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Original Article

Association between histo-blood group antigens and *Pseudomonas aeruginosa*-associated diarrheal diseases

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Abstract *Background: Pseudomonas aeruginosa* is not a common enteric pathogen. The association between human histo-blood group antigens (HBGAs) and *P. aeruginosa* enteric infection has not yet been studied.
Methods: We collected stool samples from healthy children under 2 years of age for *P. aeruginosa* gut colonization rate. Saliva samples were collected from patients with *P. aeruginosa*-associated diarrheal diseases and normal healthy children. Genomic DNA was extracted from saliva samples for ABO blood group typing and FUT2 genotyping. Lewis phenotype was detected using ELISA assay.
Results: A total of 85 patients with *P. aeruginosa*-associated diarrheal diseases and 105 healthy children were enrolled for collecting saliva specimens. The stool colonization rate was 5/101 (5%) in healthy children, 4/58 (6.9%) in infants, and 1/43 (2.3%) in children 1—2 years old, respectively. Blood group A was more frequent in patients with *P. aeruginosa*-associated diarrheal diseases 24/77 (31.2%) than in healthy children 18/102 (17.6%) ($P = 0.035$). All patients and healthy children were secretor positive. The distribution of weak-secretor genotype Se^{385}/Se^{385} was 23/84 (27.4%) in patients with *P. aeruginosa*-associated diarrheal diseases and 17/104 (16.3%) in healthy children, respectively ($P = 0.06$). Patients with *P. aeruginosa*-associated diarrheal diseases had a higher percentage of Le^{a+b+} phenotype 25/81 (30.9%) than healthy

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children 17/105 (16.2%) (P = 0.018). There was no association between ABO or secretor or Lewis status with the clinical severity of *P. aeruginosa*-associated diarrheal diseases.
Conclusion: Infants had a higher gut *P. aeruginosa* colonization rate than children. Children with blood group A and Le^{a+b+} phenotype are prone to *P. aeruginosa*-associated diarrheal diseases.

Introduction

Pseudomonas aeruginosa is an important opportunistic Gram-negative pathogen among patients with impaired immune systems. Patients undergoing chemotherapy, with urinary catheters, mechanical ventilators and burn wounds are at increased risk of infection. *P. aeruginosa* has been isolated from respiratory, urinary, and gastrointestinal (GI) mucosa. It is a major pathogen of hospital-acquired pneumonia and catheter-related urinary tract infection.[1,2] According to Taiwan Nosocomial Infections Surveillance System (TNIS), *P. aeruginosa* is the most common pathogen to cause surgical site infection and nosocomial pneumonia in critical patients admitted to ICU (TNIS, Taiwan CDC, 2015). In cystic fibrosis patients, it causes chronic respiratory infection. Although *P. aeruginosa* is not a common pathogen in GI tract, life-threatening septic infection in patients at risk such as neutropenia is supposed to originate from GI tract.[3] Community-acquired *P. aeruginosa* sepsis in previously healthy children has been reported from Taiwan, HongKong, China, and Singapore. It is a distinct *P. aeruginosa* enteric disease, Shanghai fever.[4] The clinical feature is fever, and diarrhea initially then rapidly progressing to septic shock. Necrotizing enteritis, ecthyma gangrenosum, and seizure are the main complications.

Diarrheal diseases caused by *P. aeruginosa* could range from self-limiting diarrhea to severe necrotizing enteritis with sepsis. According to our previous clinical study, patients with *P. aeruginosa*-associated diarrheal diseases could be classified into 4 groups: Shanghai fever (necrotizing enteritis with sepsis), *P. aeruginosa* enterocolitis (fever with mucoid or bloody diarrhea mimicking bacterial enterocolitis), *P. aeruginosa*-related diarrhea (watery diarrhea mimicking viral or toxin-mediated enteritis), and antibiotic-associated diarrhea (previous antibiotic treatment).[5] GI colonization is the initial step to cause subsequent infection. Two soluble lectins, PA—IL, and PA-IIL, are molecules produced by *P. aeruginosa* for adherence to epithelial cells.[6] PA-I lectin, galactose-binding lectin, facilitates the adherence of *P. aeruginosa* to the intestinal epithelium and gut-derived sepsis.[7] PA-II lectin is fucose-specific and interacts with Lewis and ABH histo-blood group antigens (HBGAs).[8]

HBGAs are carbohydrates not only expressed on erythrocytes but also in body fluids such as saliva and on the mucosal epithelium of human respiratory, GI, and genitourinary tract. These antigens are encoded by gene families expressing ABO, Lewis antigens, and secretor. The genes of ABH and Lewis blood group antigens, such as ABO, *FUT2*, and *FUT3*, are polymorphic and are speculated about evolutionary changes for host—pathogen interaction. It has been shown that some specific strains of pathogens recognize distinct HBGAs. This study is to investigate the differences of ABO blood group, secretor genotypes, and Lewis phenotypes between *P. aeruginosa*-associated diarrheal diseases and healthy children and to evaluate the association between HBGAs and the disease severity of *P. aeruginosa*-associated diarrheal diseases.

Methods

Study population

Saliva samples were collected from 2 populations, patients with *P. aeruginosa*-associated diarrheal diseases and normal healthy children from April 2018 to June 2020. Patients with *P. aeruginosa*-associated diarrheal diseases were enrolled in our previous study.[5] According to our previous clinical study mentioned earlier, patients with *P. aeruginosa*-associated diarrheal diseases were classified into 4 groups according to their clinical characteristics: group 1, Shanghai fever; group 2, *P. aeruginosa* enterocolitis; group 3, *P. aeruginosa*-related diarrhea; group 4, antibiotic-associated diarrhea. Healthy children (controls) under 2 years of age who visited the well baby clinic without any underlying diseases were enrolled.

P. aeruginosa colonization rate

Stool culture for *P. aeruginosa* was collected from healthy children under 2 years of age. *P. aeruginosa* isolates were identified by Difco™ *P.* Isolation Agar (BD Diagnostic Systems, MD, USA).

Saliva collection

Saliva samples of 1 mL were collected in a sterile 1.5-mL centrifuge tube from patients and healthy controls. Samples were stored at −20 °C for HBGAs phenotyping and genotyping.

ABO blood typing

ABO blood type was determined by PCR with sequence-specific primers as described previously.[9]

Lewis phenotype assay by enzyme-linked immunosorbent assay (ELISA)

Saliva samples were diluted 1:10 and coated on 96-well microtiter plates at room temperature for 2 h. After blocking with 5% nonfat milk for 1 h. Monoclonal antibodies specific to Lewis antigens were added. Monoclonal antibodies anti-Le^a, -Le^b were used at a dilution of 1:100. After incubating at room temperature for 1 h. HRP-conjugated goat anti-mouse IgG antibodies were added. The plates were washed 5 times with PBS after each step. The enzyme signals were detected by the TMB kit (Clinical Science Products, MA, USA) and read at a wavelength of 450 nm using an ELISA reader.

FUT2 genotyping

The genomic DNA was extracted from saliva samples using the QIAamp DNA Investigator Kit (Qiagen, Valencia, CA, USA). The coding regions of the seven *FUT2* genes were amplified by PCR (Fig. 1). The primer set used to amplify 1149-bp *FUT2* PCR product was 5′-CCTCCATCTCCCAGCTAACGTGTCCCGTT (sense primer, nucleotide −79 to −51 relative to the second initiation codon of the Se gene) and 5′-GCTTCTCATGCCCCGGGCACTCATCTTGAG (antisense primer, complementary to nucleotide positions 1042 to 1070 within 3′ untranslated regions). The PCR program consisted of 5 min at 95 °C followed by 30 cycles of 30 s at 95 °C and 1.5 min at 72 °C. The PCR products were sequenced. The DNA sequence was confirmed with the Blood Group Antigen Gene Mutation Database, available at the public website http://www.ncbi.nlm.nih.gov/projects/gv/mhc/xslcgi.cgi?cmd=bgmut/systems.

Statistical analysis

Descriptive data were presented as numbers and percentages. Categorical data were analyzed with the use of $\chi 2$ or Fisher's exact test. Two side $P < 0.05$ is considered significant. All analysis was performed with SPSS statistical software version 21.

Results

A total of 85 patients with *P. aeruginosa*-associated diarrheal diseases, including 17 Shanghai fever, 18 *P. aeruginosa* enterocolitis, 27 *P. aeruginosa*-related diarrhea, and 23 antibiotic-associated diarrhea, and 105 healthy children were enrolled for collecting saliva specimens. All patients with *P. aeruginosa*-associated diarrheal diseases developed illnessess while they were under 5 years of age. The saliva sample was collected at the median age of 12 years and 10 months. The male-to-female ratio was 1:0.6. The age distribution of healthy controls ranged from 1 to 23 months of age with a median age of 10 months old. Themale-to-female ratio was 1: 0.91.

Stool colonization of *P. aeruginosa*

Stools were collected from 101 healthy children. Fifty-eight (57.4%) were infants and 43 (42.6%) were children 1–2 years old. *P. aeruginosa* was isolated in 5 children (5.0%), 4 were infant and 1 was children 1–2 years old. The carriage rate was higher in infants (6.9%) than in children 1–2 years old (2.3%), but there was no significant difference ($P = 0.295$).

Distribution of ABO blood group

ABO blood group was identified in 77 *P. aeruginosa*-associated diarrheal diseases and 102 healthy controls. Blood group A was more often observed in patients with *P. aeruginosa*-associated diarrheal diseases 24/77 (31.2%) than healthy controls 18/102 (17.6%) ($P = 0.035$). There were no significant differences in blood types between patients with Shanghai fever and patients with other *P. aeruginosa*-associated diarrheal diseases. A higher percentage of blood group A was observed in patients with Shanghai fever (35.3%) than in healthy controls (17.6%), but no significant difference was found ($P = 0.093$) (Table 1).

Distribution of secretor genotype

Secretor genotypes were identified in 84 *P. aeruginosa*-associated diarrheal diseases and 104 healthy controls. Five secretor genotypes were identified, including Se/Se^{357}, Se/Se^{385}, Se^{357}/Se^{357}, Se^{357}/Se^{385}, and a weak-secretor genotype Se^{385}/Se^{385}. All patients with *P. aeruginosa*-associated diarrheal diseases and healthy controls were secretor-positive. No secretor-negative was found. There were no significant differences in secretor genotypes between patients with *P. aeruginosa*-associated diarrheal diseases and healthy controls. No significant differences in secretor genotypes between patients with Shanghai fever and patients with other *P. aeruginosa*-associated diarrheal diseases were observed. No significant difference in secretor genotypes

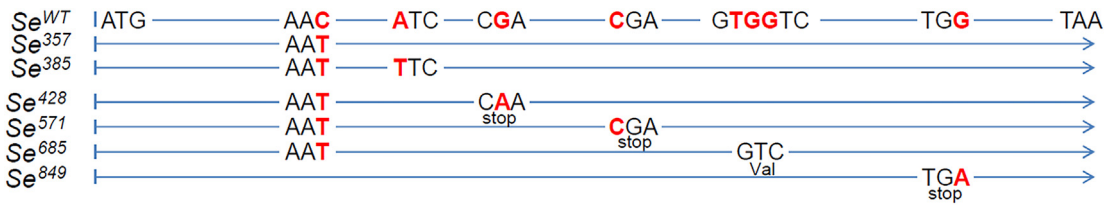

Figure 1. The coding regions of the seven *FUT2* genes.

Table 1 ABO blood group among *Pseudomonas aeruginosa*-associated diarrheal diseases and healthy control.

	Pseudomonas aeruginosa-associated diarrheal diseases[a]								
	All	Shanghai fever	*P. aeruginosa* enterocolitis	*P. aeruginosa*-related diarrhea	Antibiotic-associated diarrhea	Healthy control			
	N = 77 (%)	N = 17 (%)	N = 16 (%)	N = 22 (%)	N = 22 (%)	N = 102 (%)	P_1[b]	P_2[c]	P_3[d]
Type A	24 (31.2)	6 (35.3)	3 (18.8)	7 (31.8)	8 (36.4)	18 (17.6)	0.035*	0.677	0.093
Type B	22 (28.6)	6 (35.3)	5 (31.3)	6 (27.3)	5 (22.7)	30 (29.4)	0.902	0.696	0.625
Type AB	6 (7.8)	0 (0%)	3 (18.8)	2 (9.1)	1 (4.5)	11 (10.8)	0.449	0.456	0.155
Type O	25 (32.5)	5 (29.4)	5 (31.3)	7 (31.8)	8 (36.4)	43 (42.3)	0.186	0.761	0.321

[a] The ABO blood type could not be identified in 2 of *P. aeruginosa* enterocolitis, 5 of *P. aeruginosa*-related diarrhea, 1 of antibiotic-associated diarrhea patients and 2 of healthy control.
[b] Comparison between *Pseudomonas aeruginosa*-associated diarrheal diseases and healthy control (All).
[c] Comparison between Shanghai fever and other *Pseudomonas aeruginosa*-associated diarrheal diseases.
[d] Comparison between Shanghai fever and healthy control.

Table 2 Secretor genotypes among *Pseudomonas aeruginosa*-associated diarrheal diseases and healthy control.

	Pseudomonas aeruginosa-associated diarrheal diseases[a]								
	All	Shanghai fever	*P. aeruginosa* enterocolitis	*P. aeruginosa*-related diarrhea	Antibiotic-associated diarrhea	Healthy control			
	N = 84 (%)	N = 16 (%)	N = 18 (%)	N = 27 (%)	N = 23 (%)	N = 104 (%)	P_1[b]	P_2[c]	P_3[d]
Secretor genotype									
WT/C357T	6 (7.1)	1 (6.25)	1 (5.6)	2 (7.4)	2 (8.7)	15 (14.4)	0.429	0.647	0.371
WT/A385T	14 (16.7)	2 (12.5)	5 (27.8)	3 (11.1)	4 (17.4)	13 (12.5)	0.209	0.982	1.000
C357T/C357T	9 (10.7)	2 (12.5)	3 (16.7)	1 (3.7)	3 (13.0)	16 (15.4)	0.365	0.908	0.764
C357T/A385T	32 (38.1)	9 (56.3)	5 (27.8)	10 (37.0)	8 (34.8)	43 (41.3)	0.579	0.157	0.263
Weak-secretor genotype									
A385T/A385T	23 (27.4)	2 (12.5)	4 (22.2)	11 (40.7)	6 (26.1)	17 (16.3)	0.060	0.291	0.695

[a] The Secretor genotypes could not be identified in 1 of Shanghai fever, 2 of *P. aeruginosa* enterocolitis and 1 of healthy control.
[b] Comparison between *Pseudomonas aeruginosa*-associated diarrheal diseases (All) and healthy control.
[c] Comparison between Shanghai fever and other *Pseudomonas aeruginosa*-associated diarrheal diseases.
[d] Comparison between Shanghai fever and healthy control.

between patients with Shanghai fever and healthy controls were found (Table 2).

Distribution of Lewis phenotype

Lewis phenotypes were identified in 81 *P. aeruginosa*-associated diarrheal diseases and 105 healthy controls. Three Lewis phenotypes, Le^{a+b+}, Le^{a-b+}, Le^{a-b-}, were identified. Le^{a+b+} phenotype was more frequently observed in *P. aeruginosa*-associated diarrheal diseases than in healthy controls ($P = 0.018$). No significant differences in Lewis phenotypes between patients with Shanghai fever and patients with other *P. aeruginosa*-associated diarrheal diseases were observed. No significant difference in Lewis phenotypes was found between patients with Shanghai fever and healthy controls (Table 3).

Discussion

In this study, we found that all patients with *P. aeruginosa*-associated diarrheal diseases and normal healthy children were secretor-positive, including one weak-secretor genotype. Four common nonsecretor alleles *se*[428], *se*[571], *se*[685], and *se*[849] were not detected in this study. This is consistent with previous studies that secretor-negative are rare in Taiwanese.[10,11] Although there is no significant difference between patients with *P. aeruginosa*-associated diarrheal diseases and normal healthy children in the distribution of weak-secretor genotype (P = 0.06). A higher percentage of the weak-secretor genotype was observed in patients with *P. aeruginosa*-associated diarrheal diseases than in healthy children. Previous studies have revealed secretors and partial secretors are susceptible to some norovirus genotypes and rotavirus gastroenteritis.[12,13] However, the severity of cystic fibrosis lung disease due to *P. aeruginosa* infection was not associated with secretor status.[14] We could not find the association between secretor status and the severity of *P. aeruginosa*-associated diarrheal diseases.

PA-II lectin has a strong affinity to fucose, the most potent ligand is the Lewis[a]. We observed that Le^{a+b+} children had significant susceptibility to *P. aeruginosa*-associated diarrheal diseases. It has been disclosed that the Le^{a+b-} phenotype is replaced by the Le^{a+b+} phenotype in several Asian

Table 3 Lewis phenotypes among *Pseudomonas aeruginosa*-associated diarrheal diseases and healthy control.

	Pseudomonas aeruginosa-associated diarrheal diseases[a]								
	All	Shanghai fever	*P. aeruginosa* enterocolitis	*P. aeruginosa*- related diarrhea	Antibiotic-associated diarrhea	Healthy control			
	N = 81 (%)	N = 15 (%)	N = 18 (%)	N = 26 (%)	N = 22 (%)	N = 105 (%)	P_1[b]	P_2[c]	P_3[d]
Le^{a+b+}	25 (30.9)	3 (20)	4 (22.2)	11 (42.3)	7 (31.8)	17 (16.2)	0.018	0.313	0.711
Le^{a-b+}	35 (43.2)	9 (60)	9 (50)	10 (38.5)	7 (31.8)	57 (54.3)	0.134	0.146	0.677
Le^{a-b-}	21 (25.9)	3 (20)	5 (27.8)	5 (19.2)	8 (36.4)	31 (29.5)	0.588	0.562	0.444

[a] The Lewis phenotypes could not be identified in 2 of Shanghai fever, 1 of *P. aeruginosa*-related diarrhea, and 1 of antibiotic-associated diarrhea patients.
[b] Comparison between *Pseudomonas aeruginosa*-associated diarrheal diseases and healthy control (All).
[c] Comparison between Shanghai fever and other *Pseudomonas aeruginosa*-associated diarrheal diseases.
[d] Comparison between Shanghai fever and healthy control.

populations.[12] The Le $^{a+b+}$ phenotype is seldom found in Caucasians. The Le $^{a+b+}$ phenotype has been postulated to be the result of a weak secretor gene.[15] The frequency of Le $^{a+b+}$ phenotype is consistent with that of the weak-secretor genotype in this study. Both Le $^{a+b+}$ phenotype and weak-secretor genotype are associated with *P. aeruginosa*-associated diarrheal diseases. The unique Le $^{a+b+}$ phenotype might be one of the predisposing factors for community-acquired *P. aeruginosa* sepsis in East Asia. The affinity of PA-II lectin is higher to A and B antigens than H antigen.[8] One study showed blood group B was associated with *P. aeruginosa* sepsis in children.[16] The other study implicated patients with blood type A had a genetic predisposition to *P. aeruginosa* otitis externa.[17] Our study revealed blood type A was more susceptible to *P. aeruginosa*-associated diarrheal diseases than other blood type. However, there was no association between the ABO blood group or secretor or Lewis status with the clinical severity of *P. aeruginosa*-associated diarrheal diseases.

The carriage rate of *P. aeruginosa* in stool in healthy children is about 2% and 1% in hospitalized adult patients.[18,19] In diarrheal children, *P. aeruginosa* represents 1% in stool cultures and account for 6% of positive stool cultures.[5] We observed the stool carriage rate in children 1—2 years old was similar to older children. The stool carriage rate was 3 times higher in infants than in children. The higher gut colonization rate of *P. aeruginosa* might be the risk factor for infants predisposing to *P. aeruginosa* enteric infection and sepsis.

There are several limitations of this study. First, the male to female ratio was different between patients with *P. aeruginosa*-associated diarrheal diseases and healthy controls. The male-to-female ratio was 1:0.66 among patients with *P. aeruginosa*-associated diarrheal diseases in our previous report.[5] The male-to-female ratio in this study was similar to our previous report. The male-to-female ratio in healthy controls was 1:0.91. The gender distributions of these two groups were correspondent with their population. We found that there was no association between gender and ABO blood type (P = 0.601), Lewis phenotype (P = 0.624), and secretor genotype (P = 0.178). Second, the percentage of blood group A in healthy controls (17.6%) was lower than that in general population (25%) in Taiwan. This might be due to selection bias. However, the percentage of blood group A in all subgroups, except *P. aeruginosa* enterocolitis, of *P. aeruginosa*-associated diarrheal diseases was more than 30% which was higher than general population in Taiwan. Third, the age distribution was different between patients with *P. aeruginosa*-associated diarrheal diseases and healthy controls. Because *P. aeruginosa*-associated diarrheal diseases are infrequent, we could only retrospectively enroll these patients. Besides, genes of HBGAs are not affected by age.

In conclusion, we found that blood group A and Le $^{a+b+}$ phenotypes are prone to *P. aeruginosa*-associated diarrheal diseases. ABO blood group or secretor or Lewis status are not associated with the clinical severity of *P. aeruginosa* associated diarrheal diseases. Host factors play a role in *P. aeruginosa* enteric infection.

Declaration of competing interest

All authors declare no competing interests.

Acknowledgment

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