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Recent Progress of the Membrane Palmitoylated Protein (MPP)

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Abstract. Mycoplasma pneumoniae (MP) is a common pathogen that causes acquired pneumonia. MPP is a relatively common respiratory disease, which can be spread through droplets and direct contact in crowded environments. Smokers, infants and people with low immunity are high-risk groups, and the incidence of MPP is increasing year by year under the influence of environmental factors and impaired immune function. Understanding its pathogenesis and identifying predictive biomarkers, while assisting blood or imaging tests, is one of the hot spots of clinicians' attention. At the same time, comprehensive measures should be adopted for the treatment of MPP, because although the disease is often considered to be a self-limiting disease, with the in-depth study of the disease, it is found that drug-resistant mycoplasma pneumoniae strains are gradually increasing, the incidence of severe or refractory mycoplasma pneumoniae pneumonia is also increasing, and the difficulty of clinical treatment is also increasing. This text will talk about the history of MMP and the common symptoms and signs associated with the infection, including cough, fever, sore throat, fatigue, and other respiratory symptoms. Also, it covers the diagnostic methods used to identify MMP. Finally,this paper discuss the efficacy of different treatment options, including antibiotics commonly used to treat MMP, covering the safety of these treatments, including any potential side effects or contraindications. Additionally, it explores the potential resistance of MMP to different antibiotics and how this resistance might affect treatment outcomes.

Keywords: Mycoplasma pneumoniae; diagnose; drug resistance; treatment.

1. Introduction

Mycoplasma pneumoniae(MP) is a very small cell which has no cell wall and belongs to class Mollicutes. It is one of the most common pathogens of the community-acquired pneumonia, which accounting for 10%-40% of community-acquired pneumonia, and up to 70% in partially enclosed populations [1,2]. The disease is more common in children and adolescents over 5 years old, and can cause pulmonary complications such as pneumonia, atelectasis, pleural effusion, and extrapulmonary complications such as liver injury and toxic encephalopathy.

Mycoplasma pneumoniae pneumonia (MPP) is caused by MP infection. The clinical manifestations are fever and cough, which can induce acute asthma attack. The early symptoms are not typical, and it is easy to progress to severe and refractory mycoplasma pneumoniae pneumonia. Some severe and refractory cases may be combined with serious internal and external pulmonary complications, such as respiratory failure, cardiac insufficiency, dizziness, coma, and consciousness disorders, which increase the difficulty of clinical treatment [3].

Global mycoplasma pneumoniae infections occur every few years in a regional outbreak, an outbreak that lasts about 1 or 2 years. In the early 21st century, relatively large pneumonia outbreaks occurred in Asia and Europe, with a small peak in June to July 2023, while in China, there was a slight decline in August. With the arrival of the school season in September, its incidence has begun to show an upward trend, and there are different high incidence reports in different places. For example, in Beijing, the data show that the detection rate of MP positive among outpatient patients is as high as 1/4, inpatient patients are close to 50%, and respiratory patients are more than 60%. But the cause of this outbreak is not entirely clear [4].

How to detect severe and critical cases early, treat them reasonably, and avoid death and sequelae are the core and key issues of MPP diagnosis and treatment. This article will introduce the historical development, clinical manifestations, pathogenesis, diagnosis and treatment of MPP, with the aim of

improving the understanding of clinicians (especially pediatricians) and radiologists on MPP, with a view to early identification and intervention.

2. History of MP

In 1898, Nocard and Roux identified a microbe thought to cause cattle pneumonia, calling it microbe de la peripneumonie. Similar microorganisms to the cattle pleuropneumonia organism (PPO) were later termed pleuropneumonia-like organisms (PPLO), with many found to cause pneumonias and arthritis in lower animals.

In 1944, the American scientist Eaton isolated the pathogen eventually known as mycoplasma pneumoniae from the sputum of patients with primary atypical pneumonia. Subsequent tests and laboratory studies in the 1950s and early 1960s provided more conclusive evidence that Mycoplasma pneumoniae could cause lower respiratory tract infections in humans, but at the time it was considered a viral infection until there was clear evidence that antibiotics could cure the disease caused by the pathogen [5].

By 1961, Robert Chanock studied the Eaton agent as a virus, sharing findings with Leonard Hayflick, who speculated it might be a mycoplasma. Hayflick isolated a mycoplasma strain from egg yolk, confirmed as the cause of PAP with Chanock. Emmy Klieneberger-Nobel suggested "Mycoplasma hayflickiae," but Hayflick preferred "Mycoplasma pneumoniae."

This tiny microorganism, first linked to a human disease, led to Hayflick receiving the prestigious Presidential Award from the International Organization of Mycoplasmology. The Smithsonian keeps the microscope pivotal to this discovery [6,7].

3. Clinical Presentation of MPP

Fever is one of the main symptoms of MPP and is usually moderate-to-high fever with a temperature of more than 38.5°C. Persistent high fever is a sign of severe disease. Some patients may be afebrile early in the course of the disease. Cough is also a prominent symptom of Mycoplasma pneumoniae pneumonia and is usually a paroxysmal irritating dry cough with little sputum and a more intense cough at night. Some patients may have a convulsive, pertussis-like cough. As the disease progresses, the cough may gradually worsen, the amount of sputum may increase, and even thick or blood-streaked sputum may be coughed. Sometimes patients have symptoms such as sore throat, headache, and otalgia. Some of the patients will also experience chest pain, which may be due to inflammation that irritates the pleura or lung tissue. Patients will feel hard to breathe which is called dyspnea. As the disease progresses, some patients may develop dyspnea, particularly in infants and in critically ill patients [3,8].

Due to MP has some common antigens with heart, lung, liver, brain, kidney and smooth muscle tissue, autoantibodies can be produced after infection, and immune complexes can be formed, and immune complexes and autoantibodies can show extrapulmonary manifestations.The main manifestations of infantile infection were mild liver enlargement, abnormal aminotransferase, diarrhea, vomiting and other liver or digestive tract symptoms. The main manifestations of cardiac damage were abnormal myocardial enzyme spectrum, less chest membrane, blood system, nervous system, skin and nervous system, mild symptoms, and no kidney damage. Cardiovascular involvement was more common in slightly older children (41.3%) and extrapulmonary manifestations were heavier than in infants. In addition to myocardial enzyme spectrum abnormalities, ECG abnormalities and arrhythmias may also occur. Pleura, blood system, nervous system, skin and kidney damage are more serious than that of infants and young children. In adults, the incidence of extrapulmonary manifestations is higher than that of bacterial pneumonia. Common symptoms include fatigue, joint myalgia, head pain, poor appetite, diarrhea, lethargy, rash, nausea, low back pain, and fatigue and joint myalgia are the most common [9,10].

4. Pathogenesis of MPP

The pathogenesis of MPP is not fully understood. At present, it is believed that there are two main mechanisms: direct MP injury and abnormal host immune response. MP invaded respiratory adhesion organelles and attached to the cell surface, causing direct damage to respiratory epithelium through the release of oxygen free radicals and community-acquired respiratory distress syndrome toxins. At the same time, MP can also use the host cell's glucose, amino acids and other nutrients to increase the host cell's oxygen consumption, resulting in the host cell's nutritional failure and death. MP's CARDS TX and other substances can destroy the cilia structure, resulting in slow or even stagnant cilia movement, airway secretions difficult to discharge, cough, wheezing and other symptoms; In addition, the abnormal immune response of the host to MP infection leads to immune damage of lung and extrapulmonary tissues through autoimmune reaction, allergic reaction, immune complex formation and other ways, resulting in the diversity of MPP clinical and imaging [11].For example, IL-35 is an immunosuppressive cytokine, mainly produced by regulatory T cells, which plays an important immunomodulatory role in some autoimmune diseases, tumors, inflammatory diseases and infectious diseases. Some studies have found increased IL-35 levels in children with acute MPP, but IL-35 levels in SMPP group are lower than those in normal MPP group, and IL-35 levels in both groups are decreased during recovery. In addition, it has been found that the serum IL-35 level is increased in children with MPP, and it is negatively correlated with the number of natural killer cells and neutrophil function. This suggests that IL-35, as an important immunomodulatory factor in the body, is involved in the occurrence and development of MPP, and has important significance in the evaluation of the severity of the disease [12].

5. Diagnostic Evaluation

Imaging tests are also commonly used in the evaluation. Chest x-ray and CT examination are important diagnostic tools. X-ray is a method using high-energy electromagnetic waves to produce images of human structures. The chest X-ray mainly showed lobular and lobular consolidation, interstitial infiltration and hilar lymph node enlargement. Because of its low radiation dose and convenient operation, chest radiography can be used for the diagnosis and follow-up of ordinary MPP patients and the follow-up observation of atelectasis absorption in MPP patients with atelectasis. However, due to the low tissue and density resolution of chest X-ray, the pathological changes of the terminal airway cannot be shown, and the specific nature, location and scope of lung lesions are limited, which is not suitable for the evaluation of severe MPP. Chest CT has high spatial and density resolution, and can clearly display the characteristics of lung lesions through reconstruction technology, and can show the mediastinum, lung, pleura and other conditions, and can clearly display the characteristic imaging signs, providing a reliable basis for clinical diagnosis, improving the sensitivity and specificity of diagnosis, and ultimately improving the diagnostic accuracy. The latest research shows that different imaging types have different clinical characteristics and have certain reference value for the prognosis of diseases [11,13].

The laboratory tests are also used in the diagnostic process. Serologic testing is a kind of laboratory test，MP-IgM antibodies are early antibodies that appear after MPP and can remain for 1-3 months or even longer after infection,which ≥1:160 can be used as a criterion for recent infection. A 4-fold or more increase in serum MP antibody titers in the course of the disease is also the basis for diagnosis. For children, their immune function is imperfect, their ability to produce antibodies is low, and low titer or false negative antibodies may appear, which affects the accuracy of diagnostic results. Therefore, other comprehensive considerations should be taken into account. MP culture is the "gold standard" for the diagnosis of MP infection, but the reproduction rate of MP is relatively slow, generally 1 to 6 hours will split a generation, difficult to early clinical diagnosis. There are also some methods called Pathogen nucleic acid detection，MP-DNA or MP-RNA positive has high sensitivity and specificity, making it suitable for early diagnosis. There are also several other detection methods including colloidal gold method, enzyme-linked immunoassay, fluorescence PCR method [7,13].

6. Treatment

Assessing the combined efficacy, safety, and resistance of treatment for MPP requires analysis from multiple perspectives, including drug selection, the effect of drug combinations, the incidence of adverse effects, and the risk of drug resistance.

Macrolide antibiotics are the drug of choice for the treatment of MPP, particularly azithromycin. Azithromycin is very permeable and has relatively high drug concentration persistence. During the metabolic process in the body, it may not pass the multifunctional oxidase, which can reduce liver toxicity and improve the clinical treatment safety of children. Several studies have shown that azithromycin has good efficacy in the treatment of pediatric MPP. A controlled study of 175 MPP patients matched with 120 healthy children found that azithromycin significantly increased microRNA-146a levels and reduced proinflammatory cytokine levels. miR-146a is a microrNA with anti-inflammatory effects discovered in recent years, which can reduce the production of inflammatory cytokines induced by Staphylococcus aureus infection and reduce tissue inflammatory damage. In this study, the serum level of miR-146a in MPP children was reduced. The down-regulation of miR-146a expression was involved in promoting the occurrence and development of MPP [14].

In another control study, 48 children with MMP were randomly divided into control group and observation group, 24 cases in each group. The control group was treated with erythromycin, and the observation group was treated with azithromycin sequential therapy. The efficacy, blood routine, serum indexes and incidence of adverse reactions of the two groups of children were compared and analyzed. Results The total effective rate of control group was lower than that of observation group (79.17% vs. 95.83%),$P < 0.05$; The improvement of serum levels of IL-6, IL-10 and TNF-α was more significant in the observation group. The percentage of white blood cells and lymphocytes was lower, the platelet and hemoglobin were higher, and the disappearance time of fever, cough and lung moist rales was shorter, and the P values were statistically different [15].

In recent years, Pudilan preparations and other Chinese patent medicines have played a good effect in the treatment of pneumonia, Pudilan Xiaoyan oral liquid treatment of children with mycoplasma pneumonia related studies reported that on the basis of azithromycin treatment, adding Pudilan can effectively improve the clinical efficacy, improve the signs and symptoms of children, and the treatment effect is more ideal. A meta-analysis included 63 RCT studies with a sample size of 6410 children and observed the effect of traditional Chinese medicine oral liquid combined with azithromycin. The results showed that the combination of Podilan anti-inflammatory and azithromycin had a better effect on the disappearance time of cough and fever（cough disappearance time (MD = -2.6, 95% CrI: -3.4 to -1.7) and fever disappearance time (MD = -1.8, 95% CrI: -2.3 to -1.3)）Pudilan itself has antipyretic, anti-inflammatory and antibacterial effects, among which Pudilan and isatis root play a prominent role in antiviral [16].

Even so, the gradual increase in resistance of MPP to macrolide antimicrobials has led to refractory treatment to conventional therapy in some patients. Drug resistance testing is mainly determined by measuring 23S rRNA gene mutations, but the drug resistance status detected is not completely consistent with clinical efficacy. Alternative medicines may be considered for drug resistance issues. For example, tetracyclines and quinolones are safe when used at recommended doses and durations but be aware of their potential adverse effects. Minocycline and doxycycline are effective in the treatment of MPP in children, but the benefits and harms need to be fully assessed and parental informed consent obtained.

For patients with severe or refractory Mycoplasma pneumoniae, glucocorticoids, such as methylprednisolone, can regulate the body's immune function and excessive immune response through genetic and non-genetic pathways, thus exerting anti-inflammatory effects, usually at a dose of 1- 2 mg/(kg · d), and the dose can be increased to 4~6 mg/(kg · d) if necessary, and the total course of treatment is generally not more than 14 days, but adverse effects need to be closely monitored

[17].The physiological dose can enhance the proliferation and activity of T cells, so as to further improve the immune function of children and reduce the damage of organs.

A Mate analysis found that the use of glucocorticoids reduced the length of hospital stay, reduced the duration of fever, and reduced post-treatment CRP levels. The specific course of use should be determined according to the outcome of the child's disease, and may also be related to the dose of hormones. Usually, the conventional dose of glucocorticoid is used for 3-5 days, and attention should be paid to the course of impact treatment. After symptoms improve, the drug should be stopped in time to reduce the occurrence of related adverse reactions. For most children, a course of 3 to 7 days can improve clinical symptoms, absorb lung signs, shorten hospital stay, and no obvious adverse reactions, but its specific mechanism of action is expected to be further clarified in future studies [18].

And the total effective rate of Qinbai Lung Clearing Formula combined with glucocorticoids in the treatment of MPP was higher than that of the control group, and it performed well in improving the expression of inflammatory factors, TLR2 and TLR4 mRNA [19].

7. Conclusion

In recent years, the proportion of MPP in respiratory infections has been increasing, and the reports of refractory and drug-resistant MPP have also gradually increased. The clinical and imaging manifestations caused by MPP are usually non-specific. Therefore, the protection of children under 5 years old should be strengthened, such as avoiding crowded public places and wearing masks when necessary. Kindergartens and other places should pay attention to ventilation and disinfection, avoid clustered infections, maintain good personal hygiene habits, pay attention to indoor ventilation, keep the air fresh and so on. In addition, molecular diagnostic technology has many advantages, with higher detection efficiency, sensitivity and specificity, can achieve early diagnosis, clinical application value is high. Macrolide antibacterial drugs are still the first choice recommended by the guidelines, and delayed use is a risk factor for MPP in severe and critical cases. At the same time, it can be combined with some traditional Chinese medicine preparations. In the future, it is necessary to further carry out evidence-based clinical research on the treatment of MPP in traditional Chinese medicine, further explore the mechanism of traditional Chinese medicine treatment, and formulate the diagnosis and treatment norms of integrated Chinese and Western medicine. In addition, China's disease surveillance is mainly aimed at infectious diseases clearly identified by the state, and MP has not been included in the national statutory surveillance scope. It is suggested to incorporate MP into the monitoring network of disease control and medical institutions at all levels, and use big data to establish artificial intelligence prediction models in order to predict epidemic trends more accurately

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