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ABO and Rh Blood Groups and Risk of Myelomeningocele

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ABSTRACT

AIM: To investigate the relationship between the distribution of ABO or Rhesus (Rh) blood group antigens and the incidence of myelomeningocele.

MATERIAL and METHODS: A retrospective data was reviewed for all myelomeningocele patients operated at a tertiary academic hospital between years 2014 and 2019. Age, sex, delivery method, physical and neurological examination findings, and radiological findings alongside with blood type of each patient were recorded. The data of blood group distribution among the study patients was compared to the data of healthy individuals in the same region.

RESULTS: Patients with group B and AB showed a higher chance of developing myelomeningocele. Rh-positive blood group was associated with high incidence of myelomeningocele (93.5%), whereas Rh-negative blood group showed least association (6.5%). Rh-positive blood group was also found to be more frequent in patients with myelomeningocele with hydrocephalus and Chiari malformation.

CONCLUSION: The findings of this study show that ABO and Rh blood groups have an effect on the development of myelomeningocele under the influence of environmental or genetic factors.

KEYWORDS: ABO blood groups, Myelomeningocele, Neural tube defects, Rh blood groups

ABBREVIATIONS: GBM: Glioblastoma Multiforme, **Me-THF:** Methyltetrahydrofolate, **MMC:** Myelomeningocele, **MTHFR:** Methylenetetrahydrofolate reductase gene, **RBCs:** Red Blood Cells, **Rh:** Rhesus, **RR:** Relative ratio, **SARDH:** Sarcosine dehydrogenase gene

INTRODUCTION

Myelomeningocele (MMC), also known as open spina bifida, is the most common neural tube defect but its multifactorial etiology is still poorly understood. Both environmental and genetic factors contribute to MMC development (5,7,8,18) so that the incidence of MMC varies in different parts of the world and among ethnic groups (45). Disorders in folate-dependent single carbon metabolism may affect cellular reactions crucial for appropriate neural tube closure, such as cell proliferation, survival, differentiation, and migration (3,25). Genetic alterations in the 9q34.2 region [Sarcosine dehydrogenase gene (SARDH)] and the 1p36 regions [Methylenetetrahydrofolate reductase gene (MTHFR)], which have roles in folate metabolism, have been reported to be risk factors for the development of neural tube defects (4,10,36).

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ABO blood group and Rhesus (Rh) D antigens are polymorphic, antigenic, genetic substances found mostly on the surface of red blood cells (RBCs) but also on some other cells and tissues. Hereditary polymorphic features transferred between individuals and communities can be found in blood group antigens (16). ABO and Rh blood groups are seen at the entire human population, however their frequency and distribution are different among nations and races (6,9). The genetic localization of ABO blood group antigens is on the 9q34.2 region, whereas that for the Rh blood group antigen is on the 1p36 region (2,32).

After being defined at the beginning of the 20th century, several studies have been performed to investigate the relationship between ABO and Rh blood groups and various metabolic and malignant diseases. Early publications on this subject claimed that cancer, peptic ulcer, and thrombotic diseases were associated with ABO blood groups (19,34,36). Furthermore, recent review and meta-analysis studies have confirmed the connection between the distribution of ABO blood group antigens and the risk of developing specific types of cancer (13,20-22,27,47). Relations between blood groups and type 2 diabetes mellitus (24), obesity (17), stomach and duodenal ulcer (38,40), Hepatitis-B (37), vascular diseases (46), and abdominal aortic aneurism (11) have also been reported in previous studies.

Since ABO and Rh antigens and some important enzymes in the folate pathways share gene loci, we hypothesized that there is a relationship between RBC surface antigens and MMC development. Thus, in this study, we investigated the relationship between the distribution of ABO or Rh blood group antigens and the incidence of MMC in Turkish people.

MATERIAL and METHODS

This study was approved by Baskent University Institutional Review Board (Project no: 94603339-604.01.02/44399) and supported by Baskent University Research Fund. We retrospectively reviewed all cases of MMC referred to and operated upon at our hospital between July 2014 and November 2019. Gestational age; maternal age; sex; delivery method (vaginal vs cesarean section); physical, neurological, and radiological examination findings; and blood group were retrieved from the hospital data system and recorded for each patient. The data of blood group distribution among our patients was compared to that collected from 6041 healthy individuals in 2015 from the same region (35).

Statistical Analysis

The Kolmogorov–Smirnov test was used to determine the normality of the distribution of the continuous variables. Continuous variables with normal distribution were expressed as mean (± standard deviation). Variables with skewed distribution were expressed as median (minimum–maximum), and categorical variables were expressed as percentage (%). Chi-square test was performed for the comparison of two proportions (from independent samples), expressed as a percentage. Statistical analysis was with MedCalc Statistical Software version 18.11.3 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2019) and SPSS version 20.0 for Windows. A P value of <0.05 was defined as statistically significant.

RESULTS

A total of 77 patients were diagnosed with MMC and operated upon (Table I). The distribution of blood groups in these patients was as follows: A: 31 (40.2%), B: 15 (19.5%), O: 23 (29.9%), AB: 8 (10.4%); Rh(+): 72 (93.5%), Rh(–): 5 (6.5%) (Table I).

Table I: Demographic Features of Myelomeningocele Patients

Characteristic	**Value**
Maternal Age (years)	27.8 ± 5.97
Gender	**n (%)**
Male	36 (47)
Female	41 (53)
Method of Delivery	**n (%)**
Vaginal	15 (19)
Caesarian-section	62 (81)
Lesion Level	**n (%)**
Cervical	2 (2.6)
Thoracic	5 (6.5)
Thoracolumbar	30 (39.0)
Lumbar	34 (44.1)
Sacral	6 (7.8)
Hydrocephalus	**n (%)**
(+)	58 (75)
(-)	19 (25)
Chiari Malformation	**n (%)**
(+)	54 (70.0)
(-)	23 (30.0)
Kyphosis	**n (%)**
(+)	28 (36)
(-)	49 (64)
Syringomyelia	**n (%)**
(+)	30 (39)
(-)	47 (61)
Blood groups	**n (%)**
A	31 (40.2)
B	15 (19.5)
O	23 (29.9)
AB	8 (10.4)
Rh (+)	72 (93.5)
Rh (-)	5 (6.5)

n: *number of patients,* ***%:*** *percentage,* ***Rh:*** *Rhesus,* ***y:*** *years.*

When comparing patients with MMC with healthy blood donor controls, the presence of B and AB blood groups were found 21% and 26% higher at MMC patients. However these results were not statistically significant in association with a risk of developing MMC. Relative risk (RR) ratio of patients with B and AB blood groups compared to O blood group were 1.33 and 1.34, respectively. This suggests that individuals with group B and AB have a higher than expected chance of developing MMC. "Rh-positive" blood type was associated with high incidence of MMC (93.5%), whereas "Rh-negative" blood group showed least association with MMC (6.5%). Comparison of healthy controls with the MMC group revealed that Rh-positive patients were at higher risk of MMC development (p=0.42). Patients with Rh-positive blood group showed significantly higher probability of developing MMC when compared with Rh-negative patients (RR=2.33)

Subgroup analysis according to concomitant pathologies (such as hydrocephalus, kyphosis, syringomyelia, and Chiari malformation) revealed that Rh-positive blood group was more frequent in patients with MMC with hydrocephalus and Chiari malformation. B blood group was found more often in patients with MMC with kyphosis or syringomyelia than in healthy individuals. AB blood group was observed less frequently in patients with MMC with kyphosis,whereas O blood group was seen less in patients with MMC with syringomyelia than in the normal population (Table II).

DISCUSSION

In this study, we evaluated the relationship between the most common blood group antigens and myelomeningocele. To our knowledge, this is the first study to evaluate ABO and Rh blood groups as risk factors for the development of MMC. Among MMC cases and controls from large cohort studies in same regions, we observed a significantly elevated risk for MMC among those with B blood group compared with those with non-B blood groups. The highest risk was found in patients with B blood group, followed by an intermediate risk in patients with AB blood group. In addition, Rh positivity was found to be associated with MMC development.

Neural tube defects are among the multi-factorial disorders on the basis of genetic predisposition. One of the most environmental important risk factors for MMC is low maternal folate intake. Therefore, the preconceptional folic acid usage has been reported in the literature as one of the preventative measures used to reduce the risk of MMC development. As a result, MMC development and recurrence were reduced by 50% to 85% (14,26). However, genetic variations that cause inadequate functioning of endogenous folate metabolism, such as the 667C>T polymorphism in the MTHFR gene, are associated with increased risk of MMC (4,14).

Folate metabolites play asignificantrole as cofactors of many different enzymes involved in processes such as purine and pyrimidine synthesis, DNA and protein methylation (14). Deficiencies in folate-dependent one-carbon metabolism, which is crucial for methylation reactions and nucleic acid synthesis, play an important role in MMC development (4).

Table II: Subgroup Analysis of Blood Groups According to Concomitant Pathologies

Blood Group	MMC n=77	p	MMC+Hydrocephalus n=58	p	MMC+Chiari n=54	p	MMC+Kyphosis n=28	p	MMC+Syrinx n=30	p	Control n=6041 (%)
A	31 (40.2%)	0.5687	23 (39.6%)	0.5571	22 (40.7%)	0.6859	12 (42.8%)	0.9457	14 (46.7%)	0.7194	43.4 %
B	15 (19.5%)	0.4351	11 (19.0%)	0.6407	11 (20.4%)	0.2692	7 (25.0%)	0.1398	7 (23.3%)	0.2046	15%
O	23 (29.9%)	0.5504	19 (32.8%)	0.9589	17 (31.5%)	0.8010	8 (28.6%)	0.6167	6 (20.0%)	0.1302	33%
AB	8 (10.4%)	0.5602	5 (8.6%)	0.9870	4 (7.4%)	0.7653	1 (3.6%)	0.3502	3 (10.0%)	0.7754	8.5%
Rh(+)	72 (93.5%)	**0.0428**	54 (93.1%)	0.1182	50 (92.5%)	0.1672	25 (89.3%)	0.6107	27 (90%)	0.5241	85.9%
Rh(-)	5 (6.5%)	**0.0428**	4 (6.9%)	0.1182	4 (7.5%)	0.1672	3 (10.7%)	0.6107	3 (10%)	0.5241	14.1%

Chiari: *Chiari malformation,* ***MMC:*** *myelomeningocele,* ***n:*** *number of patients,* ***p:*** *p value,* ***Rh:*** *Rhesus,* ***Syrinx:*** *Syringomyelia,* ***(+):*** *positive,* ***(–):*** *negative.*

Disorders in this metabolism may affect cellular responses necessary for proper neural tube formation, such as cell proliferation, survival, differentiation, and migration (3,25). It is known that variations of MTHFR gene on chromosome 1p36 and SARDH gene on chromosome 9q34 in endogenous folate metabolism significantly increase the risk of MMC development (14,28,29,31,42,44). Methyltetrahydrofolate (Me-THF), the product of MTHFR, is the predominant circulating form of folate. However, folate forms like 5,10-methylenetetrahydrofolate, a substrate of MTHFR, are mainly inside the cell and do not circulate. Polymorphism in the MTHFR gene disrupts folate metabolism and causes a decrease in plasma folate levels (43). SARDH-encoded sarcosine dehydrogenase is a catalyzer at the oxidative demethylation of sarcosine glycine (a key intermediate product in folate-dependent carbon metabolism) to promote folate-mediated transfer of monocarbon units required for DNA synthesis and repair (15,31). However, significantly increased levels of homocysteine have been found at pregnancies affected by MMC, making SARDH a more valuable genetic factor for MMCs (31,39). These two molecules are very important for embryonic development. In particular, the amino acid polymorphism of SARDH (rs2073817) significantly increases the risk of MMC (31). These two enzymes, which are important for the continuity of folate metabolism, are located on the same chromosomes as ABO antigens (chromosome 9q34) and Rh antigen (1p36).

Previous studies have found associations of ABO blood groups with pathologies such as Alzheimer's disease (23,33), neurodegenerative diseases (12), neurological diseases, and neoplastic lesions of the central nervous system (20) such as glioblastoma multiforme (GBM) (1,41) or astrocytoma (30). In their study of patients with GBM, Allouh et al. reported a 2.1 times increased risk in patients with A blood group compared with those with O blood group (1). In this study, we performed a retrospective analysis of patients treated for MMC to investigate the effect of ABO and Rh blood groups on MMC development. In our study compared with patients with O blood group, those with AB, or B blood group were more likely to develop MMC (RR: 1.33 1.34, respectively). Due to the close similarity between genetic locations of important enzymes in folate metabolism and ABO and Rh antigens, allele variants in ABO and Rh genes on chromosomes 9q34 and 1p36 may be an important site for MMC hereditary susceptibility.

CONCLUSION

In conclusion, we have found differences in the distribution pattern of ABO blood groups in patients with MMC compared with the general healthy population. Individuals with Rh antigen had a high risk of developing MMC. Based on the findings of this study, we suggest that ABO and Rh blood groups have an impact on the development of MMC under the influence of environmental or genetic factors.

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