; only in the lightof understanding our internal context will we have answers.

ETHICAL ISSUES

The authors declare no conflicts of interest.

The clinical case was authorized by the patient in question to be used for research and medical teaching purposes.

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