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Vitamin D deficiency, myopathy and VDR gene polymorphism in a young woman

Genç bayan hastada D vitamini eksikliği, miyopati ve VDR gen polimorfizmi

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SUMMARY

Vitamin D deficiency can result in impaired bone mineralization and some types of bone and muscle diseases. The expression of the vitamin D receptor (VDR) gene is important for vitamin D activity and some genetic variations have been identified. In this report we examined a young woman who had a vitamin D deficiency which leads to high creatinine kinase levels and muscle weakness. Her family members also had vitamin D deficiency and her mother and her elder sister had osteoporosis. The cause of our patient's symptoms was low vitamin D level and her VDR gene polymorphism (BsmI variant) was BB homozygous. Her mother and her sister also had BB genotype. The symptoms of the patient (muscle weakness, muscle pain, fatigue) improved after vitamin D replacement therapy. Our study suggest that the VDR genotype of our patient was consistent with her level of vitamin D.

Keywords: myopathy, polymorphism, VDR gene, vitamin D

ÖZET

D vitamini eksikliği kemik mineralizasyon bozukluğu ile birlikte bazı kemik ve kas hastalıkları ile sonuçlanabilir. D vitamini aktivitesi için vitamin D reseptör (VDR) geninin expresyonu önemlidir ve bu genin bazı genetik varyasyonları tanımlanmıştır. Burada D vitamini eksikliği ile birlikte yüksek kreatin kinaz ve kas güçsüzlüğü olan bir bayan hasta incelenmiştir.Aile bireylerinde de osteoporoz olan vakanın, annesi ve ablasında da osteoporoz mevcuttu. Hastamızdaki semptomların nedeni düşük D vitamini düzeyleri idi ve VDR gen polimorfizminin (Bsml varyantı) BB homozigot olduğu saptandı. Anne ve ablasında da BB genotipi saptanan hastanın semptomları (kas güçsüzlüğü, kas ağrısı, yorgunluk) D vitamini replasman tedavisinden sonra düzeldi.Çalışmamız hastanın vitamin D düzeyinin VDR genotipi ile uyumlu olduğunu göstermektedir.

INTRODUCTION

Vitamin D binds to intracellular receptors and functions as transcription factor to modulate gene expression. Vitamin D deficiency can lead to osteoporosis in adults or rickets in children[1]. Vitamin D deficiency consists of some clinical problems such as fatigue, muscle pain, muscle cramps, poor concentration, headaches etc[2, 3]. Vitamin D deficiency can be related with malignancy, cardiovascular disorders, stroke, diabetes, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, periodontal disease, mental illness, and widespread-pain[4-6]. Some DNA sequence variations are named as "polymorphisms". Different studies have demonstrated that many polymorphisms have been detected in the VDR gene, but the effects of VDR gene polymorphisms on VDR functions have not been solved entirely.

CASE REPORT

A 17 years-old girl was admitted to our hospital for muscle weakness and pain, thus making it difficult for her to comb her hair and climb stairs. Her mother and her elder sister had osteoporosis and whole family suffered from vitamin D deficiency. She had not history of any disease, like hyperparathyroidism or kidney diseases, that might have disrupted the metabolism of vitamin D. Laboratory tests of our patient showed normal levels of haemoglobin, vitamin B12, thyroid hormones, parathormone (PTH), erythrocyte sedimentation rate, c-reactive protein (CRP), serum magnesium, potassium, sodium, serum ionized calcium, phosphate, and albumine. Auto-antibody tests (ANA, rheumatoid factor, anti-CCP, anti-dsDNA, ANCAs) were all negative. EMG analysis showed subacute denervation activity and early interference pattern with low amplitude detected in extremity muscles (particularly proximal upper extremity). These findings were compatible with myopathy. Her 25-hidroxy vitamin D was measured as 5.5 ng/mL (normal range: 9.5-55.5 ng/mL). She had vitamin D deficiency. LDH was 308 U/L (normal range: 90-247 U/L) and creatine kinase was 1446 U/L (normal range: 55–170 U/L in male and 30-145 U/L in female). She had low bone mineral density (BMD). DEXA lumbar total T score was -2.4. After vitamin D replacement (300.000 IU/mL/week) therapy for two months, her 25-hidroxy vitamin D levels increased to 34.2 ng/ml. Similarly, LDH declined to 260 and creatine kinase regressed to 781 U/L. The symptoms of the patient highly improved.

We researched VDR gene polymorphism for BsmI variant with a strip assay procedure (ViennaLab Diagnostics Vienna/Austria) in this young woman and her family. VDR genotype of our patient was BB (homozygous), the same as her sister and her mother. Her father was heterozygous (Bb). Her sister and her mother also had low levels of vitamin D (5.8 and 6.0 ng/ml respectively) before replacement therapy.

DISCUSSION

Vitamin D has a role for growing and maintaining a healthy skeleton through increased calcium absorption. Epidemiological and laboratory investigations have shown that there is a relationship between low blood levels of vitamin D and certain diseases such as osteoporosis, cancer, heart disease, hypertension, obesity, diabetes, metabolic syndrome, autoimmune diseases, multiple sclerosis, rheumatoid arthritis, tuberculosis, osteoarthritis, gout, Parkinson's disease, depression, periodontal disease, and psoriasis[6, 7]. Vitamin D receptor (VDR) and the enzymes of vitamin D metabolism are major players in the activity of vitamin D[8]. The expression of the vitamin D receptor (VDR) are essential for vitamin D functions, because vitamin D is involved in various signalling cascades[9]. Several RFLPs (including Tru9I, TaqI, BsmI, EcoRV and ApaI) in the VDR gene has been identified using some restriction enzymes. These RFLPs are located between the exon 8 and 9[10]. Recently, two meta analyses performed by Thakkinstian et al [11] demonstrated a positive association between the b allel of BsmI polymorphism and bone mass density. In a study, Morrison et al[12] suggested that BsmI RFLP, in the last intron of the VDR gene was related with serum osteocalcin concentration and and it was found to be associated with alterations in bone mineral density (BMD)[13]. A study in the United States showed that in the younger volunteers, BMD of the femoral neck was 5.4% higher ($p<0.05$) in the bb genotype group than the BB group and was 11% higher ($p<0.05$) in males with the bb genotype than males with the BB group. This study showed that the correlation between calcium intake and BMD can be dependent to VDR genotype[14]. Our results suggest that BB genotype of BsmI variant is associated with low levels of vitamin D.

In conclusion; the symptoms of our patient (muscle weakness and fatigue) and the patient's laboratory results (low 25-hidroxy vitamin D level, high creatine kinase and LDH) were consistent with a vitamin D deficiency profile. EMG of the patient showed proximal myopathy. Eventually, the patient responded to vitamin D replacement therapy. The level of vitamin D raised and muscle symptoms disappeared. VDR gene polymorphism of our patient (BB genotype) may also be

associated with low BMD. VDR gene polymorphism is important for the metabolism of vitamin D. In myopathy cases like this, vitamin D deficiency also must be thought as an etiologic factor.

REFERENCES

1. Holick MF, Binkley NC, Bischoff-Ferrari HA. Evaluation, Treatment, and Prevention of Vitamin D Deficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2011; 96: 1911-30.
2. Bordelon P, Ghetu MV, Langan RC. Recognition and Management of Vitamin D Deficiency. Am Fam Physician 2009; 80: 841-6.
3. Wang TJ, Pencina MJ, Booth SL. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008; 117: 503-11.
4. Peterlik M, Cross HS. Vitamin D and calcium deficits predispose for multiple chronic diseases. Eur J Clin Invest 2005; 35:290-304.
5. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 2004; 80: 1678-88.
6. Peterlik M, Cross HS. Dysfunction of the vitamin D endocrine system as common cause for multiple malignant and other chronic diseases. Anticancer Res 2006; 26: 2581-8.
7. Köstner K, Denzer N, Müller CS, Klein R, Tilgen W, Reichrath J. The relevance of vitamin D receptor (VDR) gene polymorphisms for cancer: a review of the literature. Anticancer Res 2009; 29: 3511-36.
8. Uitterlinden AG, Fang Y, Van Meurs JB, Pols HA, van Leeuwen JP. Genetics and biology of vitamin D receptor polymorphisms. Gene 2004; 338: 143-56.
9. Prabhakar P, Christopher R, Nagaraja D. Vitamin D Receptor (VDR) gene polymorphism and risk of ischemic stroke. Mol Cytogenet 2014; 7: 33.
10. Valdivielso JM, Fernandez E. Vitamin D receptor polymorphisms and diseases. Clin Chim Acta 2006; 371: 1-12.
11. Thakkinstian A, D'Este C, Attia J. Haplotype analysis of VDR gene polymorphisms: A meta-analysis. Osteoporosis Int 2004; 15: 729-34.
12. Morrison NA, Yeoman R, Kelly PJ. Eisman JA. Contribution of trans-acting factor alleles to normal physiological variability: Vitamin D receptor gene polymorphisms and circulating osteocalcin, Proc. Natl. Acad. Sci. U.S.A 1992; 89: 6665-9.
13. Morrison NA, Qi JJC, Tokita A, Kelly PJ, Crofts L, Nguyen TV, Sambrook PN, Eisman JA. Prediction of bone density from Vitamin D receptor alleles. Nature 1994; 367: 284-7.
14. Kiel DP, Myers RH, Cupples LA. The BsmI vitamin D receptor restriction fragment length polymorphism (bb) influences the effect of calcium intake on bone mineral density. J Bone Miner Res 1997; 12: 1049-57.