J Neurosurg 135:1203-1207, 2021

Postoperative recurrence of chronic subdural hematoma is more frequent in patients with blood type A

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OBJECTIVE Because of an aging society, the incidence of chronic subdural hematoma (CSDH) is increasing. This lesion is treated with simple burr hole irrigation, but one of the major issues is that CSDH frequently recurs. ABO blood type may be associated with a bleeding tendency and inflammation. However, its association with the recurrence of CSDH remains unknown. Therefore, the authors of the present study aimed to retrospectively investigate the association between ABO blood type and CSDH recurrence.

METHODS The authors retrospectively analyzed symptomatic CSDHs in 425 cerebral hemispheres of 376 patients who had undergone surgical treatment with irrigation of the hematoma via burr holes at their institution from January 2011 to September 2019. Among these were 366 CSDHs in 320 patients whose ABO blood type had been determined and who were included in this study.

RESULTS In the study, 307 patients with CSDHs in 350 hemispheres were followed up postoperatively until the disappearance of the CDSH or for at least 3 months. Recurrence of CSDH was observed in 37 patients (10.6%) after surgical treatment. Blood type A was found to be significantly associated with CSDH recurrence compared to non-A blood types: 24 of 153 CDSHs (15.7%) versus 13 of 197 CDSHs (6.6%) (p = 0.008). In the multivariable regression analysis, blood type A, in addition to thrombocytopenia, was a significant independent predictor of the recurrence of CSDH.

CONCLUSIONS The study results showed that blood type A is an independent risk factor for the postoperative recurrence of CSDH and that careful follow-up in these patients may be needed.

https://thejns.org/doi/abs/10.3171/2020.7.JNS202330

KEYWORDS chronic subdural hematoma; postoperative recurrence; ABO blood type; burr hole surgery; trauma

BECAUSE of an aging society, the number of patients with chronic subdural hematoma (CSDH) is increasing. This lesion can be surgically treated with simple burr hole irrigation, and the prognosis is relatively good. However, one of the major issues in CSDH is that the lesion frequently recurs after surgery (10%–22%). Bilateral hematomas, antiplatelet agents, anticoagulant agents, etc., have been considered as risk factors for CSDH recurrence.

Historically, progressive recurrent bleeding after head trauma was considered to be the cause of CSDH. Recently, a complex intertwining pathway of inflammation, angiogenesis, local coagulopathy, recurrent microbleeds, and exudates has been suggested to be associated with CSDH progression.^{2,6} However, the pathogenic mechanism involved in the recurrence of CSDH remains unclear.

The ABO blood type is distinguished by the modification of specific antigens on erythrocytes by the *ABO* gene. These antigens were recently reported to be associated

with hemostatic function or inflammation in diseases such as vascular diseases, acute respiratory distress syndrome, and acute kidney disease. To Consequently, the ABO blood type may influence the recurrence of CSDH through a homeostatic or inflammatory effect. However, the association with CSDH has not been investigated to date and remains unknown. Therefore, the aim of this study was to retrospectively investigate the association of ABO blood type with the recurrence of CSDH after surgery.

Methods

The protocol of this retrospective cohort study was approved by the ethics committee of our institution, and the board waived the requirement for informed consent from the patients. We investigated neurologically symptomatic CSDHs in 425 cerebral hemispheres in 376 patients who had undergone surgical treatment at our institution from January 2011 to September 2019. Recurrent CSDH

ABBREVIATIONS COVID-19 = coronavirus disease 2019; CSDH = chronic subdural hematoma; MMP = matrix metalloproteinase; TNFα = tumor necrosis factor α. SUBMITTED June 22, 2020. ACCEPTED July 27, 2020.

INCLUDE WHEN CITING Published online January 1, 2021; DOI: 10.3171/2020.7.JNS202330.

TABLE 1. Baseline clinical and radiographical characteristics of 320 patients with 366 CSDHs

		Blood Type				
Variable	Total	Α	В	AB	0	p Value
No. of patients	320	140 (43.8)	73 (22.8)	31 (9.7)	76 (23.8)	
Age in yrs	77.3 ± 10.9	76.5 ± 11.3	78.6 ± 9.97	76.3 ± 11.6	76.8 ± 10.7	0.56
Men	228 (71.3)	104 (74.3)	53 (72.6)	23 (74.2)	47 (61.8)	0.47
Hypertension	105 (32.8)	41 (29.3)	32 (43.8)	10 (32.3)	22 (28.9)	0.15
Diabetes mellitus	66 (20.6)	33 (23.6)	15 (20.5)	5 (16.1)	13 (17.1)	0.64
Thrombocytopenia	17 (5.3)	7 (5.0)	3 (4.1)	2 (6.5)	5 (6.6)	0.91
Coagulopathy	39 (12.5)*	18 (13.1)	6 (8.5)	2 (6.7)	13 (17.6)	0.29
Antiplatelet drugs	44 (13.8)	17 (12.1)	15 (20.5)	4 (12.9)	8 (10.5)	0.28
SAPT	37 (11.6)	12 (8.6)	14 (19.2)	3 (9.7)	8 (10.5)	
DAPT	7 (2.2)	5 (3.6)	1 (1.4)	1 (3.2)	0	
Anticoagulant drugs	50 (15.6)	28 (20.0)	4 (5.5)	3 (9.7)	15 (19.7)	0.02
Bilat surgery	46 (14.4)	18 (12.9)	10 (13.7)	9 (29.0)	9 (11.8)	0.11
Hematoma vol in ml (n = 366)	127.0 ± 43.5	131.7 ± 44.8	128.6 ± 40.8	119.2 ± 43.1	120.4 ± 43.1	0.16

DAPT = dual antiplatelet therapy; SAPT = single antiplatelet therapy.

Data are presented as the mean ± standard deviation or number (%), unless indicated otherwise. Boldface type indicates statistical significance.

was analyzed in the study. The initial diagnosis of CSDH was made using CT and/or MRI. In 56 patients with 59 CSDHs, ABO blood typing as A, B, AB, and O was not performed. The remaining 320 patients with 366 CSDHs and whose ABO blood type was determined were included in the study.

All patients underwent surgery comprising simple burr hole irrigation. After evacuation of the CSDH, its irrigation was performed with normal saline or artificial cerebrospinal fluid (Artcereb irrigation and perfusion solution for cerebrospinal surgery, Otsuka Pharmaceutical Factory Inc.).³ A closed drainage system was placed in the hematoma cavity and usually kept in place for one-half to 2 days after the surgery. In 3 patients, a drain tube could not be placed because of narrowing of the hematoma cavity after evacuating the CSDH.

The patients were followed up postoperatively until the disappearance of the CDSH or for at least 3 months. In bilateral CSDHs, recurrence was recorded separately for each side. Recurrence of CSDH was defined as a symptomatic ipsilateral enlargement of a CSDH at postoperative day 7 or later, which indicated repeat surgery. The symptoms included intolerable headache or neurological deficits such as dementia, impaired consciousness, gait disturbance, or weakness in the extremities. Postoperative early subdural hemorrhage occurring before postoperative day 6 was considered a surgical complication but not a recurrence.

The patients' baseline clinical characteristics were defined as follows. Based on each patient's condition before the occurrence of CSDH, hypertension was defined as current treatment with antihypertensive drugs, diastolic blood pressure \geq 90 mm Hg, or systolic blood pressure \geq 140 mm Hg. Diabetes mellitus was defined as > 6.5% glycosylated hemoglobin A1C or the use of hypoglycemic medications. A platelet count < 100 \times 10 3 / μ l was considered as thrombocytopenia. A prothrombin time–international normalized ratio (PT-INR) > 1.4 or an activated

partial thromboplastin time (aPTT) \geq 40 seconds was considered as coagulopathy. We also recorded if the patients were treated with oral antiplatelet or anticoagulant drugs. If the patients had received these drugs for more than a week during the postoperative follow-up period, they were recorded as users of antiplatelet or anticoagulant drugs. In addition, single and dual antiplatelet therapies were recorded; no patient had three or more antiplatelet drugs. Preoperative volumes of CSDH were calculated using the XYZ/2 method. ¹⁶ The baseline clinical characteristics of the patients are shown in Table 1.

Categorical variables were expressed as numbers (percentages). Numerical data were expressed as the median (interquartile range) or mean \pm standard deviation. SPSS version 24 (IBM Corp.) software was used for statistical analyses, and p < 0.05 was considered as statistically significant. For intergroup comparisons, Fisher's exact test, the chi-square test, or one-way ANOVA was used. Logistic regression analyses were used to investigate the risk factors for CSDH recurrence. Multivariable logistic regression analyses were performed using variables with a p value < 0.05 in the univariable logistic regression.

Results

Thirteen patients with 16 CSDHs were not followed up. Among 307 patients, there were 350 surgically treated CSDHs that were followed up, and the recurrence of CSDH after surgery was evaluated. Of the 350 surgically treated CSDHs, 37 hemispheres (10.6%) had a recurrence of CSDH from 11 to 67 days (27.3 \pm 13.6 days) after surgery. There were no occurrences of postoperative early subdural hemorrhage. The recurrence rate in patients with blood type A was the highest among all blood types, as shown in Fig. 1. Moreover, blood type A was significantly associated with CSDH recurrence compared with non-A blood types (15.7% vs 6.6%, p = 0.008). The sensitivity

^{*} Assessed in 312 patients given a lack of data in 8 patients.

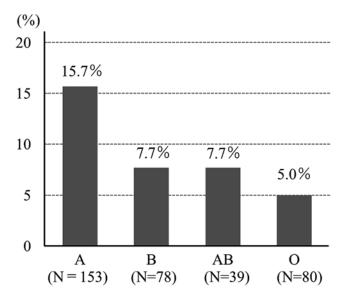


FIG. 1. Recurrence rates of postoperative CSDHs (n = 350) among patients with each of the ABO blood types.

and specificity of blood type A for the prediction of CSDH recurrence were 64.9% and 58.8%, respectively.

In the univariable logistic regression analyses, throm-bocytopenia (OR 3.92, 95% CI 1.30–11.83, p=0.02), coagulopathy (OR 3.17, 95% CI 1.36–7.39, p=0.007), use of oral anticoagulants (OR 2.59, 95% CI 1.19–5.61, p=0.02), and blood type A (OR 2.63, 95% CI 1.29–5.36, p=0.008) were found to be significant risk factors for CSDH recurrence (Table 2).

Subsequently, multivariable logistic regression analysis of the variables with statistical significance in the univariable analyses was performed (Table 3). Blood type A was a significant independent predictor of the recurrence of CSDH in the multivariable model (OR 2.83, 95% CI 1.33-6.02, p=0.007). In addition, thrombocytopenia was a significant independent predictor of CSDH recurrence (OR 5.00, 95% CI 1.53-16.30, p=0.008).

Discussion

This is the first study to investigate the association between the postoperative recurrence of CSDH and blood type. Our study results showed that blood type A, in addition to thrombocytopenia, was an independent risk factor for the postoperative recurrence of CSDH.

CSDH is a collection of blood and fluid in the subdural space encapsulated by a characteristic membrane. ¹⁷ It has been reported that repeated microhemorrhages occur from the neocapillary network in the outer membrane. ¹⁷ After a traumatic head injury, the dural border cell layer tears, leading to leakage of cerebrospinal fluid and extravasation of blood into the subdural space. An increase in the inflammatory cells and cytokines in the fluid component and encapsulating membrane of the CSDH, such as tumor necrosis factor α (TNF α), monocyte chemotactic protein-1, IL-6, matrix metalloproteinases (MMPs), and vascular endothelial growth factor, has also been

TABLE 2. Univariable logistic regression analysis of predictors of CSDH recurrence in the 350 hemispheres

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	Crude Model			
Factor	OR	95% CI	p Value	
Age (per 10-yr increase)	1.00	0.71-1.42	0.99	
Men	2.15	0.87-5.33	0.10	
Hypertension	0.85	0.40-1.79	0.67	
Diabetes mellitus	1.94	0.93-4.08	0.08	
Thrombocytopenia	3.92	1.30-11.83	0.02	
Coagulopathy	3.17	1.36-7.39	0.007	
Antiplatelet drugs				
None	Reference			
Single	1.08	0.36-3.24	0.90	
Double	3.55	0.66-19.07	0.14	
Anticoagulant drugs	2.59	1.19-5.61	0.02	
Hematoma vol (10 ml per increase)	1.05	0.97–1.13	0.23	
Surgery for contralat CSDH	1.16	0.54-2.50	0.71	
Blood type				
A	2.63	1.29-5.36	0.008	
В	0.65	0.26-1.61	0.35	
AB	0.68	0.20-2.32	0.54	
0	0.38	0.13-1.10	0.08	

Boldface type indicates statistical significance.

reported.^{2,6,18} Inflammation and angiogenesis, as well as impaired coagulation and activation of fibrinolysis, are considered to play a pivotal role and may cause a disruption of the developed neocapillary network in the CSDH membrane, resulting in repeated microhemorrhages.⁶ An increase in tissue plasminogen activator in the endothelial cells of sinusoids and capillaries in the membrane and cavity of a CSDH is considered to be associated with repeated bleeding via its fibrinolytic effect.¹⁹ In addition, it has the potential to activate MMPs in the endothelial cells and may also lead to disruption of sinusoids and capillaries in the membrane.²⁰ Therefore, inhibition of the inflammation in the membrane and cavity of a CSDH may be important to suppress the progression and recurrence of CSDH. Curative treatment of CSDH via only irrigation or drainage of the hematoma cavity may be partly attributed to the washing out of inflammatory cytokines, growth factors, and proteases from the cavity.21

ABO glycosyltransferases catalyze the antigen modifications that determine the ABO blood types, and this has been recently reported to be associated with vascular, acute inflammatory, and hemorrhagic diseases. ^{10,22} Blood type A is considered to be associated with various inflammatory conditions, and an associated increased risk of myocardial infarction and cardiovascular disease, acute respiratory distress syndrome, and acute kidney injury has been reported. ^{7,8,10,11,13–15,22} In acute subdural hematoma, blood type A was reported to be associated with an increased midline shift and postoperative seizures. ²³ Although the mechanism is unknown, blood type A—associated inflammation may facilitate cerebral swelling.

TABLE 3. Multivariable logistic regression analysis of predictors of CSDH recurrence

Factor	OR	95% CI	p Value
Thrombocytopenia	5.00	1.53-16.30	0.008
Coagulopathy	1.95	0.58-6.49	0.28
Anticoagulant drugs	1.84	0.59-5.76	0.30
Blood type A	2.83	1.33-6.02	0.007

Boldface type indicates statistical significance.

The *ABO* gene locus has been suggested to have an influence on the circulating levels of TNFα, soluble intercellular adhesion molecule-1, soluble E-selectin, and soluble P-selectin, but the exact mechanism remains unclear.^{24–26} In the recurrence of CSDH, ABO blood type–associated inflammation may play an important role.

Blood type O has been reported to be a risk factor for hematoma expansion after intracranial hemorrhage and negatively associated with venous thrombosis. 12,27,28 This was considered to be attributed to the fact that blood type O is associated with low levels of von Willebrand factor/ factor VIII.¹² However, blood type O was not significantly associated with CSDH recurrence in our study. Therefore, a blood type O-associated bleeding tendency may not be involved in CSDH recurrence. On the contrary, CSDH tended to recur less frequently in patients with blood type O, but the difference was not statistically significant. Blood type O may be negatively associated with activation of the inflammatory response. The results of our study are consistent with those of a previous study in which blood type O was associated with a decrease of midline shift in acute subdural hematoma.²³ Blood type AB has been reported to be associated with an increased risk of stroke⁹ but was not associated with CSDH recurrence in our study.

As shown in Table 1, the ABO blood type distribution of patients with CSDH in the present study was consistent with the common blood type distribution in Japan.²⁹ Therefore, we can postulate that ABO blood type is not involved in the initial formation/progression of CSDH after trauma but is associated with recurrence after surgery. The mechanisms of the initial formation/development of CSDH involve blood products and various cytokines in the hematoma itself, and these may be different from mechanisms underlying a postoperative recurrence since the blood products and various cytokines are removed after surgery. There are differences in blood types between countries and races. For example, the proportions are as follows in the United States: White (A: 40%, B: 11%, AB: 4%, O: 45%), Black (A: 26%, B: 19%, AB: 4.3%, O: 51%), Asian American (A: 27.5%, B: 25.4%, AB: 7.1%, O: 40%), Latin American (A: 31%, B: 10%, AB: 2%, O: 57%).³⁰ In Germany, it is A, 43%; B, 11%; AB, 5%; and O, 41%.²³ A study in other countries and races to compare the incidence or recurrence of CSDH is a project for further research.

Bleeding tendency due to anticoagulant medication, thrombocytopenia, and coagulopathy are important risk factors for CSDH recurrence after surgery. However, in a recent meta-analysis, antiplatelet medication was not associated with an increased risk of rebleeding. In the

present study, coagulopathy and anticoagulant drugs were significant risk factors for CSDH recurrence but not independent factors. However, this result may be attributable to a lack of statistical power.

To prevent CSDH recurrence in patients with blood type A, a new adjuvant medical treatment may be required. Tranexamic acid as an antiplasmin drug was reported to have the potential to inhibit the recurrence of postoperative CSDH.³³ This might be attributed to the suppression of fibrinolysis. However, it also has the potential to inhibit inflammation by blocking the kinin-kallikrein systems. Dexamethasone, a steroid agent, is also reported to be effective in inhibiting the progression of CSDH as a conservative treatment.³⁴ Further studies are needed to investigate whether these adjuvant medical therapies can suppress the postoperative recurrence of CSDH in patients with blood type A.

We are all suffering from the coronavirus disease 2019 (COVID-19) pandemic. To date, blood group A is reported to be associated with symptomatic infection of COVID-19; the symptoms include fever, general fatigue, and respiratory disturbance.^{35–37} On the contrary, in patients with blood type O, the symptomatic infection was less frequent. It is unclear whether patients with blood type A are more prone to infection by COVID-19 or of developing more severe disease than patients of other blood types. Thus, a different inflammatory response among blood types may be involved in the COVID-19 infection rate or its severity.

The present study has some limitations. First, it was a single-center study. Furthermore, the number of patients was somewhat limited, and all patients were Asian. Second, the ABO blood type was not determined in all patients, and some patients were not followed up for an adequate period. Although the majority of patients who had undergone surgery were included in this study, there may be a potential for selection bias. Third, the mechanism underlying the association of blood type A with the recurrence of CSDH could not be determined. Therefore, a larger prospective multicenter study is needed to confirm our findings and to elucidate the effect of ABO blood type on the recurrence of CSDH.

Conclusions

Our study demonstrated that the postoperative recurrence of CSDH occurs more frequently in patients with blood type A than in those with a non-A blood type. Therefore, patients with blood type A should be carefully followed up. Moreover, a new treatment strategy may be needed for them.

Acknowledgments

This study was partly supported by a research grant from Kawasaki Medical School.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Yagi, Hirai. Acquisition of data: Yagi. Analysis and interpretation of data: Yagi, Hirai. Drafting the article: Yagi, Hirai. Critically revising the article: Hara, Kanda, Matsubara. Reviewed submitted version of manuscript: Kanda, Uno. Statistical analysis: Hirai. Study supervision: Uno.

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