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Original Article

Role of ABO blood type in delayed cerebral ischemia onset and clinical outcomes after aneurysmal subarachnoid hemorrhage in an ethnic minority urban population

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ABSTRACT

Background: In recent years, the role of ABO blood type moved into focus through the discovery of different hemostaseologic properties with importance in many diseases including subarachnoid hemorrhage (SAH). However, the role of ABO blood type in delayed cerebral ischemia (DCI) onset, clinical progress, and outcome after SAH is to date largely unexplored. Our aim was to explore the role of ABO blood group in DCI and clinical outcomes after aneurysmal SAH (aSAH).

Methods: A retrospective analysis was made with data collected from patients who presented aSAH at our single-academic center from 2015 to 2018. We included demographic, clinical, and imaging variables in the univariate analysis and in the subsequent multivariate analysis.

Results: A total of 204 patients were included in this study. About 17.9% of "O" type patients developed a DCI while DCI was reported in only 8.2% of non-O type patients ($P = 0.04$). "O" type was an independent risk after in the logistic regression after adjusting for significant factors in the univariate analysis (OR=2.530, 95% CI: 1.040-6.151, $P = 0.41$). Compared to "non-O" type patients, "O" type patients had a trend to have poorer outcomes at discharge (25.5% vs. 21.3%, $P = 0.489$) and at 12–18 months (21.1% vs. 19.5%, $P = 0.795$). However, there were no significant differences.

Conclusion: Our study evidenced that patients with "O" blood type have higher risk of DCI onset after aSAH. Although these findings need to be confirmed, they may aid to improve DCI prevention and outcome predictions.

Keywords: ABO blood type, Aneurysm, Delayed cerebral ischemia, Subarachnoid hemorrhage

INTRODUCTION

Subarachnoid hemorrhage (SAH) caused by aneurysmal rupture (aSAH) is a devastating condition causing the 2–5% of all new strokes[17]. aSAH mortality rate is about 40%[16] and 50% of the survivors experience cognitive impairment and functional disabilities.[13,18] One of the most important predictors for morbidity and mortality after aSAH is the presence of neurological decline caused by cerebral vasospasm known as delayed cerebral ischemia (DCI).[8,17] Known

associated factors for DCI and clinical poor outcomes are Hunt-Hess grade, modified fisher grade (mFG), antifibrinolytic therapy, CSF drainage, age, female sex, values in the transcranial Doppler (TCD), and many other patient, procedure, and aneurysm related factors.[2,7,10,12,15,20]

Recently, ABO blood type has been related with hemorrhagic pathologies, because plasma vWF levels are 25–35% lower in subjects with type O blood group than in individuals without type O blood group and that has been established as the cause of excessive bleeding.[9,11] Moreover, the role of ABO blood type moved into focus through the discovery of different hemostaseologic properties such as a possible relationship between endothelial ABO antigen and eNOS that includes a genetic linkage with other genes regulating vasoconstriction, vasodilation, or direct association of blood type antigen and with vascular reactivity.[5,22] Furthermore, data obtained from recent studies showed that vasospasm after SAH was associated with a 40% reduction in NO secretion by the eNOS.[22] Due to prolonged periods of intracranial bleeding can increase the consumption of free NO by hemoglobin and oxidize hem products, we hypothesize that patients with type-O group have higher risk to develop DCI after aSAH.

In this context, ABO blood type linkage with SAH outcomes is possible. However, only few studies had assessed the relation of clinical status at admission and DCI after SAH with blood types but, any of these studies had found a significant influence of ABO blood type.[4,5] Nevertheless, the role of ABO blood type in onset, clinical progress, and outcome after SAH is to date largely unexplored and there is still a need to further understand the causal relationship between ABO antigens and hemorrhagic disorders and how these factors interact. Therefore, our aim is to explore the role of ABO blood group in DCI and clinical outcomes after aSAH.

MATERIALS AND METHODS

Study design

A retrospective analysis was made with data collected from patients who presented aSAH at a single academic center located in the Bronx, New York, between 2016 and 2018. Institutional review board approved the protocol before study initiation. Informed consent was waived due to the nature of the research.

The principal inclusion criteria were patients over 18 years of age with aSAH. Exclusion criteria comprised nonaneurysmal etiology, patients with incomplete follow-up, and patients with infectious aneurysms.

Examined data

ABO type was classified between "O" type and "non-O" type. Patient socio-demographics (sex, age, ethnicity, BMI, hypertension, and smoke status), procedure-related factors (microsurgical clipping, coiling, and EVD placement), aneurysms characteristics (location in anterior or posterior circulation and size <7 mm or ³7 mm), and clinical variables (Hunt Hess Score, mFG, DCI, and modified Rankin Scale (mRS) at discharge and at outpatient follow-up between 12 and 18 months) were included.

After SAH diagnosis, four-vessel 3D angiography was performed in every patient. Selection of patients that underwent microsurgical clipping or coiling was done by the neurointerventional team of our institution that performs both procedures. TCDs were done for 15 days after the SAH routinely every 24 h and cerebral angiography for confirmation of clinically suspected vasospasm during the hospital stay.

All patients had a clinical and neurological examination by the neurovascular team at 24 h' postprocedure, at discharge, and at 6 mo to 18 mo after treatment. mRS score was recorded in every follow-up by the physician in charge of the case.

Outcome data

The main outcome measure was development of DCI. Secondary outcomes included clinical functional outcomes at discharge and at 12–18 months with the mRS score. For this purpose, we used the following definitions: (1) DCI, the occurrence of focal neurological impairment that lasted more than 1 h (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least two points on the Glasgow Coma Scale (either on the total score or on one of its individual components [eye, motor on either side, and verbal]) and cannot be attributed to other cause[21]; and (2) clinical outcomes "Good outcomes" for patients with the following characteristic, mRS score 0–2, "Poor outcomes" when mRS score ≥3.

The aim of this study was (1) to determine the role of ABO blood type in the development of DCI, and (2) to explore the association between ABO blood type with: (a) demographic characteristics, (b) clinical presentation with Hunt-Hess (HH) score at admission, (c) imaging severity with mFG, (d) DCI, and (e) clinical outcomes assessed with mRS.

Statistical analysis

SPSS v.24 software was used to perform the statistical analysis. In regard to demographic, treatment and clinical variables, comparisons of the distributions were made by the Chi-square test) or Student's *t*-test as appropriate. Factors with $P < 0.10$ were included in a multiple logistic regression model to identify independent predictors of outcome. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. $P < 0.05$ was considered as statistically significant.

RESULTS

A total of 204 patients met the inclusion criteria for this study. The baseline characteristics of the population are summarized in Table 1. The majority of our population consisted of females n = 145 (71.1%) and non-Caucasian ethnicities (African Americans n = 80 (39.2%) and Hispanics n = 88 (43.1%). However, the "O" type and "non-O" type distribution of patients was similar (52% and 48%, respectively).

Table 2 shows the demographic, clinical, and aneurysm characteristics between groups. Regarding the treatment modality, "O" type patients had higher rates of microsurgical clipping compared to "non-O" type patients (41.5% vs. 25.5%, P = 0.016). The prevalence of DCI onset was significantly higher in "O" type patients with 17.9% (n = 19) while DCI prevalence in "non-O" type was less than a half with only 8.2% (n = 8) (P = 0.040). The other variables reported were not statistically significant. The multivariate model showed that after adjusting DCI onset for treatment modality, "O" type was an independent risk factor for DCI, increasing the risk of DCI 2.5 times more compared to "non-O" blood type patients (OR = 2.530, 95% CI: 1.040–6.151, P = 0.041) [Table 3].

Compared to "non-O" type patients, "O" type patients had a trend to have poorer outcomes at discharge (25.5% vs. 21.3%, P = 0.489) and at 12–18 months (21.1% vs. 19.5%, P = 0.795). However, there were no significant differences [Figure 1 and 2].

Table 1: Demographic and clinical characteristics of patients after aSAH.

Parameters		Count (n=204)	n (%)
Sex	F	145	71.1
	M	59	28.9
Age (Mean and SD)		153	75.0
BMI (Mean and SD)		110	60.8
Ethnicity	African American	80	39.2
	Asian	13	6.4
	Hispanic	88	43.1
	Caucasian	23	11.3
ABO type	O type	106	52.0
	Non-O type	98	48.0
Hypertension	No	71	34.8
	Yes	133	65.2
Smoke	Current	58	28.4
	Former	34	16.7
	Never	110	53.9
HH Score	I-III	78	38.2
	III-IV	19	9.3
mFG	0–2	21	10.4
	3–4	23	11.4
Treatment modality	Clipped	69	33.8
	Coiled	135	66.2
EVD placement	No	103	50.5
	Yes	101	49.5
Aneurysm Location	Anterior circulation	192	94.1
	Posterior circulation	12	5.9
Aneurysm Size	<7 mm	134	68.0
	≥7 mm	63	32.0

DISCUSSION

Our study explored the role of ABO blood type in DCI onset and clinical functional outcomes. The significant finding of

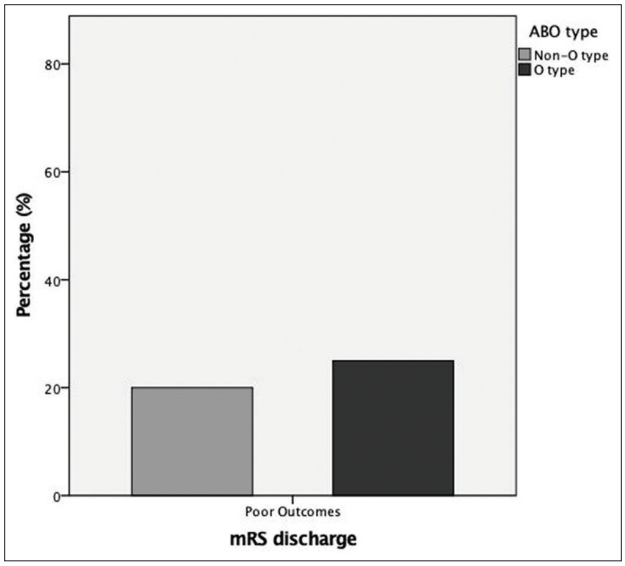

Figure 1: Frequency of discharges with an mRS >2 (poor outcomes) between "O" type and non-O type patients.

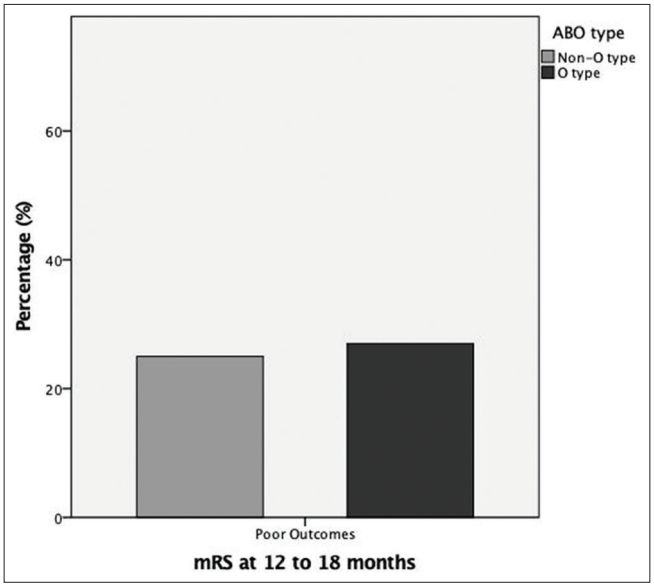

Figure 2: Frequency of "O" type and non-O type patients with an mRS >2 (poor outcomes) at 12–18 months of follow-up.

Table 2: Distribution of demographic and clinical variables between ABO type groups.

Parameters		ABO type				*P* value
		"O" type		"Non-O" type		
		Count (*n*=106)	*n* (%)	Count (*n*=98)	*n* (%)	
Sex	F	73	68.9	72	73.5	0.469
	M	33	31.1	26	26.5	
Age (Mean and SD)	54.19	14.31	56.41	14.95	0.257	
BMI (Mean and SD)	29.83	6.79	27.97	6.55	0.190	
Ethnicity	African American	38	35.8	42	42.9	0.189
	Asian	4	3.8	9	9.2	
	Hispanic	52	49.1	36	36.7	
	Caucasian	12	11.3	11	11.2	
Hypertension		69	65.1	64	65.3	0.975
Smoke	Current	34	32.1	24	24.5	0.589
	Former	15	14.2	19	19.4	
	Never	56	52.8	54	55.1	
HH Score	I–III	85	80.2	84	85.7	0.296
	IV–V	21	19.8	14	14.3	
mFG	0–2	24	22.9	20	20.6	0.700
	3–4	81	77.1	77	79.4	
Treatment modality	Clipped	44	41.5	25	25.5	0.016
	Coiled	62	58.5	73	74.5	
EVD placement	No	52	49.1	51	52.0	0.670
	Yes	54	50.9	47	48.0	
Aneurysm Location	Anterior circulation	99	93.4	93	94.9	0.649
	Posterior circulation	7	6.6	5	5.1	
Aneurysm size	<7 mm	72	69.9	62	66.0	0.553
	≥7 mm	31	30.1	32	34.0	
DCI		19	17.9	8	8.2	0.040

Table 3: Impact of ABO type on DCI onset.

Logistic regression	Model 1 (Unadjusted)	Model 2 (Model 1+Adjusted for treatment modality)
DCI	OR (95% CI)	
"Non-O" type group	Referent	
"O" type group	2.457 (1.022–5.906) *P*=0.045	2.530 (1.040–6.151) *P*=0.041

this study is the association between "O" blood type and DCI onset. Unlike other studies that have not found any ABO blood type to be related to DCI,[4,5] we found that being "O" type increases 2.5 times the risk of DCI after aSAH compared to "non-O" type patients. Several factors can explain the differences with the previous reports. First, the baseline of our study showed no differences in clinical or demographic variables between groups. Only, treatment modality was significantly different, showing "O" type patients were more likely to undergo microsurgical clipping while "non-O" type patients were more likely to undergo endovascular coiling. However, "O" type was an independent risk factor for DCI when adjusted for treatment modality in the logistic regression analysis, it is worth to mention that in our sample the onset of DCI was not influenced by treatment modality (clipping [17.9%] vs. coiling [17.8%], $P = 0.981$) (Data not shown). Second, our cohort was constituted mostly by Hispanics and African Americans and, the only study that has reported no differences in DCI onset between "O" type and "non-O" type patients was done in a German cohort which might lead to ethnicity/race and cultural-related differences. Moreover, some authors have proposed that races with specific ABO blood types might have different rates of intracranial aneurysm and intraventricular hemorrhage.[1,19]

The increased prevalence of DCI in "O" type patients can be supported in recent evidence that showed lower levels of vWF and VIII factor in plasma lead to excessive bleeding in the subarachnoid space. Although some studies have shown that peripheral vasospasm is related to increase levels of VIII factor,[6,23,24] this evidence may not be necessary transposable

to cerebrovascular conditions after aSAH. Furthermore, the amount of bleeding and presumably, a faster clot liquidation[3] in "O" type patients can propitiate an environment within the subarachnoid space in which abnormal high levels of hemoglobin and oxidized heme products can intercept with high affinity free NO[14] and synthetize endogenous eNOS[22] inhibitors, leading to dysregulation of vascular tone and therefore, DCI onset.

We showed that there was no difference between "O" type and "non-O" type groups in the mFG at admission, similar to recent reports,[4,5] thus, the transcendental variable contributing to DCI onset may not be the amount of intracranial bleeding at admission but instead a dynamic process of the amount of bleeding, the time to coagulation, the time to clot liquidation, re-bleedings, and the interactions between products from the bleeding and protective vascular mechanisms.

The blood type is currently not assessed in the clinical setting to predict any kind of outcomes in SAH patients; however, our work provides evidence that the major complication after SAH, DCI is influenced by the blood type; therefore, patients with "O" blood type may need closer monitoring of vasospasm. Further studies that propose mechanisms by which cerebrovascular tone might be influenced by blood type in SAH conditions are needed to validate these results.

Although, short- and long-term clinical outcomes were not statistically significant between ABO blood types, the "O" type group had higher rates of poor clinical outcomes. These results could be explained by the fact that clinical outcomes are influenced by clinical, socio-economic, demographic, and many other factors, therefore, are expected that the contribution of the ABO blood type is not enough to produce a significant change in the patient's functional recovery after aSAH.

Limitations

The findings of this study have to be seen in light of some limitations inherent in a single-center retrospective design. Therefore, our study is subject to biases and confounding that may have influenced our study estimates. The sample size was a constraint for the assessment of patients to meet the inclusion and exclusion criteria in this study. The high representation of hispanics and African Americans makes another limitation to translate these findings to the general population. Finally, the relatively small amount of literature makes it difficult to compare the results, we present in this study; therefore, these results should be interpreted with caution for extrapolate or compare with other studies.

CONCLUSIONS

Our study evidenced that patients with "O" blood type have higher risk of DCI onset after aSAH. Although these findings need to be confirmed, they may aid to improve DCI prevention and outcome predictions.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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