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RESEARCH ARTICLE

Analysis of Macrophage Migration Inhibitory Factor Genotype in Hemophilia a Patients

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Abstract

Background: **Hemophilia A, an X-linked bleeding disorder, is caused by a complete or partial deficiency in factor VIII. Multiple factors engage in the development and progression of bleeding episodes in hemophilia patients, especially arthropathy.**

Objectives: **Detection of macrophage migration inhibitory factor (MIF)-173 G/C polymorphism in people with hemophilia A (PWH) and the possible associations between the type of *MIF* gene polymorphism and selected disease-related variables.**

Patients and methods: **This case−control study included 95 male patients with hemophilia A and 95 non-hemophiliac subjects, all aged from 2 months to 63 years.**

An allele-specific polymerase chain reaction (AS-PCR) with a multiplex technique was used to detect *MIF* polymorphisms.

Results: **A significantly higher frequency of GG polymorphism was reported in the control group (81, 85.3%) compared to PWH (64, 67.4%), while a significantly higher frequency of GC polymorphism was found in PWH (21, 22.1%) than that in healthy subjects (10, 10.5%), $P < 0.05$.**

The G allele polymorphism was detected in 90.0% of the control group compared to 78.4% of PWH (149 subjects), while the C allele frequency was higher in PWH (41, 21.6%) compared to that in healthy individuals (18, 10.0%), $P < 0.05$.

The frequencies of varied *MIF*-173 polymorphisms did not show significant differences among patients with different clinical presentations or in relation to presence of inhibitors, $P > 0.05$.

Conclusions: **MIF-173 GC polymorphism is seen in PWH more than that in healthy individuals. Further studies are required to detect additional SNPs through sequencing of the *MIF* gene and to detect *MIF* serum levels during bleeding episodes.**

Key words: Hemophilia A, Macrophage migration inhibitory factor

1. Introduction

Hemophilia A (HA), a severe congenital bleeding disorder, is caused by reduced, dysfunctional, or absent levels of factor VIII (FVIII) [1].

The World Federation of Haemophilia (WFH) reported a prevalence rate of people with hemophilia (PWH) of 3.6/100,000 population in Iraq, a prevalence that is comparable to neighboring countries [2].

People with hemophilia develop various bleeding complications, mainly in the joints, leading to joint damage, and they require lifelong use of clotting factor replacement therapy [3]. The severity of the clinical phenotype correlates with the plasma clotting factor level, and those with severe disease may have spontaneous bleeding during the neonatal period or early infancy [4]. Treating PWH is expensive, especially for those with severe disease and those with inhibitors (neutralizing alloantibodies to FVIII) to replace clotting factors [5].

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Macrophage migration inhibitory factor (MIF) is pro-inflammatory cytokine derived from T-cells. Many autoimmune and inflammatory conditions can affect the serum levels of MIF. There are many polymorphisms in the *MIF* gene of humans, the −173 C/G single-nucleotide polymorphism is one of these polymorphisms. The variation of −173G/C increases the probability of infection in patients with chronic disease [6].

MIF has been found to be a pivotal mediator of acute and chronic inflammatory diseases, and its secretion of protein is accompanied by toxicity, apoptosis, and stress [7].

The MIF levels differ between healthy humans and patients with various diseases like neurological diseases and malignant conditions [8,9], and this difference in its levels reflects the severity of clinical presentation [9–11].

There are many polymorphisms in the *MIF* gene of humans, such as rs71891258 and rs7167333 in the introns and rs755622 and CATT repeated at 794 in the *MIF* gene promoter [12,13]. Variations of −173G/C (rs755622) increase the probability of chronic inflammation [14] and inflammatory arthritis [15].

MIF allele determination may be useful in predicting the clinical course within a particular disease and potentially in guiding patient care [16].

Genotyping of *MIF* also suggests the possibility of recognizing people in whom MIF pathways are activated and who are at greater risk for end-organ damage. Furthermore, in the context of drug development, *MIF* genotype information may allow for the selection of patients in whom pharmacologic inhibition of *MIF* offers the greatest therapeutic benefit [13].

Our study aims to identify *MIF* gene polymorphisms in PWH and evaluate whether these polymorphisms are associated with selected disease variables.

2. Patients and methods

2.1. Patients

This case–control study was conducted from October 2019 until the end of August 2020. Ninety-five male patients, aged 2 months to 63 years, with hemophilia A were recruited for the study. All patients were diagnosed and registered at Basrah Center for Hereditary Blood Diseases and were evaluated through their follow-up visits to the center.

Each patient's clinical data was collected via direct interview with the patients and/or one of the parents and reviewing the patient's records.

Clinical data included age at diagnosis, family history of similar conditions, bleeding episodes, recombinant FVIII concentrate treatment modalities (on demand or prophylaxis), and history of blood transfusion and/FFP or cryoprecipitate. The disease severity at registration (depending on FVIII levels) and the results of inhibitors to FVIII testing (Bethesda units) were also recorded.

Informed consent was obtained from all the subjects and/one of the parents of pediatric subjects.

To compare the *MIF* polymorphisms among HA patients with those in the community, a total of 95 apparently healthy individuals (sex and age-matched) were enrolled in the study. These individuals were free of chronic diseases such as thalassemia, sickle cell anemia, and other diseases requiring the transfusion of blood and blood components (e.g., FFP, cryoprecipitate).

2.2. Methods

Three milliliters of venous blood was drawn from each participant and collected in an EDTA tube; two milliliters was used for total genomic DNA extraction, and one milliliter was used for a complete blood count (CBC) test.

The Genomic DNA Purification Kit (Wizard, Promega, USA) was used for the total genomic DNA after its extraction from each blood sample, and according to the manufacturer's instructions. Next, 0.8% agarose gel was used for genomic DNA electrophoresis.

2.2.1. Macrophage inhibitory factor −173 G/C single-nucleotide polymorphism detection

The allele-specific polymerase chain reaction (AS-PCR) with multiplex technique was used to detect the *MIF* 173 G/C SNP, which was performed by mixing four primers to amplify *MIF* as follows:

Forward Outer CAGTGCGTGCAGTGGAATGAAC (60 C),

Reverse Outer TGGGGAAGTCACCGCCTGCCT (60 C),

Forward Inner (G allele) AGCCGCCAAGTGGAGAACTGG,

Reverse Inner (C allele) AGCCCGGCGCACCGCTCCTAG, with SYBR green master mix. The PCR was created using the methods of Fei BY et al., [17].

The forward and reverse outer primers produced a band size of 298 bp that appeared in all samples. Polymorphisms in G or C appeared at the size of 126 bp or 213 bp, respectively. The appearance of two bands (126 bp and 213 bp) indicated that one allele

contained a C nitrogen base, and the other contained a G nitrogen base.

2.3. Statistical analysis

All analyses of patient data, such as clinical, experimental, and demographic data, were performed using Statistical Package for the Social Sciences (v. 20). The comparisons between groups and qualitative variables were done by the chi-squared test, while the continuous and quantitative variables were assessed by Student's t test, Mann–Whitney test, or Fisher's exact test. In some MIF tables, one category was chosen arbitrarily as a reference group to which other groups were contrasted. A P value < 0.05 was considered as statistically significant.

3. Results

All subjects were males; the mean age of the patients was 16.5 ± 12.6 years while for the healthy individuals was 17.4 ± 14.2 years, P > 0.05, Table 1.

Patients with hemophilia A were divided according to the severity of hemophilia: 37 were mild (39%), 33 were moderate (34.7%), and 25 were severe (26.3%).

The mean age at diagnosis for all PWH was 4.62 ± 9.21 years. Hemarthrosis was the most common presentation, which was reported in 80 (84.2%) patients, followed by mucous membrane bleeding with or without cutaneous bleeding in 76 (80%), muscle bleeding in 60 (63.2%), and bleeding after circumcision in 20 (21.1%). Inhibitors were detected in 13 (13.7%) PWH.

All subjects were screened for the *MIF* -173 GG SNP polymorphism. The study revealed a higher frequency of GG polymorphism in healthy subjects (81, 85.3%) compared to PWH (64, 67.4%), while a significantly higher frequency of GC polymorphism was found in PWH (21, 22.1%) than that in healthy subjects (10, 10.5%), P < 0.05. No significant difference was reported in the CC polymorphism between PWH (10, 10.5%) and control group (4, 4.2%), P > 0.05.

The G allele polymorphism was detected in 90.0% of the control group compared to 78.4% (149) of PWH, while the C allele frequency was higher in PWH (41, 21.6%) compared to the control group (18, 10.0%), P < 0.05, Table 2.

Among PWH, the study did not reveal significant differences in the frequencies of different *MIF* -173 genotypes and alleles among patients with mild, moderate, and severe disease, P > 0.05. The main clinical features among hemophilia patients were hemarthrosis, muscle hematomas, and mucous membrane bleeding. The frequencies of different *MIF* -173 polymorphisms did not show significant differences among patients with different clinical presentations, P > 0.05. Furthermore, the frequency of the *MIF* -173 GC polymorphism in PWH did not show significant difference in relation to presence of inhibitors, P > 0.05, Table 3.

Table 1. Selected sociodemographic variables of PWH and the control group.

Variable		PWH Total 95 N. (%)	Control group Total 95 N. (%)	P value
Age (Years)	≤10	39 (41.1)	37 (39)	0.968*
	11–20	24 (25.3)	21 (21.1)	
	21–30	19 (20)	20 (21)	
	31–40	10 (10.5)	13 (13.7)	
	>40	3 (3.1)	4 (4.2)	
Mean age ± SD (Years)		16.5 ± 12.6	17.4 ± 14.2	0.647 **
Residence	Center	50 (52.6)	54 (56.8)	0.560 ***
	Periphery	45 47.4)	41 (43.2)	

PWH: People with Hemophilia.
* Fisher's exact test.
** Mann–Whitney test.
*** Chi-squared test.

4. Discussion

In the present study, −173 SNP *MIF* promoter polymorphisms were genotyped in PWH A and healthy individuals. Significant associations were found in the frequencies of various *MIF* genotypes between healthy subjects and hemophilia A patients. Although MIF polymorphism appears to correlate with disease severity in patients with various autoimmune disorders, it does not appear to influence clinical outcomes such as bleeding phenotype and other complications in PWH in our study.

Hemarthrosis is the hallmark of hemophilia A and B. Hemophilic arthropathy, caused by recurrent hemarthrosis, is a degenerative joint condition characterized by chronic synovitis and cartilage destruction [18].

Hemophilic arthropathy diagnosis depends on plain radiography, ultrasonography (US), and magnetic resonance imaging (MRI). Although hemophilic arthropathy resembles the characteristics of osteoarthritis and rheumatoid arthritis, data regarding the role of biomarkers in hemophilic arthropathy are few [19].

Although hemophilia is a hereditary disease, increased levels of many inflammatory and angiogenic markers may be found in PWH A. The levels of C-reactive protein (CRP) and vascular endothelial

Table 2. Distribution of the MIF -173 G/C polymorphism among the PWH and the control group

MIF polymorphisms		PWH (N. 95)	Control (N. 95)	Odds ratio	95% CI	*P value
Genotype	GG	64 (67.4)	81 (85.3)	1†	1†	–
	GC	21 (22.1)	10 (10.5)	2.66	1.17–6.01	0.017
	CC	10 (10.5)	4 (4.2)	3.16	0.96–10.48	0.051
Allele	G	149 (78.4)	172 (90.0)	1.2	1.45–4.76	0.001
	C	41 (21.6)	18 (10.0)			

MIF: Macrophage migration inhibitory factor, CI: Confidence interval. PWH: Patients with hemophilia.
* Chi-squared test.
† The wild type was chosen arbitrarily as a reference group to which other groups were contrasted.

Table 3. The MIF -173 G/C SNP polymorphism in PWH in relation to selected clinical variables

Variable		MIF polymorphisms				
		Genotype			Allele	
		GG N. (%)	GC N. (%)	CC N. (%)	G N. (%)	C N. (%)
Severity of hemophilia	Mild (N. 37)	27 (72.97)	9 (24.32)	1 (2.70)	63 (85.13)	11 (14.86)
	Moderate (N. 33)	22 (66.66)	8 (24.24)	3 (9.09)	52 (78.78)	14 (21.21)
	Severe (N. 25)	15 (60)	4 (16)	6 (24)	34 (68)	16 (32)
P value		0.113*			0.075**	
Clinical features	Hemarthrosis (N. 80)	54 (67.5)	17 (21.2)	9 (11.3)	125 (78.1)	35 (21.9)
	Muscle bleeding (N. 60)	39 (65.0)	12 (20.0)	9 (15.0)	90 (75.0)	30 (25.0)
	Mucous m. bleeding (N.76)	51 (67.1)	17 (22.4)	8 (10.5)	119 (78.3)	33 (21.7)
	Other bleedings (N. 13)	7 (53.8)	3 (23.1)	3 (23.1)	17 (65.4)	9 (34.6)
P value		0.898**			0.485**	
Inhibitors	Present (N.13)	9 (69.2)	1 (7.7)	3 (23.1)	19 (73.0)	7 (27.0)
	Absent (N.82)	56 (68.3)	19 (23.2)	7 (8.5)	131 (79.8)	33 (20.2)
P value		0.171**			0.431*	

MIF: Macrophage migration inhibitory factor, PWH: People with hemophilia.
* Fisher's exact test.
** Chi-square test.

growth factor A (VEGF) increased during joint bleeding in those with severe hemophilia A and therefore, can be of diagnostic value when joint bleeding is suspected [20].

Biomarkers are not only useful in monitoring the effect of a joint bleed but also in assessing the response to therapy of these joint bleeds. However, the role of biomarkers in PWH is still not well defined and requires further exploration [18].

Among the synovitis biomarkers, highly-sensitive CRP, ferritin, plasma matrix metallopeptidase 9, stromal cell-derived factor 1-alpha, soluble vascular cell adhesion protein 1, serum calprotectin, plasminogen, fibrin degradation products (FDPs), D-dimer, and *MIF* were significantly elevated in PWH compared to those in healthy individuals [19].

Human *MIF* is a pleiotropic pro-inflammatory cytokine that engages in many inflammatory and metabolic conditions. It has a role in the regulation of the synthesis and release of other inflammatory cytokines, like interferons, TNF-α, and IL-1. The single-nucleotide polymorphism (SNP) −173 G/C (rs755622) in the *MIF* gene has been associated with many infectious and autoimmune conditions [21,22].

In the present study, the association between the *MIF* -173 G/C gene polymorphism and hemophilia was assessed by the odd ratio and 95% CI. We found that both GC and CC genotypes were associated with hemophilia when compared with the healthy subjects. Furthermore, the G allele polymorphism was detected in 90.0% of the control group compared to 78.4% among PWH, while the prevalence of the CC genotype was significantly higher among PWH than in healthy subjects (10.5% and 4.2%, respectively). This further indicates that both GC and CC genotypes may be involved in the pathogenesis of hemophilia despite the fact that hemophilia is an X-linked recessive disease. The association of MIF with other genetic disease such as autosomal dominant polycystic kidney disease [23] and cystic fibrosis [24] suggests the role of MIF as a modifier gene in these genetic diseases.

Although the frequencies of various *MIF -173* genotypes and alleles among patients with mild, moderate, and severe disease were not significantly different, we found that 72.97% of the mild cases were associated with the wild GG genotype, which

agrees with the above finding that *MIF -173* genotypes act as a disease modifier in PWH.

Cytokine gene SNPs, in the regulatory regions, common in certain populations, can affect specific cytokine transcription and production and in turn alter the immune response. Therefore, differences in cytokine gene frequencies among ethnically different populations may have an important clinical relationship as specific genetic diagnostic and prognostic markers [25].

An increased risk of various autoimmune diseases was found to be associated with *MIF* -173G/C, including rheumatoid arthritis, inflammatory bowel disease, and atopic dermatitis [26]. Inhibitor development among PWH has been linked to autoimmune diseases [27]; however, we did not report a significant association between *MIF* SNP polymorphism and inhibitor development.

4.1. Limitations of the study

The current study has many limitations; one limitation is that *MIF* plasma protein was not evaluated at the same time as *MIF* genotyping. The role of plasma *MIF* levels also must evaluated at different time points: during hemarthrosis and during recovery. Furthermore, other inflammatory markers like CRP and hsCRP were not evaluated. Evaluation of *MIF* SNP polymorphisms in hemophilia A patients with inhibitors was also limited owing to the small number of patients with inhibitors.

The influence of recall bias can also limit the accuracy of study findings, this has been overcome, to some extent, by reviewing the patient's records.

5. Conclusions

From this study, it can be concluded that the *MIF* -173 GC polymorphism is associated with PWH more than healthy individuals. Further studies are required to detect more SNPs through sequencing of the *MIF* gene and assessing the associations between SNPs and clinical manifestations (mainly hemarthrosis) and inhibitor development in hemophilic patients. Furthermore, serial measurements of *MIF* serum levels during bleeding episodes, especially arthropathy, may help in the early detection and/or progression of these complications.

Authorship

MA, WN, and MK designed and planned the study, and MA collected the data. MA, WN, and MK analyzed the data and contributed to the writing of the manuscript. All authors read and approved the final manuscript.

Ethical approval

The study was approved by the Ethical Committee of the College of Medicine, University of Basrah.

Conflict of interest

None.

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