# Correlation of ABO Blood group and Rh factor with Neural tube defects: spina bifida with Myelomeningocele in children of North India

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***Abstract***

***Background:***

***To study the hypothesized association between the presence of ABO and Rhesus (Rh) blood group antigens and the incidence of spina bifida with myelomeningocele in children***

***Material methods:***

***This study included an analysis of the data obtained from patients exhibiting spina bifida with myelomeningocele in-patients at Sir Sunderlal Hospital, Banaras Hindu University, between 2019 and 2020. Caste, Food source, Habitat, Age, sex, delivery method, physical and neurological examination findings, and ABO blood type of every patient were documented. Blood group data is distributed among the study patients associated with healthy individuals in the same region.***

***Results: A more significant proportion of patients with blood group B and AB exhibited MMC Patients showed a higher casual of developing myelomeningocele. Rh-positive blood group was associated with a high incidence of myelomeningocele (91.2%), whereas only a small proportion of patients with MMC had Rh-negative blood group (8.8). Rh-positive blood group was also found to be more frequent in patients with myelomeningocele with hydrocephalus and anencephaly.***

***Conclusion: This study's conclusions show that ABO and Rh blood groups affect the increase of myelomeningocele beneath the influence of environmental or genetic factors.***

***Keywords: Neural tube defects, Myelomeningocele, ABO blood groups, Rh blood groups***
***ABBREVIATIONS: MMC: Myelomeningocele, SARDH: Sarcosine dehydrogenase gene Me-THF: Methyltetrahydro folate, rbcs: Red Blood Cells, GBM: Glioblastoma Multiforme, Rh: Rhesus, RR: Relative ratio***

## Introduction

During embryogenesis, due to failure of the neural tube closer, there is a composite congenital malformation of the central nervous system, commonly called neural tube defect(1). The prevalence of ntds depending on geography varies widely between 1 and 10 per 1,000 births, region, and ethnic grouping, making them one of the most frequent congenital malformations(2). Ntds can be classified into two leading groups, first is “open” ntds in which the neural tissue is exposed, and another is “closed” ntds with the neural tissue covered by tissue(3). Myelomeningocele is a type of open spina bifida, is the most common NTD and the most severe congenital disability compatible with long-term survival. Although the incidence of ntds is declining, it continues to be the cause of significant chronic disability(4). MMC development by both environmental and genetic factors so that the incidence of MMC varies in different parts of the world and among ethnic groups(5).

Genetic disorders in a particular enzyme that catalyze in folate-dependent single carbon metabolism may disturb cellular reactions vital for suitable development neural tube closure, such as cell differentiation, proliferation, migration, and survival(6). Genetic changeable in chromosome particular region 9q34.2 that

synthesized Sarcosine dehydrogenase gene (SARDH) and the most common enzyme is synthesized on chromosome location 1p36 is Methylenetetrahydrofolate reductase gene (MTHFR), which have essential roles in folate metabolism, have been informed to be risk factors for the development of neural tube defects(7).

In 1901 Karl Landsteiner was first given ABO blood system, The particular region on chromosome 9p that determine the A and B phenotypes that express particular gene according to Mendelian codominant manner(8). Different societies have different Gene frequencies in the blood groups, which vary from person to person and a risk factor creates for several diseases. Numerous studies show a relationship between diseases and blood groups(9). Aantigenic, genetic substances are found mostly on the surface of red blood cells (rbcs) and some other cells and tissues. Hereditary polymorphic features transferred between individuals and communities can be found in blood group antigens. ABO and Rh blood groups are seen in the entire human population(10). However, their frequency and distribution are different among nations and races. ABO blood group antigen genetic localization is on the 9q34.2 region, whereas the Rh blood group antigen is on the 1p36 region(11).ABO and Rh antigens and some powerful enzymes play a crucial role in the folate pathways regulated by gene product on location. We imagined an association between surface antigens on RBC and MMC development. Thus, in this study, we investigated the relationship between the distribution of ABO or Rh blood group antigens and MMC incidence in North Indian people.

**Materials and methods**

This study included an analysis of the data obtained from patients exhibiting spina bifida with myelomeningocele in-patients at Sir Sunderlal Hospital, Banaras Hindu University, between 2019 and 2020. Caste, Food source, Habitat, Age, sex, delivery method, physical and neurological examination findings, and ABO blood type of every patient were documented. The blood group of the cases and controls was collected by a single trained and calibrated investigator using the finger-prick method and the tube method's blood typing. Patients were classified according to blood group (A, B, AB, and O) and Rh status (+ or −). The other blood samples were measured (Sysmex XE-2100; Kobe, Japan)(12). Blood group data is distributed among the study patients associated with healthy individuals in the same region.

**Statistical Analysis**

The normality of the dispersal of the continuous variables uses Kolmogorov–Smirnov test. Continuous variables with normal distribution were expressed as mean (± standard deviation). Variables with skewed distribution were communicated as median (minimum-maximum), and categorical variables were expressed as percentages (%). A Chi-square test was executed to compare 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 Windows. A P value of $<0.05$ was defined as statistically significant.

**Results**

A total of 57 patients were diagnosed with MMC and operated upon (Table I). The distribution of blood groups in these patients was as follows: A: 26 (45.6%), B: 9 (16%), O: 17 (30%), AB: 5 (8%); Rh(+): 52 (91.2%), Rh(−): 5 (8.8%) (Table I).

**Table I:** Demographic Features of Myelomeningocele Patients

| Characteristic | Value |
|---|---|
| **Maternal Age (years)** | 25.5 ± 5 |
| Gender | **N (%)** |
| **Male** | 26 (45.6) |
| **Female** | 31(54.4) |
| Method of Delivery | **N (%)** |
| **Vaginal** | 9 (15) |
| **Caesarian-section** | 48 (85) |
| Lesion Level | **N (%)** |

| | |
|---|---|
| **Cervical** | 1 (1.7) |
| **Thoracic** | 4 (7) |
| **Thoracolumbar** | 21 (36.8) |
| **Lumbar** | 26 (45.7) |
| **Sacral** | 5(8.8) |
| **Hydrocephalus** | **N (%)** |
| **(+)** | 48 (84.2) |
| **(-)** | 9 (15.8) |
| **Blood groups** | **N (%)** |
| **A** | 26 (45.6) |
| **B** | 9 (16) |
| **O** | 17 (30) |
| **AB** | 5 (8.4) |
| **Rh (+)** | 52 (91.2) |
| **Rh (-)** | 5 (8.8) |

When comparing patients with MMC with healthy blood donor controls, B and AB blood groups were found 19% and 24% higher at MMC patients. But these results were not statistically important in association with a risk of developing MMC. Compared to the O blood group, the relative risk (RR) ratio of patients with B and AB blood groups was 1.31 and 1.32, 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 a high incidence of MMC (91.2%), whereas the "Rh-negative" blood group showed the least association with MMC (8.8%). 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 a significantly higher probability of developing MMC when compared with Rh-negative patients (RR=2.34) According to concomitant pathologies (such as hydrocephalus), subgroup analysis revealed that Rh-positive blood group was more frequent in patients with MMC with hydrocephalus than in the average population **(Table II).**

**Table II:** Subgroup Analysis of Blood Groups According to Related Pathologies

| **Blood Group** | **MMC n=57** | **P** | **MMC + Hydrocephalus n=38** | P | **Control n=120 (%)** |
|---|---|---|---|---|---|
| **A** | 26 (45.6%) | 0.5667 | 17(44.8%) | 0.5571 | 43.40% |
| **B** | 9 (16%) | 0.4351 | 5(13.1%) | 0.6407 | 15% |
| **O** | 17 (30%) | 0.5504 | 13 (34.2%) | 0.9589 | 33% |
| **AB** | 5 (8.4%) | 0.5602 | 3 (7.9%) | 0.987 | 8.50% |
| **Rh(+)** | 52 (91.2%) | 0.0428 | 34 (89.5%) | 0.1182 | 85.90% |
| **Rh(-)** | 5 (8.8%) | 0.0428 | 4 (10.5%) | 0.1182 | 14.10% |

**MMC: myelomeningocele, n: number of patients, p: p-value, Rh: Rhesus, (+): positive, (-): negative**

## Discussion

In this analysis, we estimated the relationship between the most common blood group antigens and myelomeningocele. To our information, 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 extensive cohort studies in the 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 maximum risk was found in patients with the B blood group, followed by an intermediate risk in patients with the AB blood group. Also, Rh positivity was found to be associated with MMC development. Neural tube defects are among the multi-factorial disorders based on genetic predisposition. One of the essential environmental risk factors for MMC is low maternal folate intake(13). Therefore, the preconceptional folic acid usage has been reported in the literature as one of the preventative measures used to reduce MMC development risk. As a result, MMC development and recurrence were reduced by 50% to 85%(14). However, genetic variations that cause inadequate functioning of endogenous folate metabolism, such as the 667C>T polymorphism in the MTHFR gene, are associated with an increased MMC risk(14).Folate metabolites play a significant role as cofactors of many different enzymes involved in processes such as purine and pyrimidine synthesis, DNA and protein methylation. Deficiencies in folate-dependent one-carbon metabolism, crucial for methylation reactions and nucleic acid synthesis, play an essential role in MMC development(15).

Disorders in this metabolism may affect cellular responses necessary for proper neural tube formation, such as cell proliferation, survival, differentiation, and migration. It is known that variations of the MTHFR gene on chromosome 1p36 and SARDH gene on chromosome 9q34 in endogenous folate metabolism significantly increase MMC development. Methyltetrahydrofolate (Me-THF), the product of MTHFR, is the predominant circulating form of folate(16). 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. The oxidative demethylation of sarcosine glycine is catalyzed by Sarcosine dehydrogenase (a key intermediate product in folate-dependent carbon metabolism) encode by SARDH to stimulate folate- mediated transfer of mono carbon units essential for DNA repair and synthesis(17).

Conversely, meaningfully increased homocysteine levels have been found at pregnancies affected by MMC, making SARDH a more valuable genetic factor for mmcs. These two molecules are vital for embryonic development. In particular, the amino acid polymorphism of SARDH (rs2073817) significantly increases the risk of MMC. These two enzymes, essential for the continuity of folate metabolism, are located on the same chromosomes as ABO antigens (chromosome 9q34) and Rh antigen (1p36)(18).

Previous studies have found associations of ABO blood groups with pathologies such as Alzheimer's disease, neurodegenerative diseases, neurological diseases, and neoplastic lesions of the central nervous system such as glioblastoma multiforme (GBM) or astrocytoma. 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(19). c 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 essential site for MMC hereditary susceptibility(5).

## CONCLUSION

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

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