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ABO Blood Type and Risk of Peyronie's Disease in Japanese Males

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Purpose: Although multiple mechanisms associated with Peyronie's disease (PD) have been proposed, details regarding etiologic factors, especially genetic, remain unclear. We examined the relationship of the ABO blood type system, known as a genetic factor associated with susceptibility to a number of diseases, with PD in Japanese males.

Materials and Methods: We compared 202 Japanese PD patients treated with surgery at our hospital between March 2004 and December 2019 with 846 randomly selected non-PD male patients who underwent urological surgery during the same period regarding distribution of ABO blood types. In addition, we assessed the risk of PD according to blood type group among all study participants using odds ratio (OR) and 95% confidence interval (CI) calculations.

Results: The distribution of individual blood types in the control group was nearly the same as that in the general Japanese population. In contrast, O, A, B, and AB blood types were noted in 37.6%, 36.1%, 14.9% and 11.4%, respectively, of the PD patients, which was significantly different from the control group, where blood type O was found in 29.1% and B in 23.2% ($p<0.05$). Our results showed that as compared with patients with blood group B, those with another blood type were more likely to develop PD, among which type O had a significantly increased OR of 2.018 (CI, 1.271–3.205).

Conclusions: These are the first reported results showing that ABO blood type may be associated with risk of PD, though further investigations are needed.

Keywords: ABO blood-group system; Genetic predisposition; Peyronie's disease; Risk factors

INTRODUCTION

Peyronie's disease (PD) is a connective tissue disorder characterized by formation of a fibrotic lesion or plaque in the tunica albuginea, which leads to penile deformity, including curvature, shortening, and narrowing. Several epidemiological studies have demonstrated that the incidence of PD is related to several risk factors, such as hypertension, diabetes mellitus (DM), smoking, hyperlipidemia, obesity, and penile trauma [1-3]. In addition, several putative molecular mechanisms and candidate genetic factors associated with PD have been proposed over the last three decades [4,5]. For example, some researchers have shown that genetic predisposition may be an underlying factor associated with incidence of PD, as shown by human leukocyte antigens (HLA) associations revealed in pedigree analyses [6-8]. However, to date, specific genetic factors predisposing individuals to PD development remain unknown. Elucidation of specific genetic

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factors associated with PD is important to facilitate development of novel biomarkers and therapies to enable earlier detection as well as treatment of PD occurrence.

The ABO blood type system, first described in 1900 by Landsteiner [9], has been speculated to be an important genetic factor associated with various types of disease, such as cancer, cardiovascular disorders, infections, and DM [10-13]. It is well known that this blood type system consists of four basic groups, namely A, B, AB, and O, based on the presence of A and B antigens controlled by the three allelic A, B, and O genes located on chromosome 9q34. Although mechanisms underlying the relationship between blood type and the above-mentioned diseases remain to be fully investigated, it is possible that differences in antigenic structures of individual blood types or the amount of serum cytokines involved in systematic inflammation may correlated with their development [10-13]. ABO antigens are expressed on the surface of blood cells as well as numerous other tissues, including normal skin of the penis [14]. In addition, an inflammatory reaction induced by various cytokines in the tunica albuginea is an important point related to onset and progression of PD [4,5]. These background issues led us to speculate that the ABO blood type system may be involved in incidence of PD. In this study, we retrospectively collected and analyzed patient records from our hospital to investigate a possible association.

MATERIALS AND METHODS

1. Data collection

We retrospectively reviewed 204 Japanese patients with PD treated with surgery between March 2004 and December 2019 at our institution. Characteristics examined included age, body mass index (BMI), serum C-reacted protein (CRP), total cholesterol, cigarette smoking status at diagnosis, surgical technique, presence of comorbidities, degree of penile deformity, and ABO blood type. Two patients with missing data regarding blood type were excluded, thus 202 patients were finally enrolled. The control subjects were randomly selected from more than 4,000 non-PD male patients who underwent surgery conducted by our department of urology during the same period after excluding those with a history of cancer, DM, active inflammation, and heart disease, using the Microsoft Excel software package. Of the 850 selected, four had unknown blood type and were also excluded, thus 846 of those cases were assigned to the control group. Surgical procedures performed in the control group included testicular sperm extraction, vas deferens anastomosis, testicular biopsy, hydrocele testis radical surgery, circumcision for phimosis, urethroplasty for hypospadias, varicocele ligation, and plication for congenital penile curvature. The presence or absence of PD in the control group was determined based on medical records, including patient interview and intraoperative penile findings. Patients in both the PD and control groups were referred to our hospital from areas throughout Japan for therapeutic purposes.

2. Diagnosis, penile deformity assessment, surgical indication

PD was diagnosed based on patient history and physical examination findings, including patient-provided photo images of the penis at best possible erection and/or following intracavernous injection of a vasoactive agent. As indications for surgery, we considered disease stabilization, that is, onset at least 6 to 12 months earlier, no worsening of the curvature within at least the previous 3 months, and no pain with erections, based on a previous study [15]. One hundred seventy-seven of the 202 patients (87.6%) were treated with non-surgical management including oral and intralesional therapy with steroid medication prior to surgery. As for the surgical technique, excision and a saphenous vein or dermal graft was applied for cases with a complex curve >60 degrees, hourglass or hinge effect, or large defect due to calcification, while a plication method was selected for the other cases. The degree of penile curvature was defined based on objective assessment by the attending surgeon during surgery.

3. Statistical analysis

Values are expressed as the mean (range) or number (percent of total). Differences in distribution of ABO type between the patient and control groups were assessed using a chi-squared test. Subsequently, a post hoc test using residual analysis was performed to confirm any significant difference between groups. Odds ratio (OR) and 95% confidence interval (CI) for the risk of PD according to ABO blood group among all study participants were estimated using a logistic regression model. For identifying factors associated with PD, univariate analyses of blood type and known PD risk factors were performed, with those showing statistical

significance included in multivariate analysis (logistic regression). Differences in patient characteristics among blood types were analyzed using ANOVA or a chi-squared test. p-values less than 0.05 were considered to indicate statistical significance. All data were analyzed using StatView 5 statistical software (SAS Institute, Inc., Cary, NC, USA).

4. Ethics statement

This study was performed in accordance with the Declaration of Helsinki and approved by the ethics committee of Toho University Omori Medical Center (approval no. M20171). The need for written informed consent was waived because of the retrospective design by the research ethics committee of Omori Hospital, Faculty of Medicine, Toho University.

RESULTS

1. Characteristics of Peyronie's disease patients

The clinical characteristics of the 202 PD patients are shown in Table 1. Mean age, BMI, serum CRP, and total cholesterol were 58.0±11.0 years, 23.9±2.8 kg/m², 0.1±0.2 mg/dL, and 202.0±37.0 mg/dL, respectively. The proportions of those patients with O, A, B, and AB blood type were 37.6% (76/202), 36.1% (73/202), 14.9% (30/202), and 11.4% (23/202), respectively. Of the 202 patients, 141 (69.8%) had a history of smoking, including cessation cases. As for comorbidities, 45 (22.3%) had hypertension, 32 (15.8%) diabetes, 4 (2.0%) Dupuytren's disease, and 13 (6.4%) history of penile trauma. Mean penile curvature was 59°±20°, while the direction of penile curve was dorsal in 79 (39.1%), ventral in 41 (20.3%), lateral in 34 (16.8%), and bi-planar in 48 (23.8%) of these cases. One hundred three patients (51.0%) had undergone plication and 99 (49.0%) a grafting method using an autologous vein or dermis.

2. Blood type distribution in patient and control groups

The distribution of ABO blood types is displayed as pie charts in Fig. 1. That in Fig. 1A shows the distribu-

Table 1. Characteristics of Peyronie's disease patients (n=202)

Characteristic	Value
No. of cases	202
Age (y)	58.0±11.0
BMI (kg/m²)	23.9±2.8
CRP (mg/dL)	0.1±0.2
Total cholesterol (mg/dL)	202.0±37.0
Blood type	
O	76 (37.6)
A	73 (36.1)
B	30 (14.9)
AB	23 (11.4)
Smoking habit	141 (69.8)
Comorbidity	
Hypertension	45 (22.3)
Diabetes mellitus	32 (15.8)
Dupuytren's disease	4 (2.0)
History of penile trauma	13 (6.4)
Curvature (degree)	59±20
Direction	
Dorsal	79 (39.1)
Ventral	41 (20.3)
Lateral	34 (16.8)
Bi-planar curvature	48 (23.8)
Surgical technique	
Plication	103 (51.0)
Grafting	99 (49.0)

Values are presented as mean±standard deviation or number (%).
BMI: body mass index, CRP: C-reactive protein.

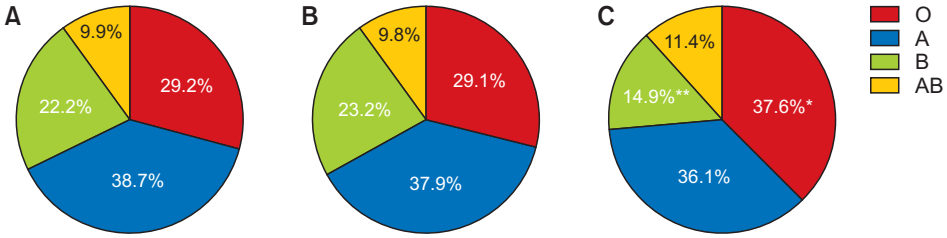

Fig. 1. Blood type distribution in different groups. (A) General population in Japan. In the Japanese general population, O, A, B, and AB blood types are found in 29.2%, 38.7%, 22.2%, and 9.9%, respectively. (B) Control group. In the control group, type A had the highest proportion at 37.9%, followed by type O at 29.1%, type B at 23.2%, and type AB at 9.8%. (C) Peyronie's disease (PD) group. In the PD patient group, type O had the highest proportion at 37.6%, significantly higher than that of the control group, while the proportion of B type was 14.9%, significantly lower than that of the control group (23.2%). *p<0.05, **p<0.01 are considered statistically significant.

tion in the general Japanese population, with O, A, B, and AB accounting for 29.2%, 38.7%, 22.2%, 9.9%, respectively [16], thus A is most common followed in order by O, B, and AB in Japan, as compared to O followed by A, B, and AB worldwide. In the present control group, type A had the highest proportion at 37.9%, followed by type O at 29.1%, type B at 23.2 %, and type AB at 9.8%, which were quite in line with that of the general Japanese population (Fig. 1B). On the other hand, the PD patients most often had O type at a rate of 37.6% (Fig. 1C), which was significantly higher than that of the control group (p=0.018). In addition, the proportion of B type in the PD cases was 14.9%, significantly lower as compared to the control group at 23.2% (p=0.009). The proportions for type A and AB in the patient group were not different from those of the general Japanese population or control group.

3. Odds ratio and 95% confidence interval for risk of Peyronie's disease associated with blood type

We assessed the risk of PD according to blood type among all study participants. The OR and 95% CI values for PD occurrence based on blood group are shown in Table 2, with blood type B was used as the reference. When compared with individuals with type B, those with type O were at greater risk of PD with an OR of 2.018 (95% CI, 1.271–3.205; p=0.003). Likewise, as compared with type B, those with blood type A or AB were more likely to develop PD, though the differences did not reach statistical significance (OR, 1.486; 95% CI, 0.937–2.325; p=0.092; OR, 1.810; 95% CI, 0.993–3.302; p=0.053, respectively).

Table 2. Odds ratio (OR) and 95% confidence interval (CI) for patients with Peyronie's disease after division by ABO blood group

Blood group	OR	95% CI	p-value
B (reference)	1.000	-	-
A	1.486	0.937–2.355	0.092
AB	1.810	0.993–3.302	0.053
O	2.018	1.271–3.205	0.003

4. Uni- and multivariate logistic regression analysis findings for identifying factors associated with Peyronie's disease

To further clarify the relationship between blood type and PD, logistic regression analysis was performed using blood type (B *vs.* other types) and known risk factors for PD, including age, obesity (BMI), penile trauma, and smoking habit. DM was not used as a factor in this analysis because affected patients were excluded from the control group. Since the control group of 846 patients also included children, after excluding those under the age of 20 years, 735 with a mean age of 34.5 years were included in this analysis (blood type distribution was the same as in the full control group). As demonstrated in Table 3, univariate analysis showed that all five factors were statistically significant, including blood type. Subsequently, multivariate analysis using these factors revealed that blood type (p=0.043) as well as age, penile trauma, and hypertension were significant factors associated with PD.

Finally, the clinical characteristics of PD patients after dividing by blood type were compared. As shown in Table 4, there was a tendency for differences between patients with Dupuytren's disease (p=0.080) and those who had undergone a surgical procedure (p=0.062), though no significant differences were found among the patient background factors examined. Regarding disease severity, the mean amount of penile curvature was 57° for type O, 61° for type A, 65° for type B, and 55° for type AB, with no significant difference related

Table 3. Uni- and multivariate analysis for identifying factors associated with Peyronie's disease

Variable		Univariate analysis		Multivariate analysis	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Age (y)	(continuous)	1.202 (1.174–1.232)	<0.001	1.224 (1.189–1.260)	<0.001
BMI (kg/m^2)	(continuous)	1.082 (1.033–1.133)	0.001	0.957 (0.880–1.041)	0.308
Blood type	(B *vs.* A, O, AB)	0.566 (0.370–0.864)	0.008	0.505 (0.260–0.980)	0.043
Penile trauma	(present *vs.* absent)	3.537 (1.635–7.654)	0.001	7.086 (1.827–27.481)	0.005
Hypertension	(present *vs.* absent)	3.609 (2.343–5.560)	<0.001	0.365 (0.184–0.725)	0.004
Smoking habit	(present *vs.* absent)	2.941 (2.106–4.107)	<0.001	1.091 (0.650–1.830)	0.742

OR: odds ratio, CI: confidence interval, BMI: body mass index.

Table 4. Patient profiles after division by ABO blood type

Characteristic	Blood type				p-value
	O (n=76)	A (n=73)	B (n=30)	AB (n=23)	
Age (y)	58.3±11.0	56.3±9.9	59.2±7.1	58.1±14.2	0.536
BMI (kg/m^2)	24.0±3.1	24.0±2.6	23.5±2.8	23.4±2.9	0.648
CRP (mg/dL)	0.1±0.2	0.1±0.2	0.1±0.1	0.0±0.1	0.495
Total cholesterol (mg/dL)	205.3±40.0	204.3±41.3	192.8±23.8	198.0±29.6	0.395
Smoking habit	52 (68.4)	50 (68.5)	24 (80.0)	15 (65.2)	0.607
Comorbidity					
Hypertension	19 (25.0)	13 (17.8)	6 (20.0)	7 (30.4)	0.544
Diabetes mellitus	12 (15.8)	14 (19.2)	2 (6.7)	4 (17.4)	0.467
Dupuytren's disease	4 (5.3)	0 (0)	0 (0)	0 (0)	0.080
History of penile trauma	3 (3.9)	7 (9.6)	1 (3.3)	2 (8.7)	0.607
Curvature (degree)	57±21	61±20	65±21	55±20	0.164
Direction					0.681
Dorsal	28 (36.8)	34 (46.6)	10 (33.3)	7 (30.4)	
Ventral	14 (18.4)	13 (17.8)	8 (26.7)	6 (26.1)	
Lateral	16 (21.1)	12 (16.4)	3 (10.0)	3 (13.1)	
Bi-planar curvature	18 (23.7)	14 (19.2)	9 (30.0)	7 (30.4)	
Surgical technique					0.062
Plication	38 (50.0)	37 (50.7)	11 (36.7)	17 (73.9)	
Grafting	38 (50.0)	36 (49.3)	19 (63.3)	6 (26.1)	

Values are presented as mean±standard deviation or number (%).
BMI: body mass index, CRP: C-reactive protein.

to blood type (p=0.164). Similarly, there was no significant difference related to direction of penile curvature among the blood types (p=0.681).

DISCUSSION

Results obtained in this retrospective study conducted in Japan indicate the possibility that blood type is closely associated with incidence of PD. Interestingly, as compared with blood type B, individuals with other types had a higher rate of incidence, with those with type O showing the highest risk of PD. Multivariate logistic regression analysis findings supported blood type as a factor strongly associated with PD. To the best of our knowledge, this is the first study to reveal a correlation between ABO blood type and development of PD.

Although details regarding the etiology and pathophysiology of PD remain largely unknown, the most widely accepted hypothesis is that PD plaque develops following either acute trauma, repeated external stress, or microtrauma to the penis. [17,18]. Such stimulation to the penis can initiate an inflammatory cascade leading to various reactions, such as fibrin deposition, attraction of macrophages and fibroblasts, stimulation of release of several cytokines including transforming growth factor beta-1 (TGF-β1), myofibroblast formation, extracellular matrix production, contraction, and calcification, ultimately resulting in tunica plaque formation and scarring [4,5]. Of those reactions, it is interesting to note that an elevated level of TGF-β1 is due, at least in part, to genetic factors such as presence of heritable single nucleotide polymorphisms [19,20]. In addition, other reports have shown that PD may also be closely associated with chromosomal abnormalities as well as specific HLA typing [6-8,21]. Together, these findings strongly support a linkage between PD and genetic factors. In the present study, we focused on ABO blood type, a genetically determined characteristic of the immune system, as a potential candidate genetic factor associated with development of PD disease. The results showed that the distributions in the present PD cohort of blood types O (37.6%) and B (14.9%) were significantly different from both the normal distributions reported nationwide in Japan (O: 29.2%, B: 22.2%) and in control cases (O: 29.1%, B: 23.2%) treated for other conditions at our hospital.

It has been widely reported that the ABO blood type

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system has important roles in transplantology and hemotherapy. However, functions except for determining blood phenotype remain unclear, though blood type been shown to be associated with various diseases. For example, blood type O individuals have been shown to have reduced risk of venous and arterial thromboembolic events, and also cardiovascular disease because they have an approximately 25% lower level of von Willebrand factor than non-type O individuals [11]. Furthermore, blood type O has a minimal association with incidence of type 2 diabetes, while blood type B is thought to be highly associated with that disease, with the difference possibly related to contrasting serum levels of cytokines associated with systemic inflammation among the blood types [13]. In the field of infectious disease, a relationship between ABO antigens and HIV infection has been pointed out by results of several investigations [12]. In addition, the relationship between ABO blood type and cancer has often been noted since the initial report by Aird et al in 1953 [22]. For example, type A is associated with increased risk of several types of malignancy, including gastric, breast, lung, and pancreatic cancer [10,23], whereas type O is associated with a reduced risk of pancreatic cancer [24]. Interestingly, it has also been demonstrated that unfavorable survival of patients with breast and lung cancer is associated with type A, while worse recurrence and progression rates of bladder and nasopharyngeal carcinoma are associated with type O [10,25]. Those findings led us to speculate that the ABO blood type may reflect the biological characteristics of certain diseases. Following our finding of a unique ABO blood group distribution in PD patients, we subsequently evaluated the association of blood type with characteristics of PD, such as penile curvature degree and direction, as well as patient background. As for Dupuytren's disease, thought to be genetically related to PD, all four of the present affected patients had blood type O. However, there was no relationship with other factors such as disease severity or blood type found.

The precise mechanism of the influence of blood type on development of PD remains unknown, though there are several possible explanations. As previously noted, microtrauma can lead to an inflammatory reaction in the tunica albuginea, which eventually leads to tunica plaque formation and scarring. Milenkovic et al [5] proposed a mechanism of molecular regulation related to PD. Briefly, tissue damage and mechanical stress initially induce the release of danger- /damage-associated molecular patterns (DAMPs) from extracellular matrix binding of DAMPs to Toll-like receptors, which can activate resident macrophages into an inflammatory phenotype. Subsequently, several proinflammatory cytokines including interleukin (IL)-6 and tumor necrosis factor α (TNF-α) are released, which produce chemotactic and T-cell activating factors. In turn, T-helper cells activate inflammatory macrophages by producing proinflammatory cytokines. Eventually, macrophages can activate fibroblasts to produce chemotactic signals that initiate a myofibroblast phenotype transformation through release of TGF-β1 and TNF-α, causing wound contraction and extracellular matrix production in the tunica albuginea. Interestingly, it has been reported that blood group O individuals had higher serum levels of TNF-α and IL-6 as compared to others [26,27]. Thus, it is likely that type O is associated with a higher incidence of PD, which is in line with the present findings. Another putative mechanism underlying the relationship of blood type with PD is genetic inheritance related to the TGF-β signaling pathway. Generally, TGF-β ligands bind to type I and type II receptors, and produce signal transduction through phosphorylation. PD cells are rich in the TGF-β1 receptor as compared to normal cells [28], which may be a factor in dysregulation of the TGF-β signaling pathway in PD. Of note, TGF-β1 receptor genes are located on chromosome 9q22 near the ABO locus (9q34). Therefore, a relatively high rate of recombination between the TGF-β1 receptor and ABO type genes occurs, increasing the likelihood that these genes will be inherited together with ABO. To verify these speculations, additional basic research investigations regarding PD genetic differences associated with blood type are needed.

This study has some limitations, including its retrospective design, and the relatively low number of PD and control cases. In addition, it is possible that all characteristics of PD patients were not evaluated, since only surgical cases were examined. Furthermore, the background of the control group, especially age, did not match that of the PD group. Also, DM, an important risk factor related to PD, was not evaluated with multivariate analysis. Finally, the results are limited to a Japanese population. Additional studies that enroll other ethnic groups are necessary to validate the present findings, because the frequency and distribution of blood types vary among nationalities and ethnicities.

CONCLUSIONS

We found that Japanese males with blood type O had a high risk of PD, while that of those with type B was low. Additional investigations of different ethnic groups as well as basic research regarding PD genetic differences are needed to confirm this association and identify the underlying mechanisms.

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: YM. Data curation: YM. Formal analysis: HK. Investigation: FY. Methodology: YM. Statistical analysis: HK. Supervision: Koichi Nagao. Validation: Koichi Nakajima. Writing – original draft: YM. Writing – review & editing: HK.

Data Sharing Statement

The data analyzed for this study have been deposited in HARVARD Dataverse and are available at https://doi.org/10.7910/DVN/CV9LXJ.

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