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Research Article

The Association of Transforming Growth Factor-β1 (TGF-β1) Gene Polymorphism and Susceptibility to Aplastic Anemia in Egyptian Patients

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ABSTRACT

Background: TGF-β1 has been described as an important regulator of hemopoiesis. TGF-β1 polymorphic variants may relate to altering the expression of TGF-β1 and hence its effect on hematopoiesis and possible role in aplastic anemia pathogenesis. Aim: We try in this study to find out the allele distribution of TGF-β1-509 C/T in Egyptian population and hence figure the association of it with the susceptibility to aplastic anemia in Egyptian patients. Methodology: A case control study was designed to assess TGF-β1-509 C/T allele distribution in healthy controls (810 subjects) from six articles that was compared to TGF-β1-509 C/T allele distribution in aplastic anemia patients (90 subjects) from 2/6 articles included in the study. Results: Statistically significant difference was found between the wild (CC) versus mutant (CT/TT) genotypes of TGF-β1 509 C/T mutation in patients and controls. Mutant genotypes are more frequent in the patients when compared to controls (p = 0.017), and TGF-β1 509 C/T mutation is associated with 1.8 times the risk of developing the disease (95% CI: 1.1-2.8). Conclusion: TGF-β1-509 C/T mutation may be associated with risk of development aplastic anemia.

Keywords: TGF-β1; Gene Polymorphism; Aplastic Anemia.

INTRODUCTION

The exact pathophysiology of aplastic anemia (AA) is still not clearly understood, genetic, environmental factors and immune mechanisms are involved[1]. AA could be caused by Immune mediated suppression of hematopoiesis[2]. Immune dysregulation mainly involves T cell function including; Th1cells and CD8+ T cells and the deficient immune regulation of CD4+CD25+ T regulatory cells, NKT cells, monocytes, and decreased NK cells[3]. TGF-β1 almost mediated the regulation of T cell responses; proliferation, differentiation, and apoptosis. TGF-β1 blocks T cell proliferation through inhibition of IL-2 production, and influences Th1 and Th2 cells differentiation by downregulating the expression of T-bet/ Stat4 and GATA-3/NFAT. TGF-β1 inhibits cytotoxic T cell differentiation and T cell activation induced cell death and plays a role in inhibiting NK cell functions through attenuating IFN-γ production[4].

Regulation of hemopoiesis byTGF-β1 could be considered as an important factor[5]. However, the effect of TGF-β1 on hematopoietic progenitor cells (HPC) depends on its level of expression; at high levels, TGF-β1 inhibits proliferation of both myeloid and lymphoid HPC, while at lower levels, TGF-β1 stimulates Myeloid HPC and inhibits Lymphoid HPC proliferation in vitro[6,7]. Polymorphic variants of, TGF-β1 especially in the promotor region could change the expression of TGF-β1 and consequently influences hematopoiesis. Two single nucleotide polymorphisms (SNPs); at the positions -800 G/A and -509 C/T are discovered in the promoter region of TGF-β1[8,9].

The association of TGF-β1-509 C/T gene polymorphism and susceptibility to aplastic anemia has been studied in different ethnic groups but the results are inconsistent[10], even in the two published studies on Egyptian patients[11, 12]. This controversy in results may be related to small sample size due to the rarity of the disease or due to wide range of patient age or due to different environmental factors[2,13]. This study aimed to combine several published data in the literature that included the analysis of TGF-β1-509 C/T gene polymorphism in different age groups (both adults and children) and from different environmental background being recruited from different areas in Egypt but having the same ethnicity as Egyptians to find out the normal allele distribution in Egyptian population included as control subjects in these studies. Normal allele distribution of TGF-β1-509 C/T was compared to the results of the two published studies on TGF-β1-509 C/T gene polymorphism in aplastic anemia patients to draw more solid conclusion about the association of TGF-β1-509 C/T gene polymorphism and susceptibility to aplastic anemia in Egyptian patients.

METHODS

Online search was confined to Google scholar, PubMed and Web of knowledge to include published articles analyzing TGF-β1-509 C/T gene polymorphism in Egyptians.

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Table 1:

TGF-β1 509 C/T	Patients (no=90)	Control (no=810)	P value
Wild (CC)	29 (32.2%)	368 (45.4%)	
Heterozygous mutant (CT)	44 (48.9%)	326 (40.2%)	0.056
Homozygous mutant (TT)	17 (18.9%)	116 (14.3%0	
C allele	56.7%	65.6%	0.094
T allele	43.3%	34.4%	

Table 2:

TGF-β1 509 C/T	Patients (no=90)	Control (no=810)	OR	CI	P value
Wild (CC)	29 (32.2%)	368 (45.4%)			
Mutant (CT/TT)	61 (67.8%)	442 (54.6%)	1.8	1.1-2.8	0.017

CI: confidence interval. OR: Odds ratio.
P-value <0.05 is considered significant.

Six articles were selected and the results of TGF-β1-509 C/T gene polymorphism in Egyptians using restriction fragment length polymorphism (PCR-RFLP) were included in the study.

TGF-β1-509 C/T allele distribution in healthy controls (810 subjects) from the six articles was compared to TGF-β1-509 C/T allele distribution in aplastic anemia patients (90 subjects) from 2/6 articles included in the study.

Statistical methods

Statistical analysis was done using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA). Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. Odds ratio (OR) with it 95% confidence interval (CI) were used for risk estimation. All tests were two-tailed. A p-value < 0.05 was considered significant.

RESULTS

The study included six articles published between 2009 and 2016. Age range of the control group was from 1 to 65 years and patients' age ranged from 1 to 50 years old. TGF-β1-509 CC genotype was expressed in 32.2% (29/90) patients, while TT and CT were expressed in 18.9% (17/90) and 48.9% (44/90) of the patients respectively. In the controls, TGF-β1-509 CC genotype was expressed in 45.4% (368/810) and the TT and CT were expressed in 14.3% (116/810) and 40.2% (326/810) of the controls respectively. The p value is borderline significant (p=0.056). The percentage of C and T allele frequency didn't show statistically significant difference between the patients and control groups. Table 1

However, statistically significant difference was found upon comparing the wild versus mutant (heterozygous and homozygous) genotypes in patients and controls. Mutant genotypes are more frequent in the patients compared to controls (p = 0.017), and TGF-β1 509 C / T mutation is associated with 1.8 times the risk of having the disease (95% CI: 1.1-2.8). Table 2

DISCUSSION

Association of TGF-β1-509 C/T gene polymorphism and plasma concentration of TGF-β1 has been determined, where TGF-β concentration is approximately twice higher in the TT genotype in comparison to CC genotype[14]. TGF-β1 has a pivotal role in some common important diseases, TGF-β1 is a multifunctional cytokine that controls cell differentiation and proliferation, and activates the extracellular matrix (ECM) components expression[15-17].

It has been reported in several studies that genotypes associated with high TGF-beta1 production were more frequent in AA patients than in controls. The distribution of genetic polymorphisms in TGF-β1 was investigated in 14 AA Italian patients and 100 healthy blood donors, and it was reported that genotypes associated with high TGF-β1 production were more frequent in patients than in controls[18]. In addition, Gidvani and colleagues compared TGF-β1-509 C/T gene polymorphism in73 AA patients to previously published normal controls. A statistically significant higher expression in hypersecreting genotypes TT of the TGF-β1 -509 was found in patients when compared to controls[19]. El Mahgoub et al, found that hypersecreting TT genotypes TGF-β1 −509 was more frequent in AA patients[11]. However, contradictory data from other studies didn't find an association between the hypersecreting TT genotype and AA[12,20].

Interesting enough, two studies on Egyptian patients have contradictory results regarding the association of TGF-β1-509 C/T gene polymorphism and AA. It was concluded in the two published studies on AA in Egyptians patients that the number of the patients and controls included is limited and that further studies on larger sample size is recommended to assess the actual significance of TGF-β1-509 C/T gene polymorphism on disease susceptibility. Due to financial limitations we decided to pool the patients' data from both studies and compare it to published normal controls in order to conclude whether or not TGF-β1-509 C/T gene polymorphism has a role in the pathogenesis of AA in Egyptian patients.

The hypersecreting T allele of TGF-β1-509 C/T gene polymorphism was found comparable in AA patients and controls, while TGF-β1-509 C/T mutation is associated with increased risk of AA, denoting that TGF-β1-509 C/T mutation may be associated with AA due to mechanisms other than the presence of hypersecretory genotype.

To conclude, the findings of the present study which included pooled data of patients recruited from Kasr Alainy hospital, the largest university hospital in Egypt. Patients suffering from rare disease as AA from different areas in in the Country seek medical care at Kasr Alainy

hospital, therefore patients recruited in both studies at Kasr Alainy hospital represent diverse sample from different areas in Egypt, together with pooled controls' data from six articles including patients from different geographical areas in Egypt. Therefore, we can state that TGF-β1-509 C/T mutation may be associated with AA due to mechanisms other than the presence of hypersecreting TT genotype.

CONFLICT OF INTEREST

The authors declare no conflict of interest was found.

DECLARATION

All procedures performed in this study were in accordance with the ethical standards Helsinki declaration or comparable ethical standards. Oral and written informed consent was obtained from all individual participants included in the study.

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