Original Article
Diagnostic value of immunoglobulin combined with complement C3 and C4 in mycoplasma pneumonia

Fuying Zhu, Jie Yang, Jin Li

Department of Medical Laboratory, Qijiang District People's Hospital of Chongqing, Chongqing 400020, China

Abstract: Objective: To investigate the diagnostic value of combined detection of immunoglobulin (Ig)M, IgA, IgG and complement C3 and C4 in mycoplasma pneumonia. Methods: From November 2015 to April 2018, 114 patients with mycoplasma pneumonia hospitalized in our hospital were selected and enrolled in the disease group, including 52 mild to moderate mycoplasma pneumonia patients and 62 severe mycoplasma pneumonia patients, and the control group consisted of 80 healthy subjects. The expression levels of Ig and complement C3 and C4 in venous blood of patients in each group were compared, the changes of pulmonary function of patients were detected and recorded, and the correlation between pulmonary function and detection indexes was analyzed. ROC was used to plot the diagnostic value of Ig and complement C3 and C4 combined detection in patients with different severity of mycoplasma pneumonia. Results: The levels of serum IgM, IgG, complement C3 and C4 in the disease group were notably higher than those in the control group, and IgA levels were notably lower than those in the control group, and the above indexes showed statistical difference between severe and mild to moderate mycoplasma pneumonia (P<0.05). Compared with mild to moderate mycoplasma pneumonia group, the predicted values of FEV1/FVC and FEV1% in severe mycoplasma pneumonia group were notably reduced (P<0.05). Correlation between FEV1/FVC and the detection indexes was analyzed by Spearson method. Pulmonary function of patients with mycoplasma pneumonia was negatively correlated with serum IgM, IgG, C3 and C4 levels, and positively correlated with IgA levels. ROC curve showed that detection of IgM, IgA, IgG and complement C3 and C4 and their combination could reveal the severity of mycoplasma pneumonia. Conclusion: The expression of Ig and complement C3 and C4 in patients' serum has high diagnostic value for mycoplasma pneumonia.

Keywords: Immunoglobulin, complement C3, complement C4, mycoplasma pneumonia, diagnostic value

Introduction

Mycoplasma pneumonia is an acute community-acquired lung inflammation with a high incidence rate in children and young people, accounting for 30% of all pneumonia. It has clinical characteristics such as long course of disease and is easy to be repeated [1, 2]. Chest imaging manifestations of mycoplasma pneumonia are mostly nonspecific and variable. It is difficult to identify mycoplasma, bacterial and viral pneumonia in clinical practice [3, 4]. Typical symptoms of mycoplasma pneumonia include fever, cough, slight phlegm (fatigue, weakness and myalgia) and other non-specific manifestations, among which the most common symptoms and signs are lower respiratory tract fever, cough and rales [5]. If it is not treated in time, it can give rise to serious pulmonary

diseases, complicated cardiovascular system and nervous system damage, hematuria, hemolytic anemia and other multi-system multi-organ diseases [6]. At present, the pathogenesis of mycoplasma pneumonia has not been clearly defined, and some scholars have reported that immune dysfunction may become its pathogenic factor [7]. When mycoplasma pneumoniae infection occurs in a patient, the whole body of the patient presents an inflammatory stress state, and the response reaction of the body's immune system function is regulated by strengthening a series of pathological changes of pro-inflammatory and anti-inflammatory factors [8]. Therefore, early detection of pathogenic microorganisms inducing respiratory tract infection and comprehensive study of the changes of immune function in patients with mycoplasma pneumoniae infection have impor-

tant significance in clinical analysis of the onset, control and treatment of mycoplasma pneumonia.

Complement and immunoglobulin (Ig) are important substances in the body to complete immunoregulation reactions. Complement is involved in the process of local tissue damage after infection with virus and mycoplasma by intervening inflammatory response and immune response. Ig directly eliminates mycoplasma by participating in the body's humoral immune response [9, 10]. Relevant reports [11, 12] show that cytomegalovirus antibody detection is generally used for early infection detection, and the detection items mainly include IgM antibody, IgA and IgG antibody, among which IgM antibody exists from the initial infection to the end of infection. IgA has the function of immune barrier in the epithelial tissue of respiratory tract, and can be reflected by the expression of IgG antibody in acute infection. The activation of serum complement C3 and C4 in different pathways can directly affect the immune response of the body [13]. However, the diagnostic value of the combined detection of the above indicators for mycoplasma pneumonia has not been clearly defined. Therefore, in this paper, the diagnostic efficacy of the combined detection of Ig and complement C3 and C4 in patients with mycoplasma pneumonia was reviewed and analyzed, so as to explore a more efficient and accurate diagnostic scheme for mycoplasma pneumonia.

Materials and methods

General data

Totally 114 patients with mycoplasma pneumonia hospitalized in our hospital from November 2015 to April 2018 were selected and enrolled in the disease group. Among them, 52 patients with mild to moderate mycoplasma pneumonia in the disease group were set as the mild to moderate mycoplasma pneumonia group, and 62 patients with severe mycoplasma pneumonia were considered as the severe mycoplasma pneumonia group. And 80 healthy subjects undergoing physical examination were enrolled in the control group.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients were diagnosed as mycoplasma pneumonia according to their own symptoms, signs, etiology, chest X-ray ex-

amination and other results, all of which met the diagnostic criteria for mycoplasma pneumonia [14]. (2) Mycoplasma pneumonia patients with antibody titer ≥ 1:160. (3) Patients met the condition of complete clinical data. Exclusion criteria: (1) Patients with lung diseases other than pneumonia. (2) Patients with congenital heart disease. (3) Patients with hypoxic-ischemic encephalopathy or cerebrovascular disease. The content of this research was approved by the ethics committee of our hospital. All the research subjects were informed of the research process and projects and signed informed consent forms.

Research methods

In this study, the serum complement levels of C3 and C4 were detected by immune scatter turbidity, and the Ig index levels were detected by immunoturbidimetry. American Beckman Kurt IM-MAGE 800 protein analyzer and its supporting reagents were used. Five ml of fasting venous blood was collected from the patient in the morning, and the serum was centrifuged at 1500×g, and stored at -20°C to be tested. Easy One pulmonary function instrument manufactured by NDD (USA) was used to measure the forced expiratory volume in 1 second (FEV1) and FEV1/forced vital capacity (FVC) in patients with mycoplasma pneumonia of different degrees. Each index was tested at least 3 times to optimize the best results.

Outcome measures

(1) The levels of serum complement, IgA, IgM and IgG in each group of patients were compared and observed. (2) The changes of pulmonary function in patients with different pathological changes were compared. (3) Spearson method was used to analyze the correlation of IgM, IgA, IgG, C3 and C4 levels with pulmonary function of patients with mycoplasma pneumonia. (4) The diagnostic significance of combined detection of serum complement, IgA, IgM and IgG levels between healthy persons and patients with mycoplasma pneumonia was analyzed. (5) The diagnostic significance of combined detection of serum complement, IgA, IgM and IgG levels in patients with different pathological change was analyzed.

Statistical analysis

The statistical software SPSS 20.0 was used for data analysis. The measurement data were

Table 1. Comparison of general data between the two groups

Group	Control group (n=80)	Disease group (n=114)	X^2/t	p
Gender (case)			0.051	0.821
Male	46 (57.50)	67 (58.77)		
Female	34 (42.50)	47 (41.23)		
Age (years)	36.95±26.95	37.32±28.14	0.092	0.927

Table 2. Comparison of IgM, IgA, IgG, complement C3 and C4 Levels in the two groups (g/L)

Group	IgM	IgA	IgG	Complement C3	Complement C4
Control group (n=80)	1.16±0.43	1.26±0.95	8.82±2.18	1.15±0.65	0.31±0.11
Disease group (n=114)	1.61±0.52	0.67±0.39	10.87±2.37	2.03±1.12	0.45±0.19
t value	6.362	5.959	6.128	6.318	5.927
P value	<0.001	<0.001	<0.001	<0.001	<0.001

Table 3. Comparison of serum IgM, IgA, IgG, complement C3 and C4 levels in patients with different diseases (g/L)

Group	IgM	IgA	IgG	Complement C3	Complement C4
Mild to moderate mycoplasma pneumonia group (n=52)	1.39±0.48	0.69±0.44	9.35±2.16	1.69±0.70	0.34±0.15
Severe mycoplasma pneumonia group (n=62)	1.78±0.53	0.38±0.26	11.34±2.21	2.11±0.84	0.52±0.23
t value	4.084	4.663	4.838	2.866	4.844
P value	<0.001	<0.001	<0.001	0.005	<0.001

expressed as mean ± standard deviation, and the comparison was conducted by T test. The correlation between FEV1/FVC and each detection index in this paper was detected and analyzed by Spearman method. ROC was used to draw the curve of diagnostic value of Ig and complement C3 and C4 combined detection in mycoplasma pneumonia. Graphpad Prism8 was used to draw the picture in this experiment. P<0.05 was considered statistically significant difference.

Results

Comparison of general data between the two groups

There was no statistically significant difference in gender and age between the two groups (P>0.05). See **Table 1** for details.

Comparison of IgM, IgA, IgG, complement C3 and C4 levels in the two groups

The serum levels of IgM (1.61±0.52), IgG (10.87±2.37), complement C3 (2.03±1.12) and C4 (0.45±0.19) in the disease group were significantly higher than those in the control group (IgM (1.16±0.43), IgG (8.82±2.18), comple- ment C3 (1.15±0.65) and C4 (0.31±0.11)), but the level of IgA (0.67±0.39) in the disease group was significantly lower than that in the control group (1.26±0.95), with statistically significant differences (P<0.05). See **Table 2** for details.

Comparison of IgM, IgA, IgG, complement C3 and C4 levels in patients with different severity of mycoplasma pneumonia

The serum levels of IgM (1.78±0.53), IgG (11.34±2.21), complement C3 (2.11±0.84) and C4 (0.52±0.23) of patients in the severe mycoplasma pneumonia group were significantly higher than those in the mild to moderate mycoplasma pneumonia group (IgM (1.39±0.48), IgG (9.35±2.16), complement C3 (1.69±0.70) and C4 (0.34±0.15)), and IgA level (0.38±0.26) in severe mycoplasma pneumonia group was significantly lower than those in the mild to moderate mycoplasma pneumonia group (0.69±0.44) (P<0.05). See **Table 3** for details.
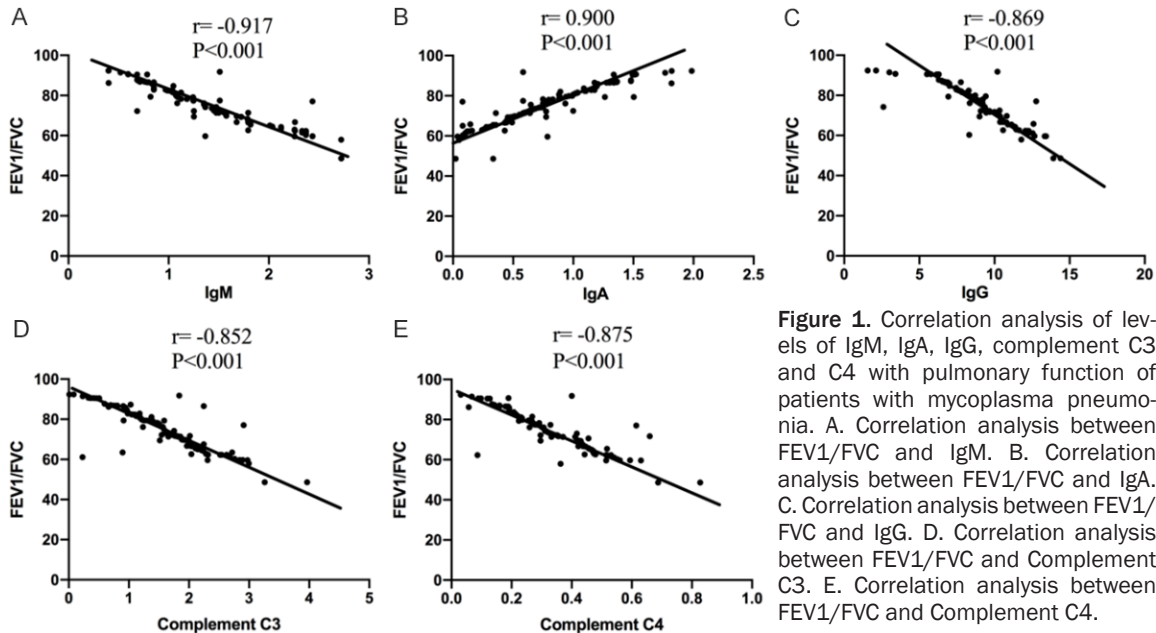
Pulmonary function test results of each group

The predicted values of FEV1/FVC and FEV1% in the severe mycoplasma pneumonia group

Table 4. Pulmonary function test results of each group

Group	FEV1/FVC (%)	FEV1 (%)
Mild to moderate mycoplasma pneumonia group (n=52)	75.54±8.73	86.93±9.12
Severe mycoplasma pneumonia group (n=62)	64.37±9.10	75.64±8.93
t value	6.649	6.658
P value	<0.001	<0.001

Figure 1. Correlation analysis of levels of IgM, IgA, IgG, complement C3 and C4 with pulmonary function of patients with mycoplasma pneumonia. A. Correlation analysis between FEV1/FVC and IgM. B. Correlation analysis between FEV1/FVC and IgA. C. Correlation analysis between FEV1/FVC and IgG. D. Correlation analysis between FEV1/FVC and Complement C3. E. Correlation analysis between FEV1/FVC and Complement C4.

were 64.37±9.10 and 75.64±8.93, respectively, which were significantly lower than those in the mild to moderate mycoplasma pneumonia group ((75.54±8.73) and (86.93±9.12), respectively) (P<0.05). As shown in **Table 4**.

Correlation analysis of levels of IgM, IgA, IgG, complement C3 and C4 with pulmonary function of patients with mycoplasma pneumonia

The changes of the predicted values of FEV1/FVC and FEV1% were consistent with the development trend of lung function. One of FEV1/FVC was selected to represent the development trend of lung function, and Spearson method was applied to detect and analyze the correlation between FEV1/FVC. It was found that the levels of serum IgM, IgG, complement C3 and C4 in patients with mycoplasma pneumonia were negatively correlated with their pulmonary function (r=-0.917, -0.869, -0.852, -0.875, P<0.001), and IgA level was positively correlated with their pulmonary function (r=0.900, P<0.001). More details were shown in **Figure 1**.
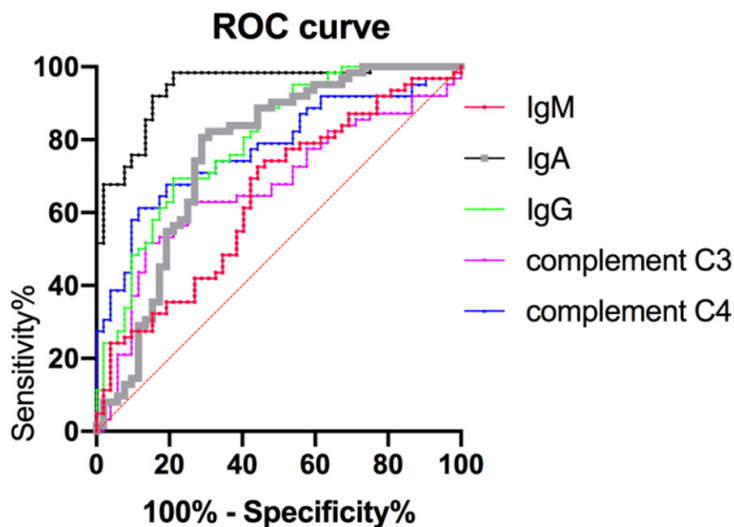
Analysis of diagnostic efficacy of individual and combined detection of each index for patients with mycoplasma pneumonia

AUC of patients with mycoplasma pneumonia detected by IgM was 0.738, with 95% CI of 0.669 to 0.807. AUC of patients with mycoplasma pneumonia detected by IgA was 0.675, with 95% CI of 0.592 to 0.757. AUC of patients with mycoplasma pneumonia detected by IgG was 0.741, with 95% CI of 0.670 to 0.812. AUC of patients with mycoplasma pneumonia detected by complement C3 was 0.781, with 95% CI of 0.717 to 0.845. AUC of patients with mycoplasma pneumonia detected by complement C4 was 0.786, with 95% CI of 0.722 to 0.850. AUC of patients with mycoplasma pneumonia detected by combination of IgM, IgA, IgG and complement C3 and C4 was 0.939, with 95% CI of 0.908 to 0.970. Through comparative analysis of combined detection and individual detection, the AUC of patients with combined detection of various indicators for mycoplasma pneumonia was higher than that of patients with
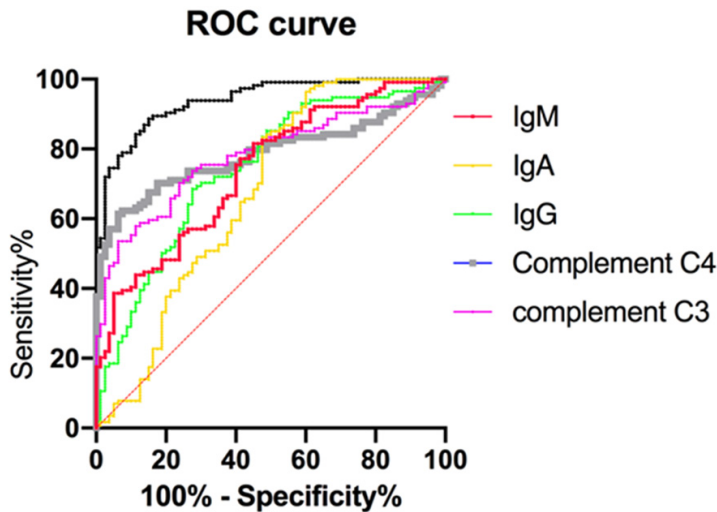
Figure 2. Analysis of diagnostic efficacy of individual and combined detection of each index for patients with mycoplasma pneumonia.

Figure 3. Analysis of diagnostic efficacy of individual and combined detection of each index for patients with severe pneumonia and mild to moderate pneumonia.

individual detection of each index (P<0.05). See **Figure 2**.

Analysis of diagnostic efficacy of individual and combined detection of various indicators for patients with severe pneumonia and mild to moderate pneumonia

AUC of patients with different severity mycoplasma pneumonia detected by IgM, IgA and IgG were 0.642, 0.762, and 0.799, respectively, with 95% CI of 0.540 to 0.744, 0.669 to 0.856, and 0.718 to 0.880, respectively. AUC

of patients with different severity mycoplasma pneumonia detected by complement C3 and C4 were 0.669 and 0.775, respectively, with 95% CI of 0.568 to 0.770 and 0.690 to 0.861, respectively. AUC of patients with mycoplasma pneumonia of different severity detected by IgM, IgA, IgG and complement C3 and C4 was 0.942, with 95% CI of 0.901 to 0.983. More details were shown in **Figure 3**.

Discussion

Mycoplasma is common in nature and can be colonized in human oral cavity and respiratory tract. Mycoplasma pneumonia is a common pathogen of respiratory tract infection without cell wall [15, 16]. The pathological changes of mycoplasma pneumonia are mostly inflammatory manifestations between bronchioles and interstitium. When mycoplasma proliferates in the body, it can deposit in the lung tissues and the basement membrane of blood vessels in combination with humoral immune factors. A series of immune responses promoted by the body's immune system against mycoplasma invasion stimulate T lymphocytes, monocytes and macrophages to mediate cellular immune responses, release a large amount of toxins to damage epithelial cells, affect ciliary movement of respiratory system, thus damaging the integrity of mucosal surface of respiratory system [17, 18]. The massive release of inflammatory medium covers alveolar capillaries, causing congestion-like edema in capillaries, increasing vascular permeability load, and the severity of exudation and infiltration of inflammatory cells in alveoli also increase [19-21]. Mycoplasma infection not only affects the respiratory system, but also affects the nervous system to a certain extent, which may cause damage to various tissues

and organs such as encephalitis, cranial nerve inflammation, bacterial meningitis and infectious cerebral infarction [22]. Studies on the pathogenesis of mycoplasma pneumonia have revealed that Ig is an important active substance involved in humoral immune response. After mycoplasma pneumonia infection occurs in the body, IgM, IgA and IgG are secreted and released into the blood by cells due to the induction effect, which changes the antigen structure of the body, leading to damage of the immune function of the body and multiple organs of the body [23, 24]. Complement C3 and C4 are the most common immunologically active substances in the complement activation pathway. Mycoplasma pneumonia infection can activate the body to promote the infiltration and activation of immune cells, and finally trigger autoimmune injury to the body [25]. The role of the above indicators in the body's immune function is elaborated in numerous studies. In order to understand its diagnostic value for mycoplasma pneumonia and in different severity of illness, we conducted experiments to discuss this purpose.

The comparative study of the changes of detection indexes in this experiment between normal subjects and patients with mycoplasma pneumonia showed that the serum IgM, IgG, complement C3 and C4 levels were higher and IgA levels were lower in patients with mycoplasma pneumonia. Mycoplasma pneumonia infection leads to the formation of immune complexes and a series of immune response reactions. It activates complement alteration and lysis (bacteria and cells) and other effects. Cell-mediated antibodies can exhibit cytotoxic effects and have the effect of killing and destroying infected target cells [26]. It has been observed in previous studies [27, 28] that the longer the illness duration and the more severe the disease in patients with mycoplasma, the more severe the lung consolidation. Detection of serum in patients with multiple extrapulmonary complications showed a decrease in Ig A, an increase in IgG, IgM and complement C3 and C4 contents, and the values return to normal at the recovery stage. It is consistent with the results of this study, suggesting that mycoplasma pneumonia influences the expression of Ig and complement through mediating cytotoxicity regulation. Further exploration of the experimental selection of detection indicators in

patients with mycoplasma pneumonia of different severity revealed that the levels of serum IgM, IgG and complement C3 and C4 in patients with severe mycoplasma pneumonia were notably higher than those in patients with mild to moderate mycoplasma pneumonia, and IgA levels were notably lower than those in patients with mild to moderate mycoplasma pneumonia. Previous studies have shown that [29] serum Ig levels in patients with mycoplasma pneumonia of different disease courses are different, and there is a significant correlation between malignant transformation of patients' diseases and serum Ig expression. Complement is a key macromolecular substance derived from liver cells to complete humoral immune response. It mainly acts on two aspects in vivo, one is to kill bacteria and viruses by dissolving Ig complexes, the other is to directly neutralize or dissolve viruses, and the total complement content is determined by the amount of virus in vivo [30]. The combined results suggest that Ig and complement C3 and C4 can be used as indicators to judge the severity of inflammatory response of mycoplasma pneumonia. In order to accurately observe the correlation between pulmonary function changes of patients with mycoplasma pneumonia and the detection indexes in the study, the correlation between pulmonary function and various indexes was analyzed, and it was found that the change trend of each index and the deterioration degree of pulmonary function showed similarities. Therefore, we draw pictures of the diagnostic efficiency and combined diagnostic efficiency of each index in mycoplasma pneumonia and draw a conclusion that the condition of patients with mycoplasma pneumonia can be detected under separate detection of each index, and the combined application of detection can improve the diagnostic efficiency and accuracy.

In conclusion, the expression of Ig and complement C3 and C4 in patients' serum has high diagnostic value for mycoplasma pneumonia, and can assist in judging the therapeutic effect of mycoplasma pneumonia patients. At present, in clinical practice, there have been related descriptions on the connection mechanism and diagnostic function between each detection index and mycoplasma pneumonia. In this study, we mainly analyzed the expression changes of each index when pulmonary func-

tion changes to understand the monitoring of each index by different lung function changes at multiple time points, and analyzed the change range of each index in the patient's body in real time to carry out targeted treatment and further disease judgment for mycoplasma patients. However, there are still some deficiencies in this experiment. Although data statistics and correlation analysis are carried out on pulmonary function, the change of lung function and the trend of each index in mycoplasma pneumonia were not analyzed to reduce errors in this experiment. This is the research direction of our follow-up inquiry to provide a more reliable diagnostic scheme for mycoplasma diagnosis and treatment.

Disclosure of conflict of interest

None.

Address correspondence to: Jin Li, Department of Medical Laboratory, Qijiang District People's Hospital of Chongqing, 4-22-4, Bishuilanwan, Wenlong Street, Qijiang District, Chongqing 400020, China. Tel: +86-17783265887; E-mail: lijin800316@163.com

References

[1] Kutty PK, Jain S, Taylor TH, Bramley AM, Diaz MH, Ampofo K, Arnold SR, Williams DJ, Edwards KM, McCullers JA, Pavia AT, Winchell JM, Schrag SJ and Hicks LA. Mycoplasma pneumoniae among children hospitalized with community-acquired pneumonia. Clin Infect Dis 2019; 68: 5-12.

[2] Wu PS, Chang LY, Lin HC, Chi H, Hsieh YC, Huang YC, Liu CC, Huang YC and Huang LM. Epidemiology and clinical manifestations of children with macrolide-resistant Mycoplasma pneumoniae pneumonia in Taiwan. Pediatr Pulmonol 2013; 48: 904-911.

[3] Ma X, Ding MJ, Zhao XX, Sun J, Yang JZ and Han YL. Features of lung dysfunction in children with Mycoplasma pneumoniae pneumonia with different chest imaging findings. Zhongguo Dang Dai Er Ke Za Zhi 2014; 16: 997-1000.

[4] Zhong MF and Zhao JM. Diagnostic values of plasma CD64 and sTREM-1 for pediatric pneumonia. Zhongguo Dang Dai Er Ke Za Zhi 2016; 18: 599-602.

[5] Ficko C, Andriamanantena D, Flateau F, Mangouka L, Soler C, Carmoi T and Rapp C. Mycoplasma pneumoniae: a cause of febrile hemolytic anemia in travelers. Med Sante Trop 2012; 22: 344-345.

[6] Ding Y, Chu C, Li Y, Li G, Lei X, Zhou W and Chen Z. High expression of HMGB1 in children with refractory Mycoplasma pneumoniae pneumonia. BMC Infect Dis 2018; 18: 439.

[7] Sun H, Chen Z, Yan Y, Huang L, Wang M and Ji W. Epidemiology and clinical profiles of Mycoplasma pneumoniae infection in hospitalized infants younger than one year. Respir Med 2015; 109: 751-757.

[8] Matsunaga M, Kodama Y, Maruyama S, Miyazono A, Seki S, Tanabe T, Yoshimura M, Nishi J and Kawano Y. Guillain-Barre syndrome and optic neuritis after Mycoplasma pneumoniae infection. Brain Dev 2018; 40: 439-442.

[9] Gunn BM, Jones JE, Shabman RS, Whitmore AC, Sarkar S, Blevins LK, Morrison TE and Heise MT. Ross River virus envelope glycans contribute to disease through activation of the host complement system. Virology 2018; 515: 250-260.

[10] Sarathchandran P, Al Madani A, Alboudi AM and Inshasi J. Mycoplasma pneumoniae infection presenting as stroke and meningoencephalitis with aortic and subclavian aneurysms without pulmonary involvement. BMJ Case Rep 2018; 2018: bcr2017221831.

[11] Kim YH, Lee J, Kim YE, Chong CK, Pinchemel Y, Reisdorfer F, Coelho JB, Dias RF, Bae PK, Gusmao ZPM, Ahn HJ and Nam HW. Development of a rapid diagnostic test kit to detect IgG/IgM antibody against Zika virus using monoclonal antibodies to the envelope and non-structural protein 1 of the virus. Korean J Parasitol 2018; 56: 61-70.

[12] Renegar KB, Small PA, Jr., Boykins LG and Wright PF. Role of IgA versus IgG in the control of influenza viral infection in the murine respiratory tract. J Immunol 2004; 173: 1978-1986.

[13] Ding Y, Chu C, Li Y, Li G, Lei X, Zhou W and Chen Z. High expression of HMGB1 in children with refractory Mycoplasma pneumoniae pneumonia. BMC Infect Dis 2018; 18: 439.

[14] Jin X, Zou Y, Zhai J, Liu J and Huang B. Refractory Mycoplasma pneumoniae pneumonia with concomitant acute cerebral infarction in a child: a case report and literature review. Medicine (Baltimore) 2018; 97: e0103.

[15] Weitzman CL, Tillett RL, Sandmeier FC, Tracy CR and Alvarez-Ponce D. High quality draft genome sequence of Mycoplasma testudineum strain BH29 (T), isolated from the respiratory tract of a desert tortoise. Stand Genomic Sci 2018; 13: 9.

[16] Principi N and Esposito S. Macrolide-resistant Mycoplasma pneumoniae: its role in respiratory infection. J Antimicrob Chemother 2013; 68: 506-511.

[17] Baloira A, Xaubet A, Rodriguez Becerra E, Romero AD, Casanova A and Ancochea J.

Desquamative interstitial pneumonia and respiratory bronchiolitis-associated interstitial lung disease: data from the Spanish patient registry. Arch Bronconeumol 2008; 44: 499-503.

[18] Deutscher AT, Jenkins C, Minion FC, Seymour LM, Padula MP, Dixon NE, Walker MJ and Djordjevic SP. Repeat regions R1 and R2 in the P97 paralogue Mhp271 of Mycoplasma hyopneumoniae bind heparin, fibronectin and porcine cilia. Mol Microbiol 2010; 78: 444-458.

[19] Porter DW, Wolfarth M, Young SH, Rao MK, Meighan T, Barger M, Andrew ME and Huffman LJ. PGJ2 inhibition of LPS-induced inflammatory mediator expression from rat alveolar macrophages. J Toxicol Environ Health A 2007; 70: 1967-1976.

[20] Guo L, Akahori H, Harari E, Smith SL, Polavarapu R, Karmali V, Otsuka F, Gannon RL, Braumann RE, Dickinson MH, Gupta A, Jenkins AL, Lipinski MJ, Kim J, Chhour P, de Vries PS, Jinnouchi H, Kutys R, Mori H, Kutyna MD, Torii S, Sakamoto A, Choi CU, Cheng Q, Grove ML, Sawan MA, Zhang Y, Cao Y, Kolodgie FD, Cormode DP, Arking DE, Boerwinkle E, Morrison AC, Erdmann J, Sotoodehnia N, Virmani R and Finn AV. CD163+ macrophages promote angiogenesis and vascular permeability accompanied by inflammation in atherosclerosis. J Clin Invest 2018; 128: 1106-1124.

[21] Takimoto K, Kawashima N, Suzuki N, Koizumi Y, Yamamoto M, Nakashima M and Suda H. Down-regulation of inflammatory mediator synthesis and infiltration of inflammatory cells by MMP-3 in experimentally induced rat pulpitis. J Endod 2014; 40: 1404-1409.

[22] Jin X, Zou Y, Zhai J, Liu J and Huang B. Refractory Mycoplasma pneumoniae pneumonia with concomitant acute cerebral infarction in a child: a case report and literature review. Medicine (Baltimore) 2018; 97: e0103.

[23] Fan Q, Gu T, Li P, Yan P, Chen D and Han B. Roles of T-cell immunoglobulin and mucin domain genes and toll-like receptors in wheezy children with mycoplasma pneumoniae pneumonia. Heart Lung Circ 2016; 25: 1226-1231.

[24] Kumar S, Garg IB, Sethi GR, Kumar S and Saigal SR. Detection of immunoglobulin M and immunoglobulin G antibodies to Mycoplasma pneumoniae in children with community-acquired lower respiratory tract infections. Indian J Pathol Microbiol 2018; 61: 214-218.

[25] Miklaszewska M, Zachwieja K, Drozdz D, Pallinger E, Takacs B, Szilagyi A, Csuka D and Prohaszka Z. Hemolytic uremic syndrome with Mycoplasma pneumoniae infection and membrane cofactor protein mutation - case report. Przegl Lek 2016; 73: 862-864.

[26] Gao M, Wang K, Yang M, Meng F, Lu R, Zhuang H, Cheng G and Wang X. Transcriptome analysis of bronchoalveolar lavage fluid from children with mycoplasma pneumoniae pneumonia reveals natural killer and T cell-proliferation responses. Front Immunol 2018; 9: 1403.

[27] Dong Y, Lv W and Lin Z. Value of serum Mycoplasma pneumoniae immunoglobulin in the diagnosis of mycoplasma-related pneumonia in newborns. Exp Ther Med 2018; 16: 1036.

[28] Beersma MF, Dirven K, van Dam AP, Templeton KE, Claas EC and Goossens H. Evaluation of 12 commercial tests and the complement fixation test for Mycoplasma pneumoniae-specific immunoglobulin G (IgG) and IgM antibodies, with PCR used as the "gold standard". J Clin Microbiol 2005; 43: 2277-2285.

[29] Ryan LJ, Bowman R, Zantek ND, Sherr G, Maxwell R, Clark HB and Mair DC. Use of therapeutic plasma exchange in the management of acute hemorrhagic leukoencephalitis: a case report and review of the literature. Transfusion 2007; 47: 981-986.

[30] Whitington PF, Vos MB, Bass LM, Melin-Aldana H, Romero R, Roy CC and Alvarez F. Humoral immune mechanism of liver injury in giant cell hepatitis with autoimmune hemolytic anemia. J Pediatr Gastroenterol Nutr 2014; 58: 74-80.