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ORIGINAL ARTICLE

The clinical implications of ABO blood groups in *Pseudomonas aeruginosa* sepsis in children

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Background: Pseudomonas aeruginosa (*P. aeruginosa*) sepsis is a fetal disease with rapid progressive shock for infants and children in hospital and in the community, without initial treatment with appropriate antibiotics. Because underlying risk factors remain unclear for affected patients, it is still difficult for early diagnosis and therapy. Recently, ABO blood group antigens were associated with several infectious diseases. However, it was not reported whether the ABO blood group could be the clinical implications for pediatric *Pseudomonas* sepsis.
Methods: This study retrospectively reviewed the medical records of 23 infants and children with *P. aeruginosa* sepsis, who were hospitalized at Kaohsiung Chang Gung Memorial Hospital from 2003 to 2009.
Results: Eight cases had nosocomial infections, with a higher mortality rate (50%) than 15 cases (26.7%) in the community. Thirteen patients (86.7%) with community-acquired sepsis were infants, significantly younger than the nosocomial cases. ABO blood group antigens were known in 21 cases and B phenotype was the most significant. In the community-acquired group, fever and diarrhea were the most prevalent symptoms on initial presentation. Moreover, pneumonitis was the most concomitant disease in fatal cases.
Conclusion: Blood group B was highly associated with pediatric *P. aeruginosa* sepsis. This could be a risk factor, and play an important role for the pathogenesis of *P. aeruginosa* sepsis. Furthermore, if a previously healthy infant with fever and diarrhea suddenly had septic

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presentation, *P. aeruginosa* infection should be considered. In addition, more intensive care could be needed for such blood group B pediatric patients, if pneumonitis was concomitant on admission for the high mortality rate.

Introduction

Pseudomonas aeruginosa (*P. aeruginosa*) sepsis often occurs in patients with malignancies, immunodeficiency, cystic fibrosis or burns.[1] These immunocompromized patients have a high mortality rate. The infections may result from strains acquired in the community or the hospital, but are mostly nosocomially acquired.[2,3] Community-acquired *P. aeruginosa* sepsis has been reported in previously healthy patients, especially infants and in children.[4–6] However, initial antibiotics for community-acquired sepsis in previously healthy infants and children do not include effective anti-pseudomonal agents empirically, although gram negative organisms were considered.[7] Reports about pediatric community-acquired *P. aeruginosa* bacteremia or sepsis in northern and central Taiwan by Huang et al[5] and Wu et al,[4] respectively, indicated that a high mortality rate was noted with an initial inappropriate antimicrobial regimen and septic shock. They also showed that it was not rare in pediatric populations and that its early clinical manifestation was difficult to determine. Therefore, we conducted this retrospective study to unearth more clinical implications of the infectious disease, sampled from pediatric cases in Kaohsiung Chang Gung Memorial Hospital in southern Taiwan. Recently, several experimental and clinical research studies have postulated that blood carbohydrates of blood group substances could interact with microbial surface lectins, which could be associated with pathogenesis in infection.[8–15] In a review article, the relationship between infection diseases and selection for ABO blood group antigens was mentioned and organized by Anstee.[8] We believe that this may play a role in this infectious disease, which has not been previously reported. Thus, ABO blood groups of our cases were also evaluated in this study. We reviewed medical records of children with *P. aeruginosa* sepsis hospitalized at our hospital and report 23 cases during a 7-year period. In this study, we describe the clinical characteristics of these cases and try to delineate the features of such cases.

Materials and methods

Study population and definition

This retrospective cross-sectional study was conducted at the Kaohsiung Chang Gung Memorial Hospital, a medical center with 170 pediatric ward beds and 53 intensive care unit beds providing primary and tertiary care for infants and children in southern Taiwan. The annual ER census in this hospital is approximately 55,000 visits. The database at our clinical microbiology laboratory was reviewed in order to identify patients with *P. aeruginosa* bacteremia from January 1, 2003 to August 31, 2009. Community-acquired bacteremia was defined as a positive blood culture taken on or within 48 hours of admission. Only the first bacteremic episode for each patient was included in the analysis.Patients with polymicrobial bloodstream infections were excluded.The case definition was a patient with blood culture positive for *P. aeruginosa* and clinical and laboratory evidences of infection. Antimicrobial therapy was considered 'appropriate' when the initial treatment included at least one antibiotic that was active *in vitro* against the causative microorganisms, and administered within 24 hours of blood drawn for bacterial culture. The study methods and definitions were as described previously.Medical records of these cases were retrospectively reviewed for demographic data, underlying diseases, clinical manifestations, laboratory data, clinical outcome, antibiotic therapy and antibiotic susceptibility of *P. aeruginosa*. All enrolled cases were categorized by definition into the two groups of community-acquired and nosocomial modalities. Moreover, patients in the community-acquired group were divided into two subgroups, nonfatal and fatal.

Babies born in the Kaohsiung Chang Gung Memorial Hospital all received the blood group antigens test of ABO and RH phenotype free of charge and with their parents' agreement. In this study, we randomly sampled 100 newborns born in our hospital during the period and recorded their blood group phenotype as the control group for these cases in ABO blood group analysis.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) for Windows (Version 12.0; SPSS Inc., Chicago, IL, USA) was used for analysis of data. Continuous variables were analyzed by Student t test or Mann-Whitney *U* test. Categorical variables were compared by means of Chi-square test or Fisher's exact test. The prevalence of the samples and the population was compared with goodness of fit test. Statistical significance was determined at $p < 0.05$.

Results

We identified 26 infants and children with *P. aeruginosa* bacteremia in the study period. Three cases lacking clinical and laboratory evidence of sepsis and treatment without anti-pseudomonas agents were excluded. Therefore, a total of 23 cases were evaluated in our study. Fifteen cases (65%) were enrolled in the community-acquired group and 8 cases (35%) in the nosocomial group. Their clinical manifestations are listed in Table 1. Of the 23 cases with

Table 1 *Pseudomonas aeruginosa* sepsis in our pediatric patients

Total ($n = 23$)	Nosocomial group ($n = 8$)	Community group ($n = 15$)	p
Mortality	4 (50)[a]	4 (26.7)	0.371
Sex			
Male	3 (37.5)	8 (53.3)	0.667
Female	5 (62.5)	7 (46.7)	
Age (mo)	86.7 ± 21.8	17.5 ± 8.4	0.02*
Infant (≤1 y)	0 (0)	13 (86.7)	<0.001*
Children(>1 y)	8 (100)	2 (13.3)	
ABO blood group	7	14	NS
A	0	1	
B	5	8	
O	2	5	

* $p < 0.05$, statistically significant; NS = not significant.
[a] Numbers in parentheses, percent.

P. aeruginosa sepsis (aged 4 months—17 years), 11 were male and 12 were female. The mean age of the community-acquired group (17.5 ± 8.4 months) was significantly less than that of the nosocomial group (86.7 ± 21.8 months). Thirteen cases (86.7%) were infants < 1 year of age in the community- acquired cases. The other two cases (13.3%) were 3 and 11 years of age. The 3-year-old boy had *P. aeruginosa sepsis* initially, and acute lymphocytic leukemia was proven later. The 11-year-old girl was a case of biliary atresia and received the Kasai procedure before. All of the nosocomial cases were beyond infantile age. The mortality rate was 26.7% in the community- acquired group, and 50% in the nosocomial group. Although the mortality of the nosocomial group was higher than that of the community-acquired group, the difference was not statistically significant. Moreover, of the eight fatal cases in the two groups, seven cases (87%) were complicated with pneumonitis (patch infiltration with or without pleural effusion) validated by chest X-ray and they died from respiratory failure. By reviewing ABO blood grouping of 21 cases, 13 cases with a B blood group and 7 cases with O blood group were significantly more than the single A blood group. This finding has not been mentioned in any clinical study of *P. aeruginosa* sepsis with the exception in cystic fibrosis, to the best of our knowledge.

The detailed clinical characteristics of community-acquired *P. aeruginosa* sepsis on admission are shown in Table 2. They occurred during May to October in 13 cases (87%). Fever (100%) and diarrhea (80%) were the most common symptoms. Because of other symptoms such as cough, coryza, headache or lethargy being extremely rare or non-specific in previous studies, they are not listed in Table 2. Leukopenia (white blood cell count < 5000/mm^3) was present in 9 cases (60%), thrombocytopenia (platelet count < 100,000/mm^3) in 4 cases (27%), and hyponatremia (serum Na < 130 mEq/L) in 7 cases (47%) on admission. In 12 cases with diarrhea, 50% had *P. aeruginosa* enteritis proven

Table 2 Clinical manifestations of community-acquired *P. aeruginosa* sepsis on admission

Characteristics	Total case ($n = 15$)	Fatal case ($n = 4$)	Non-fatal case ($n = 11$)	p
Sex (male:female)	8:7	3:1	5:6	0.569
Fever	15 (100)[a]			
<3 days	4 (27)	2	2	
≥3 days	11 (73)	2	9	0.516
Diarrhea	12 (80)	4	8	0.516
Vomitus	5 (33)	2	3	0.560
Tachycardia (≥150/min)	10 (67)	3	7	NS
Hyponatremia (≤130 mEq/L)	7 (47)	2	5	NS
Leukocyte count < 5000/mm^3	9 (60)	2	7	NS
Platelet count < 10^5/mm^3	4 (27)	2	2	0.516
Elevated AST (>60 IU/dL)	5 (33)	2	3	0.580
Appropriate therapy	11 (73)	2	9	0.516
Concomitant diseases				
Infectious enteritis	6	2	4	NS
Pneumonitis	4	4	0	0.001*
Cellulitis	2	0	2	NS
Urinary tract infection	3	0	3	NS

AST = aspartate aminotransferase; NS = not significant.
* $p < 0.05$, statistically significant.
[a] Numbers in parentheses, percent.

by a positive pure single stool culture. All fatal cases had pneumonitis with patch infiltration or pleural effusion; surviving patients did not. Two nonfatal cases had *P. aeruginosa* cellulitis and abscess on admission, and received plastic debridement. Moreover, three non-fatal cases had an initial concomitant *E. coli* urinary tract infection. The incidence rates of thrombocytopenia, hyponatremia, elevated AST, inappropriate therapy and vomitus were higher in the fatal cases than in the nonfatal cases but the difference was not significant. Immunological studies were performed in eight patients. A girl had hypogammaglobulinemia, a boy had mild natural killer (NK) cell deficiency, and another five cases had mild low serum IgA levels (<70 mg/dL).

All 15 isolates of *P. aeruginosa* were 100% susceptible to amikacin, gentamicin, piperacillin, ciprofloxacin and imipenem; one was resistant to ceftazidime and cefepime. Most cases (73%) were treated with an appropriate regimen. However, the rate of an inappropriate initial antibiotic regimen was higher in the fatal cases (50%) than in the nonfatal cases (18%).

In Table 3, the ABO blood group phenotypes of the 100 newborns, which were sampled randomly as the control population, showed 24, 20, 46 and 10 cases with A, B, O and AB blood groups, respectively. The prevalence of this newborn control group in ABO blood phenotypes was consistent with Taiwanese reference of the Taiwan Blood Services Foundation under the analysis of goodness of fit test ($p = 0.311$). When compared with the control group of these newborns, the prevalence of blood phenotype B was statistically significant in our pediatric *P. aeruginosa* sepsis cases. This finding indicated that presentation of human ABO blood group antigens was highly associated with pediatric *P. aeruginosa* sepsis and may play a role in the pathogenesis of this organism.

Discussion

We conducted a retrospective study of 23 pediatric *P. aeruginosa* sepsis cases at a single institute and documented 15 community-acquired cases and 8 nosocomial cases during 7 years. This study may lead to a better understanding of pediatric *P. aeruginosa* sepsis. When compared with the nosocomial group, the community-acquired group had a lower mortality rate and significantly higher prevalence in infants. These findings were in accordance with the results of previous studies.[2–6,16] However, our results showed more cases of community-acquired bacteremia than those in the nosocomial classification, which did not match previous reports.[3,16] This could be explained by the following reasons: firstly, our limitation was a small number of cases enrolled during this period; secondly, empiric antibiotics with at least one anti-pseudomonal agent for febrile episodes were usually given to our immunocompromized patients, who were initially admitted for their underlying diseases such as leukemia, prematurity and immunodeficiency. In our research, the antimicrobial susceptibility of all agents to this bacillus was still high in these cases.

The ABO (H) antigens are not only confined to red cells but also are widely expressed in body fluids and tissues, which are regulated by the secretor gene (FTU2).[17] The gene encodes a glycosyltransferase, which transfers N-acetyl D-galactosamine (group A) or D-galactose (group B) to the nonreducing ends of glycans on glycoproteins and glycolipids. Recently, considerable evidence has been accumulated showing that carbohydrate-containing blood group substances represent prime candidates for the specific interaction with microbial surface lectins in infectious diseases.[8,14,18] *Pseudomonas aeruginosa* produces two lectins in close association with virulence factors, PA-IL and PA-IIL, which bind to galactose- and fucose/mannose-containing glycoconjugates, respectively.[13,18–22] These experimental studies implied that these lectins were relative to their putative roles in cell surface adhesion, biofilm formation, and host recognition associated with Lewis, P, ABO (H), or Bombay blood group antigens.[18–21,23,24] Moreover, these interactions of the carbohydrate containing substances over cells surface, virus, or bacteria played an important role in the pathway of innate and adaptive immunity for infections. Characteristics of the interaction between host glycoconjugation and organism lectins were discovered recently by researches. There are examples of infectious diseases in which the severity of infection can be directly linked to the ABO phenotype. Previous studies revealed that presentation of the ABO blood group antigen was highly associated with some bacteria, such as *Helicobacter pylori*, *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae*.[9–12,15,25] Therefore, the survey of ABO blood group correlation with disease was included in this study. *Pseudomonas aeruginosa* was the causative microorganism in chronic purulent otitis externa and in pneumonitis with cystic fibrosis. Clinical evidence was offered to indicate blood group A phenotype was associated with human otitis externa or chronic otitis media, which might be *P. aeruginosa* lectins apparently adhering to GalNAc (N-acetyl-galactosamine) as terminal

Table 3 Comparison between *P. aeruginosa* sepsis cases and newborn control group

Group blood phenotype	Cases ($n = 21$)	Control ($n = 100$)	OR (95% CI)	p
A	1	24	0.158 (0.020–1.242)	0.072
B	13	20	6.5 (2.373–17.808)	<0.001*
O	7	46	0.587 (0.218–1.578)	0.288
AB	0	10		0.27

CI = confidence interval; OR = odds ratio.
* $p < 0.05$, statistically significant.

blood group A.[26,27] However, the ABO blood group antigens were unlikely to play a major role in susceptibility to *P. aeruginosa* infection in patients with cystic fibrosis.[24,28] This could be explained by the fact that the ABO blood group antigen plays a different role in different populations and infectious diseases. According to reference of the Taiwan Blood Services Foundation, the prevalence of the ABO blood group was, respectively, phenotype O (44%), A (26%), B (24%), and AB (6%) in the Taiwanese population. Surprisingly, our study revealed that the B (62%) and O (33%) phenotypes were the most predominant in the ABO blood group antigen incidence of these patients with *P. aeruginosa* sepsis, which has not been published in English literature. In a further statistic analysis of ABO group antigens, our results indicated that blood phenotype B was the greatest risk factor associated with pediatric *P. aeruginosa* sepsis (odd ratio = 6.5). The result was at first reported in the clinical implications of human *P. aeruginosa* bacteremia or sepsis, which need further experimental and clinical studies.

In Taiwan, *P. aeruginosa* sepsis is not rare in previously healthy infants and children. This infection might be the first manifestation of an underlying medical problem, such as malignancy or immunodeficiency. In this study, there were 14 previously healthy cases found in 15 cases with community-acquired sepsis. Only three cases of ALL, hypogammaglobinemia and mild NK cell deficiency were diagnosed by following studies. Community-acquired *P. aeruginosa* sepsis in previously healthy children significantly occurred at an infantile age, which was found in this study and previous reports. This could be explained by the fact that infants had lower and fluctuant serum IgA levels, which will be sustainable until the age of 4 years. Therefore, healthy infants were more susceptible to *P. aeruginosa* infections than children beyond the age of 1 year.

Pneumonitis, with or without pleural effusion, was a concomitant disease in all four fatal cases. Previous literature has demonstrated selective IgA deficiency associated with *P. aeruginosa* pulmonary infection, and this indicates that the cell wall components of this gram negative organism may induce the loss of cellular effector function by serum IgA cleavage.[29–31] We considered that *P. aeruginosa* sepsis with pneumonitis could have a higher mortality rate and severity by more immune system disruption. Our findings also agreed with these opinions, although we did not have enough evidence. This implies that the mortality rate may increase, while *P. aeruginosa* bacteremia is accompanied with pneumonitis on admission, although an appropriate regimen was used. In addition, the prevalence of this isolate in stool culture was 50% in all community-acquired sepsis cases with diarrhea. This indicated that concomitant gastrointestinal infections may have played a role in pathogenesis. This is consistent with earlier findings, suggesting that the initial infection route of community-acquired sepsis might be from *P. aeruginosa* enteritis in infants.[5,32] We suggest that more intensive care, such as early intubation or inotropic agents, may be considered initially for these patients with pneumonitis.

In conclusion, we found that B or O phenotypes of ABO blood group antigens were associated with *P. aeruginosa* sepsis or bacteremia in infants and children; the B blood phenotype was statistically significant. They may play an important role in the pathogenesis of *P. aeruginosa* sepsis. In previously healthy infants and children, partial humoral system deficiency was the most apparent in this study, especially transient low serum IgA level. In addition, empiric antimicrobial therapy for sepsis should include at least one aminoglycoside or anti-pseudomonal agent, if the patient is an infant with fever and diarrhea, developing a septic appearance suddenly during the warm season. If these patients' chest X-rays revealed pneumonitis with patch infiltration or pleural effusion initially, they may need more intensive care in the initial therapeutic strategy.

Competing interests

The authors declare that no competing interests exist.

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