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Association between *Mycoplasma pneumoniae* Infection and Coronary Artery Aneurysm in Children with Kawasaki Disease

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Abstract

Background: The epidemiology of Kawasaki disease (KD) suggests that an infectious agent may be a potential disease trigger in susceptible children. Several studies have shown that the cause of KD may be associated with *Mycoplasma pneumoniae* (*M. pneumoniae*) infection.

Objectives: We aimed to investigate the relationship between *M. pneumoniae* infection and coronary artery aneurysm (CAA) in children with KD in China.

Methods: From January 2015 to December 2018, a total of 330 children with KD met the inclusion criteria. Relevant data were extracted and analysed.

Results: The children were stratified into two groups according to *M. pneumoniae* infection status. Significant differences were identified in the proportion of patients with fever > 10 days, the occurrence of small CAA, and the average serum sodium, prealbumin (PA), and albumin levels but not in the occurrence of medium and giant CAA between the two groups. According to binary logistic regression, *M. pneumoniae* infection (OR: 0.515; 95% CI: 0.309 - 0.860; P = 0.011), serum sodium levels (OR: 0.910; 95% CI: 0.851 - 0.972; P =0.005), and PA (OR: 0.900; 95% CI: 0.854 - 0.949; P $\leq$ 0.001) levels were independently associated with occurrence of small CAA.

Conclusions: We demonstrated that *M. pneumoniae* infection, serum sodium and PA levels are inversely related to the occurrence of small CAA. These results suggest that *M. pneumoniae* infection may be associated with a decreased incidence of small CAA. Further large-sample studies are needed.

Keywords: *Mycoplasma pneumoniae*, Coronary Artery Aneurysm, Kawasaki Disease, China

1. Background

The epidemiology of Kawasaki disease (KD) suggests that an infectious agent may be a potential disease trigger in susceptible children (1). In Taiwan, a cohort study with 5280 patients matched one-to-one with 5280 control children showed a significantly greater rate of KD in the adenovirus-infected children than in the uninfected children (2). Another study investigating the blood samples of patients with typical KD found viral signatures, including signatures for poliovirus (vaccine strain), measles (vaccine strain), rhinovirus and bocavirus, in more than half of the patients (3). Kawano et al (4) reported that human herpesvirus HHV-6 and HHV-7 reactivation was frequent in KD patients. HHV-6 reactivation, as well as *M. pneumoniae*, might exacerbate the severity of KD. In recent years, *M. pneumoniae* has emerged as one of the most common causes of pediatric community-acquired pneumonia (CAP), accounting for 10 - 40% of cases (5, 6). Wang et al (7) found that the occurrence of KD was associated with *M. pneumoniae* infection, which was subsequently corroborated by Merlin and Chemli (8, 9). In a case series, Vitale et al (10) found that *M. pneumoniae* may be a possible trigger of KD. A retrospective analysis of 358 patients with KD was performed by Lee (11); 12 patients had high anti-*M. pneumoniae* antibody (AMA) titres (> 1:640), indicating that KD patients can be concurrently infected, with evident pulmonary symptoms. A prospective study including 450 KD patients demonstrated that *M. pneumoniae* infections were

present in a significant proportion of KD patients (13.8%) (12). The cause of KD was considered to be associated with *M. pneumoniae* infection.

The major complication of KD is coronary artery aneurysm (CAA), which may result in myocardial ischaemia, myocardial infarction, or sudden death. Many studies have reported risk factors associated with CAA. Intravenous immunoglobulin (IVIG) treatment during the first 10 d of illness has been shown to reduce the prevalence of CAA five-fold (13). Risk factors for persistent CAA include long duration of fever and failure to respond to initial IVIG therapy, which manifests as persistent abnormal laboratory findings. These abnormal findings include low hemoglobin (Hb), low serum albumin, and low serum sodium (i.e., < 135 mEq/L) levels, an elevated heart rate, elevated alanine aminotransferase (ALT), elevated C-reactive protein (CRP), an elevated erythrocyte sedimentation rate (ESR), and elevated white blood cell (WBC) count (14-19). However, no studies have reported a correlation between *M. pneumoniae* and CAA. We used logistic regression models to evaluate the strength of this correlation.

2. Methods

2.1. Study Population

This retrospective study was conducted from January 2015 to December 2018 and included children with KD in a tertiary children's hospital in Fujian Province, China. The criteria for the diagnosis of *M. pneumoniae* infection were positive serological results before administration of IVIG (MP-total antibody test $\geq$ 1:640 and positive MP-IgM) and related clinical manifestations (fever, dry or productive cough, and pulmonary imaging abnormalities). KD was diagnosed according to the 2017 Guidelines of the American Heart Association (AHA) (20). The calculation of accurate z-scores for coronary artery measurements in children was based on the following formula (21):

$$Z_{scores} = \frac{[ln\,(M) - \beta 1 - \beta 2 \times ln\,(BSA)]}{\sqrt{MSE}}$$

where M equals the measurement value of the coronary artery; BSA equals the body surface area; and β1, β2, and MSE are constants. Small CAA was defined as a z-score $\geq$ 2.5 ~ < 5, medium CAA was defined as a z-score $\geq$ 5 ~ < 10, and giant CAA was defined as a z-score $\geq$ 10.

2.2. Demographic and Clinical Data Collection

Medical records were reviewed and the following data were collected: (1) a description of the patient, including age, sex, BSA, length of hospitalization, duration of fever, the presence of conjunctival hyperaemia, the presence of a skin rash, the presence of a strawberry-like appearance of the tongue, enlarged lymph nodes and changes in extremities; (2) laboratory data (the most severe values within 24 h of hospital admission), including a complete blood count, biochemical tests, pre-albumin (PA) levels, CRP levels, the ESR, blood culture results, electrocardiogram results, and chest radiography findings; and (3) co-infection within 24 h after admission according to blood culture results for bacterial infection, passive agglutination test results for MP (Fujirebio Inc.), indirect fluorescent antibody test results for nine common viruses and bacteria known to cause CAP (Vircell.S.L Pneumoslide IgM), PCR-fluorometric test results for Epstein-Barr virus (EBV) and cytomegalovirus (CMV), colloidal gold method test results for enterovirus type 71 (EV71) and enzyme-linked immunosorbent assay (ELISA) results for herpes simplex virus.

2.3. Ethics

The study was approved by the ethics committee of the University (no. 2017-042). All patients and their family members signed the informed consent form, and the data from the patients were analyzed anonymously.

2.4. Statistical Analysis

Data were analysed using IBM SPSS, version 23.0 (Chicago, USA). Descriptive analyses were performed, and the findings were reported as absolute frequencies or rates for categorical variables, the median (min-max) values for quantitative variables with a non-parametric distribution, and the means $\pm$ SDs for quantitative variables with a normal distribution. Comparisons of quantitative variables between the two groups were performed using Student's t test or the Wilcoxon rank sum test when appropriate. Comparisons of categorical variables were performed using the χ^2 test. Based on the group analysis results, a binary multivariate logistic regression analysis was conducted. P values below 0.05 were considered to indicate statistical significance.

3. Results

3.1. Demographic Characteristics

From January 2015 to December 2018, a total of 357 children with KD were hospital-ized. *M. pneumoniae* infections (165 cases) were present in a high proportion of the KD patients (46.2%). During data collection, 27 children without complete clinical data before IVIG therapy were excluded, Therefore, our study included 330 children with KD; 201 children were males, and 129 children were females (1.6:1 male: female ratio). We divided our cohort into two

groups: the KD with *M. pneumoniae* infection group (n = 159) and the KD without *M. pneumoniae* infection group (n = 171). The KD with *M. pneumoniae* infection group was significantly older than the KD without *M. pneumoniae* infection group ($P < 0.05$). However, the two groups had similar sex distributions.

3.2. Clinical Characteristics of the Study Cohort

No significant differences were identified in the proportions of children with a maximum temperature > 39°C and a length of fever > 7 days. However, a significant difference was found in the proportion of those with a length of fever > 10 days. Conjunctival hyperemia, skin rash, a strawberry-like appearance of the tongue, enlarged lymph nodes and changes in extremities were common clinical manifestations of KD. Table 1 shows no significant differences in the proportions of those with conjunctival hyperemia, skin rash, a strawberry-like appearance of the tongue, enlarged lymph nodes, and changes in extremities between the two groups.

Regarding laboratory examinations, the average lymphocyte counts, serum sodium levels, PA levels, and albumin levels were significantly different between the two groups. In addition, a significant difference in the incidence of small CAA was ob-served between the two groups ($P < 0.05$), although no differences were observed for medium and giant CAAs and associated variables (Table 1).

3.3. Correlation Between M. pneumoniae Infection and Small CAA

Statistically significant clinical and laboratory parameters were analysed to assess as-sociations between independent variables and small CAA using binary logistic regression modelling. The categorical variables were the proportion of patients with a length of fever > 10 days and *M. pneumoniae* infection. The continuous variables were age, PA level, lymphocyte count, serum sodium level, and albumin level. We found that *M. pneumoniae* infection (OR: 0.515; 95% CI: 0.309 - 0.860; P = 0.011), serum sodium lev-el (OR: 0.910; 95% CI: 0.851 - 0.972; P = 0.005), and PA level (OR: 0.900; 95% CI: 0.854 - 0.949; $P \leq 0.001$) were independent variables according to the final model, suggesting that *M. pneumoniae* infection may be associated with a decreased incidence of small CAA. However, decreased serum sodium and PA levels increased the risk of small CAA independently (Table 2).

4. Discussion

The prevalence of *M. pneumoniae* infection among KD patients (46.2%) in this cohort was much higher than that reported in the literature (12). A major cause may be the epidemics of *M. pneumoniae*. Cyclic outbreaks of *M. pneumoniae* infections tend to occur in different regions every 3 - 7 years. Since 2010, outbreaks of *M. pneumoniae* have been reported in some European countries (22), with similar reports in China (23). In the last five years, the prevalence of *M. pneumoniae* infections has increased annually in Fujian Province, China. Another major reason for the increased prevalence may be the fact that the children in this study were presenting to a tertiary children's hospital; therefore, patients with KD and *M. pneumoniae* may have been over-represented.

The pathological mechanisms of KD due to *M. pneumoniae* infection remain largely unknown. Currently, the consensus by researchers is that indirect tissue injury by *M. pneumoniae* triggers an inflammatory response and overall activation of the immune system (24). Immune-stimulatory components of *M. pneumoniae* (including the *M. pneumoniae* N602 protein, whose inflammatory capacity has been estimated to be 100-fold higher than that of other proteins) can stimulate a high percentage of T cells by binding to the Vβ region of T cell receptors, which can stimulate the production of proinflammatory cytokines/chemokines and reactive oxygen/nitrogen species (ROS/NOS) and prolong the length of fever, subsequently eliciting systemic vasculitis (25, 26). However, our data indicated that the coronary arteries were not severely affected by *M. pneumoniae* infection, which is consistent with previously reported data (7, 27). Our data also indicated that no differences existed between medium and giant CAAs, possibly because the natural course of KD due to *M. pneumoniae* is likely similar to that of pulmonary infection with *M. pneumoniae*, which is usually mild and self-limiting (28), but severe, fulminant or fatal cases have also been found as the condition deteriorates. Additionally, the genetic background of an individual likely affects disease susceptibility (26). We postulate that *M. pneumoniae* infection might be associated with a decreased incidence of small CAA. However, our sample population was small; therefore, further studies with larger numbers of patients are needed.

According to the data in the present study, serum sodium and PA levels were independent risk factors for small CAA. Hyponatremia increases the secretion of aldosterone, which regulates contraction and remodelling of the vessel walls. The severity of vascular inflammation in acute KD with hyponatremia might worsen the prognosis of coronary vasculature. The sodium level may be a simple predictor of KD's cardiovascular sequelae. Our results corroborate the results of other reports (29-31). Hypoalbuminemia has been reported to be independently associated with the occurrence of progressive coronary dilata-

Table 1. Comparison of Characteristics Between KD Patients with *M. pneumoniae* Infection and KD Patients with No *M. pneumoniae* Infection

Characteristics	ALL (N = 330)	KD with *M. pneumoniae* Infection (N = 159)	KD with No *M. pneumoniae* Infection (N = 171)	F/Z/χ^2	P - Value
Age (y)	1.50 (0.08 - 13.00)	1.57 (0.26 - 8.00)	1.42 (0.08 - 13.00)	- 3.823	0.000
Gender (n, % males)	201 - 60.9	95 - 59.7	106 - 62.0	0.174	0.677
Maximum temperature > 39°C (n, %)	243 - 73.6	122 - 76.7	121 - 70.8	1.512	0.229
Fever > 7 d (n, %)	167 - 50.6	86 - 54.1	81 - 47.4	1.488	0.222
Fever > 10 d (n, %)	71 - 21.5	43 - 27.0	28 - 16.4	4.515	0.034
Conjunctival hyperemia (n, %)	204 - 61.8	104 - 65.4	100 - 58.4	1.676	0.195
Skin rashes (n, %)	207 - 62.7	101 - 63.5	106 - 62.0	0.083	0.773
Strawberry-like tongue (n, %)	196 - 59.4	92 - 57.9	104 - 60.8	0.299	0.585
Enlargement of lymph nodes (n, %)	120 - 36.3	66 - 41.5	54 - 31.6	3.511	0.061
Changes in extremities (n, %)	194 - 58.8	95 - 59.7	99 - 57.9	0.117	0.732
WBC $\times 10^9$/L	19.86 (5.14 - 45.64)	19.63 (5.14 - 45.63)	20.08 (7.18 - 39.63)	- 0.911	0.362
Neutrophil percentage (%)	68.23 $\pm$ 13.94	68.02 $\pm$ 13.60	68.44 $\pm$ 14.28	14.448	0.074
Neutrophil counts, $\times 10^9$/L	10.31 (0.92 - 30.88)	10.24 (1.44 - 30.88)	10.38 (0.92 - 26.25)	- 0.561	0.575
Neutrophil counts/ Lymphocyte counts	1.87 (0.16 - 17.56)	1.90 (0.25 - 9.42)	6.21 (0.16 - 17.56)	- 0.533	0.594
RDW (%)	14.63 (0.03 - 28.50)	14.52 (0.03 - 28.50)	14.74 (1.57 - 27.70)	- 1.230	0.219
HB, g/L	101.33 (54.0 - 143.0)	102.46 (62.0 - 177.0)	100.29 (54.0 - 143.0)	- 1.765	0.078
PLT, $\times 10^9$/L	610.47 (165.0 - 1653.0)	596.04 (165.0 - 1351.0)	623.89 (202.0 - 1653.0)	- 0.934	0.351
CRP, mg/L	81.46 (0.50 - 316.80)	74.74 (0.50 - 316.80)	87.71 (0.50 - 266.40)	- 1.634	0.102
ESR	65.45 (3.0 - 140.0)	69.23 (3.0 - 140.0)	61.92 (3.0 - 140.0)	- 1.782	0.075
Serum sodium, mmol/L	135.06 (110.0 - 145.0)	134.38 (110.0 - 145.0)	135.71 (110.0 - 145.0)	- 2.337	0.019
Serum chloride, mmol/L	102.55 (86.0 - 112.0)	102.36 (86.0 - 112.0)	102.72 (86.0 - 112.0)	- 0.985	0.324
Serum potassium, mmol/L	4.31 $\pm$ 0.70	4.28 $\pm$ 0.62	4.34 $\pm$ 0.78	0.245	0.494
Serum calcium, mmol/L	2.29 (1.66 - 2.82)	2.27 (1.66 - 2.82)	2.31 (1.66 - 2.82)	- 1.768	0.077
ALT, U/L	81.31 (7.70 - 968.00)	72.62 (7.70 - 842.80)	89.49 (8.60 - 968.00)	- 1.061	0.289
AST, U/L	69.80 (9.60 - 852.30)	60.33 (9.60 - 622.50)	78.70 (9.60 - 852.30)	- 0.146	0.884
GGT, U/L	66.34 (5.50 - 600.00)	60.99 (5.60 - 600.00)	71.52 (5.50 - 455.20)	- 1.625	0.104
TBIL, μmol/L	9.56 (1.20 - 157.40)	8.45 (1.20 - 101.40)	10.62 (1.70 - 157.40)	- 0.934	0.350
TC, mmol/L	3.78 (1.61 - 63.40)	3.64 (1.61 - 7.00)	3.92 (1.80 - 63.40)	- 1.189	0.234
TG, mmol/L	1.49 (0.27 - 6.64)	1.45 (0.27 - 4.16)	1.52 (0.46 - 6.64)	- 0.568	0.570
LDL, mmol/L	2.17 (0.49 - 5.18)	2.17 (0.60 - 5.18)	2.17 (0.49 - 5.18)	- 0.584	0.559
HDL, mmol/L	0.89 (0.30 - 2.18)	0.88 (0.30 - 1.55)	0.91 (0.31 - 2.18)	- 0.917	0.359
PA, mg/dL	12.11 (4.20 - 34.90)	11.43 (4.53 - 29.38)	12.73 (4.20 - 32.23)	- 2.241	0.025
Albumin, g/L	36.42 (19.40 - 51.40)	35.90 (19.40 - 48.40)	36.91 (23.50 - 51.40)	- 2.209	0.042
LDH, U/L	392.33 (12.11 - 2150.00)	407.36 (109.30 - 2150.00)	378.35 (12.11 - 1867.00)	- 0.874	0.382
CK, U/L	74.34 (6.70 - 5200.00)	62.26 (6.70 - 1000.00)	85.69 (7.80 - 5200.00)	- 0.135	0.892
CKMB, U/L	26.10 (2.80 - 161.00)	24.73 (2.80 - 144.80)	27.40 (3.00 - 161.00)	- 1.032	0.302
Length of hospitalization (d)	9.52 (2.0 - 32.0)	9.41 (2.0 - 32.0)	9.63 (2.0 - 32.0)	- 0.420	0.674
Involving bilateral coronary arteries (n, %)	101 - 30.6	42 - 26.4	59 - 34.5	2.538	0.111
Small CAA (n, %)	210 - 63.6	92 - 57.8	118 - 69.0	4.422	0.035
Medium and Giant CAA (n, %)	13 - 3.9	8 - 5.0	5 - 3.0	0.967	0.242
Intravenous immunoglobulin non-responsive KD (n, %)	45 - 13.6	26 - 16.4	19 - 11.1	1.922	0.166

Abbreviations: KD, Kawasaki Disease; *M. pneumoniae*, *Mycoplasma pneumoniae*; WBC, white blood cell count; RDW, red blood cell volume distribution width; HB, hemoglobin; PLT, platelet count; CRP, C-reactive protein; ESR, the erythrocyte sedimentation rate; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, γ-glutamyl transpeptidase; TBIL, total bilirubin; TC, total cholesterol; TG, triglycerides, LDL, low-density lipoprotein; HDL, high-density lipoprotein; PA, pre-albumin; LDH, lactate dehydrogenase; CK, creatinine kinase; CKMB, MB isoenzyme of creatine kinase; CAA, coronary artery aneurysm.

Table 2. Independent Variables for Small CAA by Binary Logistic Regression Analysis

	B	S.E.	Wals	Df	Sig	Exp (B)	Exp (B) 95% Confidence Interval	
							Lower Bound	Upper Bound
***M. pneumoniae* infection**	-0.663	0.261	6.434	1	0.011	0.515	0.309	0.860
Serum sodium	-0.095	0.034	7.871	1	0.005	0.910	0.851	0.972
PA	-0.105	0.027	15.073	1	0.000	0.900	0.854	0.949

Abbreviations: CAA, coronary artery aneurysm; *M. pneumoniae*, *Mycoplasma pneumoniae*; PA, pre-albumin.

tion and is an effective predictor of IVIG resistance (32, 33). Kim JH reported that the KD with adenovirus group was significantly associated with presence of hypoalbuminemia compared with the adenoviral infection group. However, hypoalbuminemia was not the significant predictive factor of KD in the multivariate analysis (34). Our study also showed that the albumin level was not an independent risk factor for small CAA, but the PA level was an independent risk factor. A possible reason for this result is that PA has a short average lifespan; therefore, it can better estimate the nutritional and inflammatory status of a child at the precise time at which it is measured (35).

In this study, we showed that children with KD who had *M. pneumoniae* infection were older and tended to experience longer periods of fever than the controls, possibly because *M. pneumoniae* infection is more frequently observed in children, particularly school-age children, than in adults (36). Older children are more immunologically mature than younger children, and the production of cytokines in response to *M. pneumoniae* increases, consequently increasing the likelihood of extrapulmonary complications, including KD, in older children infected with *M. pneumoniae*. Fever is the most common symptom of KD plus *M. pneumoniae* infection. Our results indicate that long-term fever (i.e., > 10 d) in children with *M. pneumoniae* infection may induce complications associated with KD.

This study has some limitations. First, this was a retrospective observational study in a single centre, which may have resulted in certain inherent selection biases. Second, the results might be limited because the children in this study were presenting to a tertiary children's hospital; therefore, patients with KD and *M. pneumoniae* may have been overrepresented. Third, only obvious, severe infections on admission were considered, and some patients may have had subclinical infection, which would bias our study towards severe disease. Nevertheless, we believe that this study serves as a preliminary survey of the relationship between *M. pneumoniae* and CAA. Larger, prospective, multicenter studies may be justified to better quantify the risk and to investigate whether any other associations exist.

In conclusion, the present study demonstrated that *M. pneumoniae* infection occurred in a significant proportion of KD patients (46.2%). *M. pneumoniae* infection might be associated with a decreased incidence of small CAA. Further studies with large sample sizes are needed. Serum sodium and PA levels were important independent risk factors for small CAA and should be closely managed.

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Footnotes

Authors' Contribution: WANG Cheng-yi was responsible for the concept and design of the study and writing of the manu-script. SONG Chao-min participated in preliminary data collection and data analysis and co-wrote the manuscript. LIU Guang-hua supervised the design and execution of the study. Zhang Hui-Jie and Chen Fang-sheng participated in patient care, data collection, and data analysis. All authors read and approved the final manuscript.

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Conflict of Interests: No conflicts of interest exist in the submission of this manuscript, and the manuscript has been approved for publication by all authors.

Ethical Approval: This study was approved by the Institutional Ethics Committee of Fujian Provincial Maternity and Children's Hospital of Fujian Medical University, China (No. 2017-042).

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