The Effect of TMPRSS6 , Hemojuvelin and Ferroportin-1 Gene Polymorphisms On the Severity of Iron Overload and Cardiac Dysfunction in Egyptian β-Thalassemia Patients

Thesis
Submitted for partial fulfillment of MD degree in
Clinical and Chemical Pathology

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2020

Summary

Background:

B-thalassemia is one of the most common genetic disorders in the world. Frequent blood transfusion improved the life expectancy but also led to iron overload with many complications including cardiovascular problems. In thalassemic patients iron overload results primarily from different mechanisms as repeated red cell transfusion, increased intestinal iron absorption, ineffective erythropoiesis as well as peripheral hemolysis. Normally, iron is tightly regulated via peptide hormone; hepcidin. Regulation of hepcidin expression by iron is a complex process that requires the coordination of multiple proteins, including hemojuvelin, ferroportin-1 and TMPRSS6**.** Contribution to the development of iron overload in thalassemic patients may be linked to the presence of one or more genetic variants leading to suboptimal iron balance in the tissue.

Aim of the study:

The aim of the study was to investigate the prevalence of TMPRSS6 (rs855791), HJV (I222N & G320V) and Feroportin-1(-8CG) gene polymorphisms in Egyptian β-Thalassemia patients and their effect on the severity of iron overload in those patients and to investigate correlation of the studied polymorphisms to the cardiac dysfunction in β-Thalassemia patients.

Subjects and methods:

The present study included 97 patients with clinical and laboratory signs consistent with β-thalassaemia major and 50 age and sex matched normal controls. They were subjected to full clinical evaluation, laboratory investigations, PCR-REFLP to determine the status of the 4 SNPs and assessment of cardiac function by echocardiography and MRI.

Results:

In the present study, the FPN1 -8CG (C/G) genotype was statistically significantly higher in patients when compared to the controls. MRI LIC was significantly higher in patients harboring the (G/G) FPN1 genotype when compared to those with the wild type (C/C) genotype. PAP was significantly higher in patients harboring the (GG+GC) FPN1 genotype in comparison to those with the wild (CC) genotype.

Regarding the incidence of TMPRSS6 (rs855791) polymorphism, the (C/C) genotype was statistically significantly higher in patients when compared to the controls. The current study didn’t detect any significant relation between the different TMPRSS6 genotypes and the studied aspects of iron overload in the thalassemia major patients.

HJV 1222N SNP study showed that variant genotypes (AA, TA, AA+ TA) showed no statistically significant difference between patients and controls. LVPWT was significantly higher in patients harboring the variant HJV1222N genotype. MRI studies showed significantly lower T2 among variant HJV 1222N SNP. Regarding the HJV G320V genotyping, the frequency of the variant T allele in HJV G320V did not differ among patients and controls.

Conclusion & Recommendations:

Our results strongly suggest that established genetic risk factors might be modulated by specific genetic backgrounds, making patients differently suited to manage iron overload thus resulting in different clinical phenotypes. Confirmation in larger cohorts of patients' longer follow-up periods is recommended.