ORIGINAL ARTICLE

Polymorphisms of Methyltetrahydrofolate Genes among Patients with Diffuse Large B Cell Lymphoma in Oman

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Abstract

Background: Non-Hodgkin's lymphoma (NHL) is a heterogeneous group of neoplasms with complex etiology. There is a significant geographical variation in sub-types. Diffuse Large B Cell Lymphoma (DLBCL) is the most common sub-type, more common in some parts of the world than others. The increasing incidence of DLBCL has been attributed to chronic antigen stimulation. In addition, several genetic polymorphisms, including methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms have been implicated.

Objective: To examine the association between MTHFR (C677T and A1298C) polymorphisms and DLBCL in Omani population.

Methods: This case-control study was performed at a tertiary referral hospital for cancer care in Oman. Consecutive patients with DLBCL under follow up during the period were invited to participate. Blood was extracted from consenting patients and age- and gender-matched controls. The DNA was examined for polymorphisms using polymerase chain reaction (PCR), restriction fragment length polymorphism (RFLP), and sequencing.

Results: Blood samples from 80 patients with DLBCL and 115 controls were assessed. Alleles and genotype frequencies of MTHFR genes were compared. A non-significant increase in the frequency of mutant alleles MTHFR 677T and MTHFR 1298C was observed among patients with DLBCL compared to the controls. A weak association between heterozygous MTHFR1298 AC and DLBCL risk was found; 54% among patients and 42% among controls (p=0.036).

Conclusion: The heterozygous form of MTHFR genes may be implicated in the pathogenesis of DLBCL in Omani patients. Further validation in a larger cohort and identification of similar genes can help to understand the increasing incidence of DLBCL in some regions of the world.

Keywords: *Non-Hodgkin's lymphoma, diffuse Large B Cell lymphoma, methylenetetrahydrofolate reductase, DNA, single nucleotide polymorphisms.*

INTRODUCTION

Non-Hodgkin Lymphoma (NHL) is one of the 10 most common malignancies worldwide and makes up around 90% of lymphoid malignancies [1]. Overall, NHL accounts for 3% of the cancer burden. According to GLOBOCAN, more than half a million cases of NHL were diagnosed in 2020, however, there was a huge geographic variation [2, 3]. NHL was more common in Eastern Asia and Northern America, and least common in South Central Asia. While the incidence rates were higher in Australia and North America, mortality rates were highest in Africa and Western Asia. Whereas the age-standardized incidence rates doubled in North America between 1975 and 2007 and then stabilized, the incidence rates have not plateaued in Asia [3]. The incidence has risen steadily among all age groups. NHL is a heterogenous group of neoplasms, with over 100 sub-types [4]. Diffuse Large B cell lymphoma (DLBCL) is the single largest category, accounting for 40% of NHL in the Western world and for up to 60% of cases in some other geographical areas, such as parts of the Middle East [5].

The etiology of NHL is complex, resulting from interactions between genetic and environmental factors [6]. Environmental factors include immunosuppression, infectious agents, occupational exposure (insecticides, pesticides, dust, and nitrate) autoimmune diseases, and chronic inflammatory disorders; all are known to be risk factors for NHL [7]. These factors lead to chronic inflammation, antigenic stimulation, induction of inflammatory cells, and release of cytokine, which subsequently increase the chances of random replication error [8]. In addition, variation in tumor suppressor genes, oncogenes, and DNA repair genes can change the expression or function of the gene product, therefore, enhancing the risk of development of NHL [9].

Folate plays a key role in maintaining genomic stability and providing methyl groups required for DNA synthesis and repair [10]. Deoxy uridine monophosphate (dUMP) accumulates in a low folate environment, producing DNA strand breaks Methylenetetrahydrofolate reductase (MTHFR) catalyzes the conversion of 5,10-methylenetretrahydrofolate into 5-methyltetrahydrofolate. Several studies have

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documented the modification of enzyme activity by single nucleotide polymorphisms (SNP) in the genes encoding for MTHFR [11]. Functional polymorphisms of the MTHFR gene, 677C>T and 1298A>C lead to reduced enzyme activity and have been implicated in the pathogenesis of cardio and cerebrovascular disease, neurodegenerative disorders, autoimmune diseases, and cancer [12]. C667T, and A1298C polymorphisms have also been also reported to have a pharmacogenetic role in predicting drug toxicity [13].

These SNPs are associated with an increased risk of acute lymphocytic leukemia (ALL), colon cancer, and endometrial cancer, especially in patients with Lynch syndrome [14-16]. However, contrasting findings have been reported regarding the risk of NHL and MTHFR polymorphisms [17]. For example, MTHFR 677TT was shown to be associated with a lower risk for NHL including DLBCL. This lower risk was caused by increased thymidylate synthesis due to the greater availability of MTHFR enzyme substrate 5, 10-methylene-THF required for DNA synthesis. Also, a reduction in MTHFR enzyme activity can control the amount of methionine involved in DNA methylation. Low level of methionine decreases the risk of chromosomal translocations and DNA hypermethylation; common features of NHL [18]. On the other hand, reduced MTHFR enzyme activity associated with 677TT was reported to be associated with an increased risk possibly because of the incorporation of uracil in DNA, diminished DNA repair, and increased incidence of chromosomal damage .

Thus increasing the risk of NHL [19]. Furthermore, the association between polymorphisms in folate metabolizing genes and the risk of NHL may be different in different ethnic backgrounds [20].

There is scant literature on the association between MTFR gene polymorphisms and the risk of developing DLBCL and outcomes among patients in the Middle East [21, 22]. This study was designed to examine the association between MTHFR (C677T and A1298C) polymorphisms and DLBCL in the Omani population.

PATIENTS AND METHODS

This case-control study was performed at a tertiary referral hospital for cancer care in Oman. The study was approved by the Institutional Ethics Review Committee. A written informed consent was obtained from each subject. Consecutive adult patients (18 years or more) who were diagnosed with DLBCL at a single institution were the subjects of this study. Age-and-gender matched controls were recruited from healthy blood donors or patients admitted to surgical wards, but not with a diagnosis of cancer.

Detailed characteristics and clinical data were recorded. Information about prognostic features of DLBCL (age, clinical stage, performance status, serum LDH level, and number of extra-nodal sites) was collected and used to determine the International Prognostic Index (IPI) risk group. Other prognostic features such as gender and B symptoms (drenching night sweats, weight loss of more than 5% from baseline in the preceding 6 months before diagnosis, and fever) were also recorded.

Typing of MTHFR C677T and A1298C

Two sets of SNPs primers were used to amplify two fragments of MTHFR harboring SNPs C677T and MTHFR A1298A as described by Sirag ***et al.***, 2007. The cycling temperature profile consisted of 95°C 15 min, followed by 35 cycles at 95°C 30 second, 59°C 30 seconds and 72°C 30 seconds. The final elongation step was 10 min at 72°C. The MTHFR PCR containing mutation C677T (198bp) was digested with Hinf I, as described by manufacturers (New England Biolabs, UK.) The Hinf I cleaved the 198bp amplified product in two fragments (175bp and 23bp). The MTHFR 677CC genotypes (wild type) produced one band (198bp), MTHFR TT (homozygote mutation) produced one band of 175bp, while MTHFR 677 CT (heterozygote) exhibited two bands (198bp and 175bp) when digested with Hinf I. Similarly, MTHFR PCR containing mutation A1298C was digested MboII as described by the manufacturer (New England Biolabs, UK). MTHFR 1298 AA (wild type) produced 2 bands (56bp and other band containing 31bp, 30bp and 28bp fragments), MTHFR 1298 CC (homozygote mutation) also produced 2 bands (84bp and other band containing 31bp, 30bp fragments), while MTHFR 1298 AC (heterozygote) samples exhibited pattern of 3 bands (84bp, 56bp, 31bp, 30bp and 28bp fragments)

Statistical Analysis

The genotype distributions of different polymorphic loci in the controls were compared to those expected from Hardy-Weinberg equilibrium by $\chi 2$ tests. The difference in frequency distributions of genotypes between the patient and the control groups was also tested by $\chi 2$ test. The likelihood of DLBCL associated with any allele or genotype of the above genes was estimated using an odds ratio (OR) with a 95% confidence interval. In addition, the risk of the disease due to the possible combined effect of the polymorphisms of the above genes was assessed using the same procedure. This was done by assigning the ordinal values 1, 2, and 3 to wild-type, heterozygous, and mutant homozygous genotypes, respectively. The frequency of wild types of each polymorphism was used as a reference value. P-value less than or equal to 0.05 was taken as statistically significant. Analysis of data was performed using SPSS 21.0 software.

RESULTS

Using the convenience sampling method, consecutive patients diagnosed with DLBCL were invited to participate over the study period of 2 years. For each case, 1.5 controls were chosen. A total of 80 consenting patients and 115 age and gender-matched controls

were enrolled in this study. There were 58.8% male and 41.3% female patients 44.3% male and 55.7% female controls. The median age was 45 (IQR=31-55) years and 48 (IQR=34.3-60.8) years for the patients and controls, respectively. Age (p=0.142) and gender (p=0.058) were not significantly different among patients and controls (**Table 1**).

Table 1: Age and gender distribution of DLBCL patients and healthy controls.

Variables	DLBCL Patients	Controls	p-value
Age (in years) Median (IQR)	45 (IQR=31-55)	48 (IQR=34.3-60.8)	0.142
Gender			
Male, n(%)	47(58.8)	51(44.3)	0.058
Female, n(%)	64(55.7)	33(41.3)	

The clinical characteristics of the patients enrolled in this study are shown in Table **2**.

Table 2: Clinical characteristics of 80 DLBCL patients from different parts in Oman.

Clinical Characteristic	Frequency (%)
B symptoms	
Present	18 (22.5)
Absent	50 (62.5)
Missing	12 (15.0)
Performance status	
0 to 1	42 (52.5)
2 to 4	28 (35.0)
Missing	10 (12.0)
Ann Arbor stage	
1 to II	29 (36.3)
III to IV	50 (62.5)
Missing	1 (1.3)
Serum LDH	
<200 IU/L	20 (25.0)
≥200 IU/L	50 (62.5)
Missing	10 (12.5)
Extra-nodal sites	
Present	44 (55.0)
Absent	30 (37.5)
Missing	6 (7.5)
IPI risk	
0 risk, low risk and low intermediate risk (0 to 2)	33 (41.3)
intermediate risk, high intermediate risk and high risk (3 to 5)	36 (45.0)
Missing	11 (13.6)

MTHFR C677T and A1298C Alleles and Genotypes among DLBCL Patients and Controls

The distributions of MTHFR C677T allele and genotype frequencies are shown in Table **3**. Both patients and controls were found to have an identical allele frequency for the wild-type allele C and the mutant allele T, respectively. Among the patients, 56 (70%) were homozygous for MTHFR 677C allele, 24 (30%) were heterozygous for MTHFR 677C/T allele and no homozygous MTHFR 677T allele was seen. Among the controls, 82 (71.3%) were found to be homozygous for MTHFR 677C allele, 31 (27%) were heterozygous MTHFR 677C/T and 2 (1.7%) were homozygous for the mutant MTHFR 677T allele. No significant difference was seen in the frequency of the MTHFR 677TT genotype between patients and controls.

The frequency of MTHFR 667C was similar in cases and controls (85% versus 84.8%). There was no significant difference in the distribution of MTHFR C667T alleles and genotype was not significantly different among cases and controls (OR=0.676-2.109, p=0.542).

The MTHFR A1298C allele frequency was higher in patients (43.7%) than in the controls (34.8%), but this trend was not significant; 95% CI 0.960-2.202; p=0.077). Among the patients, 23 (29.1%) were homozygous for MTHFR 1298A allele, 43 (54.4%) were heterozygous MTHFR 1298A/C and 13 (16.5%) were homozygous for the MTHFR 1298C allele. Among the control subjects, 51 (44.3%) were homozygous for the MTHFR 1298A allele, 48 (42%) were heterozygous and 16 (14%) were homozygous for the allele MTHFR 1298C. There was a noticeable difference in the wild-type MTHFR 1298A genotype in patients compared to the control (29% *vs.* 44%), but this difference was not statistically significant (p= 0.100). However, there was a significant difference in frequency of the heterozygous MTHFR 1298A/C genotype between the DLBCL patients (54%) and controls (42%) (OR=1.98; 95% CI 1.045-3.772; p=0.036), indicating that the relative risk might be confined to the A/C heterozygote.

The Combined Effect of the MTHFR (C677T and A1298C) Polymorphisms in DLBCL Patients

The combined effect of mutations of the cytokine genes MTHFR C677T and A1298C was also examined (data not shown). When the MTHFR 677CC and 1298AA

Table 3: Genotype and allele frequencies for MTHFR (C677T and A1298C) among 80 DLBCL patients and 115 age and sex matched controls and overall association with DLBCL.

Polymorphism	Controls n(%)	DLBCLs n (%)	OR	95% CI	p-value
MTHFR C667T genotype					
CC	82 (71.3)	56 (70.0)	Reference Category		
CT	31 (27)	24 (30)	1.134	0.603-2.133	0.697
TT	2 (1.7)	0 (0)	-	-	-
CT+ TT	33 (28.7)	24 (30)	1.065	0.569-1.992	0.844
MTHFR C667T alleles					
MTHFR 667C	195 (84.8)	112 (85.0)	Reference Category		
MTHFR 667T	35 (15.2)	24 (15.0)	1.194	0.676-2.109	0.542
MTHFR A1298C genotypes					
AA	51 (44.3)	23 (29.1)	Reference Category		
AC	48 (41.7)	43 (54.4)	1.986	1.045-3.772	0.036
CC	16 (13.9)	13 (16.5)	1.801	0.746-4.351	0.191
AC+ CC	64 (55.6)	56(70.9)	1.940	1.055-3.568	0.033
MTHFR A1298C alleles					
MTHFR 1298A	150 (65.2)	89 (56.3)	Reference Category		
MTHFR 1298C	80 (34.8)	69 (43.7)	1.454	0.960-2.202	0.077

(wild genotypes) were defined as a reference, the combination of MTHFR 677CT/TT and MTHFR 1298AC/CC genotypes (heterozygous and mutant homozygous) were found to be associated with DLBCL (OR=2.179; 95% CI 1.042-4.557; P=0.039). The combination of heterozygous MTHFR 677 (C/T) plus wild-type MTHFR 1298 (A/A) genotypes occurred at a much higher frequency among DLBCL patients (OR=2.071; 95% CI 0.931-4.609; p=0.074). However, the lack of significant levels may be attributed to the relatively small sample size.

DISCUSSION

This study examined the association of single nucleotide polymorphisms in MTHFR C667T and MTHFR A1298C genes with the pathogenesis of DLBCL among Omani patients. Although a higher frequency of mutant alleles of MTHFR 667T and MTHFR 1298C were observed among patients with DLBCL compared to controls, there was no association between MTHFR C677T polymorphisms and DLBCL. However, there was a weak association between genotypes of heterozygous MTHFR 1298 AC and DLBCL.

DLBCL constitutes 60% of cases of NHL in Oman [23]. The pathogenesis of DLBCL is multifactorial, involving a complex interplay between genetic and environmental factors [9]. MTHFR plays a pivotal role in folate metabolism, affecting DNA synthesis and methylation processes critical for cellular function [10]. Polymorphisms such as C677T and A1298C alter enzymatic activity, with potentially conflicting effects on cancer risk in different populations [20]. Previous studies have linked these polymorphisms to multiple cancers, however, their specific impact on DLBCL in Omani Arab populations remains underexplored.

Our results of no association between MTHFR C677T polymorphisms and DLBCL are consistent with several previous studies from different ethnic groups [24, 25]. However, our results are at variance with a study from a mixed population in the US, where this polymorphism was associated with an increased risk of NHL [26]. On the other hand, a significantly lower risk of NHL was reported with MTHFR 677 CT/TT genotypes from Japan [27]. Significant geographical and ethnic variations in the frequencies of the C677T in the folate metabolism pathway may explain the discrepant results [20].

The MTHFR A1298C polymorphism, in particular, the heterozygous MTHFR 1298 A/C genotype was associated with an increased DLBCL risk by 2 folds among Omani patients. The homozygous MTHFR 1298CC genotype and not the heterozygous (A/C) genotype was associated with an increased risk of DLBCL [21]. However, some reports suggested that MTHFR A1298C polymorphism in general may not have such an effect among Caucasian patients with NHL [24, 26].

A large-scale epidemiological study demonstrated that the combined effect of MTHFR C677T and A1298C polymorphisms is more predictive than the single MTHFR polymorphism [27]. The underlying principle for combining MTHFR C677T and MTHFR A1298C is that both polymorphisms are associated with reduced enzyme activity of the MTHFR enzyme which is closely associated with DNA synthesis and methylation [28, 29]. The lack of association between the combined effect of MTHFR C677T and A1298C polymorphisms and DLBCL in the present study could be attributed to the high frequency of the heterozygous genotype MTHFR 1298A/C which is suggested to have an intermediate enzyme activity.

The limitation of the study was the relatively small sample size, which may limit the statistical power, especially for the subgroup analyses. Alternatively, the diverse ethnicity of the indigenous Omani population may explain the lack of clear association.

Our findings highlight the need for larger, multicenter studies to validate these associations and explore the mechanistic underpinnings of MTHFR polymorphisms in DLBCL pathogenesis and prognosis. Additionally, integrating these genetic markers into predictive models could enhance risk stratification and inform personalized therapeutic approaches. Further research should also investigate gene-environmental interactions, particularly in populations with unique exposures and genetic backgrounds.

CONCLUSION

The critical role of MTHFR polymorphisms, C677T and A1298C, in the pathogenesis and prognosis of DLBCL in the Omani population was evaluated. The study revealed no significant difference in MTHFR C677T allele and genotype frequencies between patients and controls, indicating that this polymorphism alone may not be a significant risk factor for DLBCL in this cohort. However, the heterozygous A1298C genotype was significantly more frequent among DLBCL patients, suggesting a potential association with increased disease susceptibility. A combined analysis of both polymorphisms demonstrated that individuals with heterozygous or mutant homozygous genotypes exhibited a significantly elevated risk for DLBCL. This finding underscores the potential synergistic impact of these genetic variants on disease risk. This study contributes to a growing body of literature investigating genetic variations influencing cancer susceptibility and outcomes, particularly in geographically and ethnically distinct populations.

ETHICS APPROVAL

The ethical exemption was obtained from the Medical Research and Ethics Committee of the College of Medicine and Health Sciences, Sultan Qaboos University. All procedures performed in studies involving

human participants followed the ethical standards of the institutional and/ or national research committee and the Helsinki Declaration.

CONSENT FOR PUBLICATION

Informed consent was taken from the participants.

AVAILABILITY OF DATA

The data set may be acquired from the corresponding author upon request.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

IB, Study concept, study design, writing grant application, consenting patients, managing experiments, manuscript writing. AAB and BAS, performing experiments in the laboratory, extracting clinical data from electronic patient records, AB: writing manuscript, HB: writing the grant application, overseeing laboratory work, result interpretation, critical review, and revision of the initial draft.

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