An SP1-binding Site Polymorphism in the COLIA1Gene and Its Relation to Osteoporosis in Egyptian Patients with GaucherDisease

Thesis

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Abstract

Introduction: Gaucher disease (GD) is a recessive disorder, classified as an orphan disease.Mutation of the glucocerebrosidasegene (GBA)leads to a reduction in β-glucocerebrosidase (GCase) activity, accumulation of glucosylceramide and abnormal levels of other sphingolipids. Features includehepatosplenomegaly, cytopenias and bone disease including osteopenia andosteonecrosis. Enzyme replacement is the most common therapy; however, bonemanifestations can be slow to respond.Some patients show no improvement orcontinue to suffer bone events.

Aim of work: Toexamine the distribution of the polymorphic variant in the regulatory region of collagen type I alpha 1 (COLIA1) gene at a recognition site for transcription factor SP1 and its relation to bone mineral density (BMD) in Egyptian patients with GD compared to a control group.

Patients and Methods: Thirty Egyptian patients with GD were recruited from hematology unit, Abo-ElRish,Cairo University and 30 healthy age and sex matched individuals from Fayoum University Hospitals were included as controls. Clinical examination and BMD scanningusing dual energy X-ray absorptiometry (DXA) were done for both patients and controls. A venous EDTA sample was collected from both groups and SP1 binding site polymorphic variant at COLIA1 gene was detected by PCR-RFLP (polymerase chain reaction restriction fragment length polymorphism).

Results: Forty three percent of GD patients had low lumbar BMD (osteopenia) and 36.7 % showed very low BMD (osteoporosis). Seventy three percent of GD patients 73.3%experienced bone pain, 13.3% had history of long bone fracture related to minor trauma,three patients had avascular necrosis (AVN) and only one patient gave history for bone crisis.A totalof 66.6% of the GD patients had wild genotypefor G/G),26.7% were heterozygous for G/T polymorphism andtherewere 6.7% homozygous for T/T genotype. Inthe control group, 93.3% and 6.7% had GG and GT genotypes,respectively. There was no significant difference betweenZ-score of patients with GG and GTor TTat lumbar spine (P =0.3). By combining both groups, there wasa high statistical significant difference between various COLIA1 genotypes as regards Z-score which indicates association between COLIA1 genotypes, and lumbar spine Z-score. However among patients, presence or absence of T- allele as regards bone fracture and lumbar spine Z-score approached the borderline of significance (p = 0.07) with increased risk of decreased BMD among those had T-allele by 1.7 times 95% CI 1.2-2.4.

Conclusion: These findings make the hypothesis of an association between Sp1 COLIA1 gene polymorphism and bone disease in GDprobably feasible. However, it remains to be elucidated why the incidence of this polymorphicvariant is so different from that in healthy controls. Genetic components strongly influence bone remodeling.Thus the puzzle of the pathogenesis of GD-induced osteoporosis and osteopenia remains far from being solved.

Key words: Gaucher disease (GD), bone mineral density (BMD), Sp1 at COLIA1 rs1800012,osteoporosis, osteopenia.