



Evaluation of variation in coagulation among children with *Mycoplasma pneumoniae* pneumonia: a case–control study

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Abstract

Objective: Acute organ embolism in children with *Mycoplasma pneumoniae* pneumonia (MPP) has been reported, but changes in coagulation are unclear. This study aimed to investigate changes in coagulation in children with MPP.

Methods: A total of 185 children with MPP (cases) and 117 healthy children (controls) were recruited. We measured prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and plasma fibrinogen (FIB) and D-dimer levels.

Results: Plasma FIB (3.39 ± 0.96 g/L vs 2.93 ± 0.6 g/L, $t = 4.50$) and D-dimer (326.45 ± 95.62 mg/L vs 263.93 ± 103.32 mg/L, $t = 5.36$) in MPP children were higher than controls and PT (9.54 ± 4.97 s vs 11.48 ± 5.96 s, $t = 3.05$) and APTT (31.41 ± 12.01 s vs 38.38 ± 11.72 s, $t = 4.95$) were shorter than controls. FIB, D-dimer, PT, and APTT were not different between the high IgM-titre and low-titre groups. The areas under the receiver operating characteristic curves in cases and controls for plasma FIB and D-dimer levels were 0.654 (95% confidence interval [CI], 0.593–0.716, $P = 0.031$) and 0.682 (95% CI, 0.619–0.744, $P = 0.032$), respectively.

Conclusions: Children with MPP have a higher risk of blood coagulation and thrombosis. Controlling these problems should be considered as soon as possible.

Keywords

Mycoplasma pneumoniae, coagulation function, children

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Background

Mycoplasma pneumoniae (MP) is the pathogen of *Mycoplasma pneumoniae* pneumonia (MPP), and is one of the most prevalent pathogens causing community-acquired

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pneumonia (CAP) in children.^{1–3} Some studies have reported that MPP might account for as many as 40% of CAP cases, nearly 20% of which require hospitalization.^{1,4} The pathogenesis of MP is complex. The main cytotoxic effects of MP include local disruption of tissue and cell structure along the respiratory tract epithelium. MP produces the community-acquired respiratory distress syndrome toxin, which most likely aids in leading to inflammation and airway dysfunction. Formation of some virulence factors, such as lactoferrin, hydroxyl radicals, superoxide anions, and hydrogen peroxide, aggravate tissue damage. The immunological responses by MP may cause other systemic symptoms.⁵

MPP is usually characterized by a persistent dry cough and fever, and is considered as a mild and self-limited disease that is cured with no medication. Nevertheless, even when MPP is treated with macrolide antibiotic in a timely manner, severe pulmonary and extra-pulmonary complications may lead to respiratory failure and hypoxia. These complications can develop into severe life-threatening pneumonia in some severe cases.^{6–10} Clinicians need to identify severe and complicated MPP at earlier stages. Other severe complications that have been identified from fulminant MPP cases include acute organ embolism and infarction, such as carotid artery embolization and cerebral infarction. The majority of acute cerebral infarction cases have occurred in children with MPP in recent years.^{11–20} Pulmonary embolism and paediatric femoral artery thrombosis have also been reported in children with MPP.^{21–23} These studies also showed that there were coagulation abnormalities in children with MPP.

Blood coagulation might be abnormal in cases of MP infection and blood coagulation abnormalities can cause embolization.^{11–23} Studies have shown that some cases of MPP show coagulation abnormalities.^{12,13,17,19} A girl with MPP and acute

cerebral infarction was reported in Weifang Hospital in 2011, whose FIB and D-dimer levels in blood were significantly higher than normal.¹⁵ The relationship between MP infection and embolization is still unclear. Few multiple-case studies have reported changes in coagulation in children with MPP.^{14,18} In this study, we performed a case-control study to analyse the changes in coagulation in children with MPP.

Materials and methods

A case-control study was conducted in Weifang People's Hospital, Shandong Province, China from January, 2011 to December, 2014. All children who had symptoms and signs indicative of pneumonia, such as fever, cough, abnormal lung auscultation, and a new infiltrate on chest radiograph, were admitted to the Department of Paediatrics and tested for mycoplasma by samples of throat swabs within 3 h by a quick method (MP 3 h Culture Identification Kit, Wuhan Showtime Technology Co., Ltd). This study was approved by the ethics committee of Weifang People's Hospital (No: P2010019). All of the parents of the children who participated signed an informed consent form.

All of the children with pneumonia who had MP-positive throat swabs had a 5-ml sample of venous blood collected using IMPROVACUTER EDTA K2 tubes (Improve Medical Technology, Guangzhou, China) before treatment. During 60 min after collection, blood samples were centrifuged at 2000 r/min for 10 min in a BY-320 C centrifuge (Baiyang Medical Instrument Company, Beijing, China) and the plasma was immediately separated. Indices of coagulation, including prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and plasma fibrinogen (FIB) and D-dimer levels were detected in 2 h. The coagulation test and plasma D-dimer kit were from Mitsubishi Chemical Corporation. Detection was

performed using the ACLTOP700 automatic blood coagulation analyser (Beckman Coulter). Other clinical indices, such as C-reactive protein (CRP) (IMMAGE 800 Turbidimetric Inhibition Immunoassay System; Beckman Coulter Inc., Brea, CA, USA), platelet (PLT) count (XE-2100 Automated Hematology System; Sysmex, Kobe, Japan), and the erythrocyte sedimentation rate (Westergren's blood sedimentation tube; Hull Medical Science and Technology Co., Ltd., Hefei, China), were analysed by routine methods.

After approximately 2 weeks of symptoms, all of the children with pneumonia and MP-positive throat swabs had 2 ml of venous blood collected using IMPROVACUTER® EDTA K2 tubes. Blood samples were centrifuged at 2500 r/min at room temperature for 10 min in a BY-320 C centrifuge (Baiyang Medical Instrument Company) and the plasma was immediately separated, frozen, and stored at -80°C until later analysis. IgM antibody was detected by a diagnostic kit for measurement of antibodies to MP according to the manufacturer's instructions (passive particle agglutination test, Serodia-Myco II; Fujirebio Inc., Japan).

Patients who were MP IgM-positive and had an antibody titre $\geq 1:160$ were selected as cases. Cases were divided into two subgroups: the low-titre group with an MP IgM titre equal to 1:160–320 and the high-titre group with an MP IgM titre equal to 1:640–1280. Healthy children without MPP were selected as controls from the Health Evaluation Clinic at the same hospital during the study period. Similarity of sex and age between the children with MPP and healthy children was considered when the healthy children were selected. Samples of venous blood to detect MP IgM antibody and four indices of coagulation and plasma D-dimer levels were also collected. The IgM antibody of controls needed to be negative (IgM titre $< 1:40$). All of the children in the case and control groups had a routine

clinical examination. Sex, age, medical history, and laboratory data were recorded by clinical doctors. Children with other respiratory tract infections and tuberculosis, rheumatic diseases, haematological diseases, and immunodeficiency were excluded from the case and control groups. Children who took some medicine or other substances that affect the blood system were also excluded.

SPSS 19.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Continuous data are shown as mean \pm standard deviation ($\bar{x} \pm s$). All continuous data were tested for normality and homogeneity of variance. Analysis of variance or the Student's t-test was used to determine differences in continuous variables among the groups. The Student–Newman–Kueuls (SNK) method was used to identify significant differences between group means. Categorical data are shown as frequencies. Pearson's chi-square test or Fisher's exact test was used to analyse differences between categorical variables. $P < 0.05$ was designated as the level of statistical significance. Receiver operating characteristic (ROC) analysis was used to further assess differences in coagulation between children with MMP (cases) and controls. The areas under the curves (AUCs) were calculated.

Results

Basic characteristics of the study subjects

A total of 185 children with MPP-positive antibody (IgM antibody titre $\geq 1:160$) were selected as cases and 117 healthy children (IgM antibody titre $< 1:40$) were recruited as controls. The age and sex of the control group were 8.3 ± 1.6 years and 53/74, respectively. There were no significant differences in age and sex between cases and controls ($P = 0.18$ and $P = 0.16$, respectively). The number of children in the two subgroups was 88 in the low-titre group and 97 in the high-titre group. Table 1 shows the clinical characteristics of children with MPP.

Table 1. The clinical characteristic of children with MPP (n = 185).

Characteristics	Value or percentage	Characteristics	Value or percentage
Boys (%)	106/185	Cough (%)	183/185
Age ($\bar{x}\pm s$)	8.1 \pm 1.8	Wheeze (%)	84/185
Weight ($\bar{x}\pm s$)	25.0 \pm 5.3	Fever (%)	176/185
Course of disease ($\bar{x}\pm s$)	9.55 \pm 4.67	Dyspnoea (%)	13/185
WBC \uparrow or \downarrow (%)	69/185	Gastrointestinal symptoms (%)	24/185
CRP \uparrow (%)	61/185	Shortness of breath (%)	32/185
PLT \uparrow (%)	58/185	Cyanosis (%)	15/185
ALT \uparrow (%)	16/185	Changes in chest X-ray (%)	185/185
CK-MB \uparrow (%)	32/185	Pleural effusion (%)	18/185

Table 2. Coagulation function and D-dimer values for the case and control groups ($\bar{x}\pm s$).

Group	n	Prothrombin time (s)	Activated partial thromboplastin time (s)	D-dimer (mg/L)	FIB (g/L)	Thrombin time (s)
Controls	117	11.48 \pm 5.96	38.38 \pm 11.72	263.93 \pm 103.32	2.93 \pm 0.66	15.52 \pm 5.94
Cases	185	9.54 \pm 4.97	31.41 \pm 12.01	326.45 \pm 95.62	3.39 \pm 0.96	15.63 \pm 6.89
t	–	3.05	4.95	5.36	4.50	0.152
P	–	0.002	< 0.001	< 0.001	< 0.001	0.880

Coagulation function and D-dimer values in cases and controls

Plasma FIB and D-dimer levels in cases were higher than those in controls ($P < 0.001$ respectively). The PT and APTT in cases were shorter than those in controls ($P = 0.002$ and $P < 0.001$ respectively). The TT was not different between cases and controls (Table 2).

Multiple comparisons of coagulation function and D-dimer levels

Plasma FIB and D-dimer levels in the high-titre group were significantly higher than those in controls. The PT and APTT in the high-titre group were significantly shorter than those in controls. Plasma FIB and D-dimer levels in the low-titre group were higher than those in the control group. There were no differences in the PT and

APTT between the low-titre group and the control group. There were no differences in plasma FIB and D-dimer levels, PT, and APTT between the low-titre group and the control group (Tables 3 and 4).

ROC curve analysis

The ROC curves of plasma FIB and D-dimer levels for discriminating the case group from the control group were analysed. The AUC for plasma FIB levels was 0.654 (95% confidence interval [CI], 0.593–0.716, $P = 0.031$). The AUC for plasma D-dimer levels was 0.682 (95% CI, 0.619–0.744, $P = 0.032$) (Figure 1).

Discussion

The indices of blood coagulation in 185 children with MPP changed in this study, including plasma FIB and D-dimer levels,

Table 3. Coagulation function and D-dimer values for the low-titre, high-titre, and control groups ($\bar{x} \pm s$).

Group	n	PT (s)	APTT (s)	D-dimer (mg/L)	FIB (g/L)	TT (s)
Controls	117	11.48 ± 5.96	38.38 ± 11.72	263.92 ± 103.32	2.94 ± 0.66	15.52 ± 5.94
Low-titre	88	9.45 ± 5.14	32.78 ± 11.86	312.11 ± 89.95	3.28 ± 1.10	15.36 ± 5.25
High-titre	97	9.62 ± 4.84	30.18 ± 12.08	339.45 ± 99.15	3.49 ± 0.80	15.89 ± 8.12
F	–	13.42	4.67	16.30	11.59	0.168
P	–	0.000	0.010	0.000	0.000	0.846

Table 4. Comparison of PT, APTT, FIB, and D-dimer results (SNK-q test).

Groups	PT (s)	APTT (s)	D-dimer (mg/L)	FIB (g/L)
1 vs 3	P < 0.05	P < 0.05	P < 0.05	P < 0.05
1 vs 2	P < 0.05	P < 0.05	P < 0.05	P < 0.05
2 vs 3	P > 0.05	P > 0.05	P > 0.05	P > 0.05

Note: 1, control group; 2, low-titre group; 3, high-titre group.

and the PT and APTT. We found that children with MPP had higher plasma FIB and D-dimer levels, and a shorter PT and APTT than did healthy children. These findings indicated that children with MPP were more likely to have blood coagulation and a higher risk of thrombosis. There were no differences between the high-titre MP antibody group and the low-titre group.

FIB is a glycoprotein in blood, and is synthesized in the liver by hepatocytes and helps in formation of blood clots.²⁴ FIB can form bridges between platelets, by binding to their GpIIb/IIIa surface membrane proteins. FIB deficiency or disturbed function of FIB can lead to either bleeding or thromboembolic complications.²⁵ FIB can function as a cofactor in aggregation of platelets, and an increase in FIB indicates easier blood agglutination. An increase in plasma FIB levels is always identified in various diseases, such as diabetes, pregnancy-induced hypertension, acute nephritis, and cancer. An increase in plasma FIB levels can also be found in infectious

diseases and has a major effect on the coagulation system. Nevertheless, few studies have focussed on an increase in FIB levels in children with MPP.

D-dimer is a specific degradation product that is produced in hydrolysis of fibrin, which is regarded as an important indicator of hyperfibrinolysis. Detection of D-dimer is able to reveal early thrombotic disease and reflect generation of thrombin and plasmin. Plasma D-dimer levels are a specific marker of the fibrinolysis process in the clinic. D-dimer is often elevated in many diseases, such as disseminated intravascular coagulation, venous thrombosis, coronary heart disease, severe infection, tissue necrosis, and colorectal cancer.²⁶ D-dimer levels are also closely related to the inflammatory response and may reflect the effects of infection on coagulation in infectious diseases. Some studies have reported that plasma D-dimer levels are significantly increased in children with acute MPP, which suggests that blood is in a hypercoagulable state and the presence of thrombosis.²⁷ A study in Taiwan reported that MP-infected adults were in a hypercoagulable state and had a high risk of stroke through 5 years of observation among more than 1000 cases of MP infection.²⁸

There have been many reports on MPP with acute cerebral infarction or hemiplegia, most of which were cases of MMP in children.^{11–23} However, the cause of abnormal coagulation function and thrombosis is not fully understood.²⁹ Some authors concluded that cytokines and mycoplasma

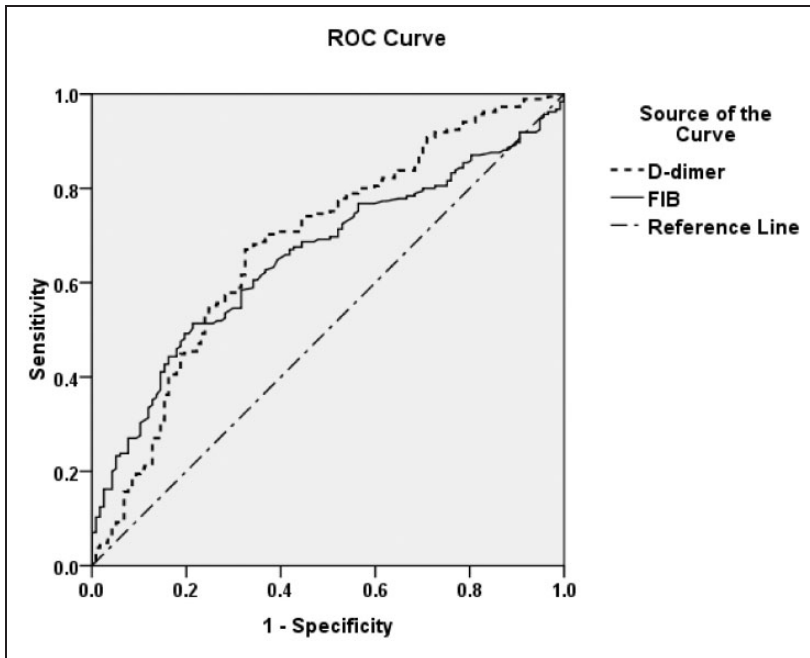


Figure 1. Receiver operating characteristic (ROC) curve analysis for plasma FIB and D-dimer levels.

infection produced damage to the vascular wall, leading to local vasculitis and thrombotic vascular occlusion.^{30,31} Some studies have shown that activation of the complement system caused by mycoplasma activates the coagulation system.³² In fact, MP infection activates exogenous and endogenous coagulation systems by multiple pathways, resulting in abnormal coagulation and promotion of thrombosis.

Vascular endothelial cells are damaged by MP, and this leads to an imbalance in coagulation and anticoagulation factors. Some inflammatory factors, such as tumour necrosis factor- α and interleukin, accelerate coagulation.³³ When liver cells are damaged by inflammation, synthesis of some anticoagulation factors, including antithrombin III (AT-III) and protein C, are affected, and this also leads to promotion of coagulation. AT-III levels and protein C activity are significantly different in MP-infected children compared with health children,³⁴ and after

anti-mycoplasma treatment, protein C activity returns to normal. *In vitro* experimental studies have suggested that lipoglycans from some mycoplasma can induce procoagulant activity through human mononuclear cells.³⁵

Many studies have reported that blood coagulation function in children with MP infection and venous or arterial thrombosis return to normal after anticoagulant therapy.^{36,37} Additionally, after this therapy, antiphospholipid antibodies disappear and anti-clotting factor activity normalizes.^{36,37} Treatment of children with MPP should be considered for controlling thrombosis according to mechanisms of thrombus due to MP infection. Thrombolytic therapies should be considered as soon as possible when clinical circumstances arise.³⁸

There are several limitations in the study. First, this study was performed in only one hospital. The representativeness of the sample should be considered when the conclusions are generalized. Second, the findings

in this study should be confirmed by studies with a large sample size. Finally, there may have been some unknown factors that affected the results because of the complexity of MPP.

Contributions

(I) Conception and design: Tianhua Li and Lihong Wang; (II) administrative support: Zhiyong Li, Tianhua Li, and Weina Hou; (III) provision of study materials or patients: Haiying Yu and Chunfang Han; (IV) collection and assembly of data: Tianhua Li, Zhiyong Li, Haiying Yu, and Chunfang Han; (V) data analysis and interpretation: Lihong Wang and Tianhua Li; (VI) manuscript writing: all authors; and (VII) final approval of the manuscript: all authors.

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Declaration of Conflicting Interest

The authors declare that there is no conflict of interest.

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