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Review Article

Mycoplasma pneumoniae as a causative agent in children having community acquired pneumonia

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ABSTRACT

This article deals with understanding the basis of *Mycoplasma Pneumoniae* by studying and understanding its functional modalities. The history along with cellular biology has been looked at for having a broader understanding. Even though the exact pathogenesis that causes these various symptoms are underway, it has been found that the constant rise in cases by this agent especially in children has raised a concern for more data regarding it for sufficient understanding of its incidence and target of more susceptible population. The epidemiology of *Mycoplasma pneumoniae* affecting children having community acquired pneumonia is poorly understood and there is a dire need for its in-depth evaluation. Due to all these factors the need to study about this agent has become all the more crucial and this article looks at the rapidity and rising nature of *M. pneumoniae* as a causative agent and what makes the young school going population of children a susceptibility. The aim of the study was to have an insight into the complex pathogenesis it elucidates along with the features seen in children affected. The understanding of its prevalence in children is also looked at so that various treatment options that are available can be established and can provide for the most appropriate remedy.

Keywords: *Mycoplasma pneumoniae*, Community acquired pneumonia, Children, Macrolides, Pathogenesis, Epidemiology

INTRODUCTION

The incidence estimates *M. pneumoniae* have risen exponentially and there is a need to update data on the various serological and diagnostic tests exclusively for *Mycoplasma pneumoniae* due to its prevalence in affecting children and causing respiratory infections leading to the pneumonia.

The objective of this study were to find out the incidence of *M. pneumoniae* as the primary pathogen in children having community acquired pneumonia and to explain various complications associated with it by describing the pathogenesis and epidemiology so that appropriate treatments can be undertaken.

HISTORY

Mycoplasma mycoides determined by Nocard and Roux in 1898 was the first mycoplasma to be cultured and identified which was then known as pleuropneumonia like organism (PPLO) which was first discovered by.[1] Later on it was identified by Dienes and Edsall in 1937 as the first mycoplasma from a gland infection in humans.[2] This mycoplasma that was isolated is suggested to be the organism that is now known as *Mycoplasma hominis*. The agent that is now known as *Mycoplasma pneumoniae* was first discovered by Monroe Eaton in1944 by culturing a sputum sample of an individual suffering from atypical pneumonia and hence was also called the Eaton agent.[3] In the mid nineteenth century, multiple tests and experiments conducted on volunteers and field studies provided solid

evidence that *Mycoplasma pneumoniae* was known to cause infection of the lungs in humans. However due to its morphology it was mistaken to be a virus which was proven wrong when evidence of antibiotics effectiveness was found much later. The term "mycoplasma" is derived from a Greek term that emerged in the 1950s where "myco" means fungus like and "plasma" denotes the variable plasticity of shape. The expression "mycoplasma" was framed due to its filament forming fungus growth that it exhibits but currently the growth of *M. mycoides* can only be described as similar. Nevertheless, the term was undertaken and still continues to be in use.[4]

CELL BIOLOGY

Mycoplasmas are the smallest microbes that undergo replication by self, in consideration to both cell structure and genome size.[4] They are related closely to gram-positive bacteria like *Streptococcus*, bacilli etc. A typical trait of mycoplasma species that is the small genome size is assumed to be due to the result of a progressive decrease in size that was ideally similar to gram-positive bacteria over the course of evolution through degeneration.[5] *M. pneumoniae* are seen to be spindle-shaped cells with length of 1-2 µm and width og 0.1-0.2 µm.[6] Mycoplasma are the smallest prokaryotic organisms that are known to be existing in nature. These cell wall lacking, flexible microbes can breed and proliferate *in vitro* in a cell-free system and pass-through various cell filters.[7]

Mycoplasma contains a genome of about a 600-1,350 kbp. There reproduction is predominantly via binary fission and its main characteristic is the ability to produce 'fried egg' appearance in media such as PPLO agar.[8] *M. pneumoniae* with its reduced genome as well as its restricted biochemical abilities is capable of multiple living features and necessities required for its culture *in vitro* using various supplementation mediums. The absence of a firm cell wall additionally causes these organisms to exhibit pleomorphism thus making it difficult to be categorised under the typical bacteria. Mycoplasmas are largely reliant on host cell for the production of numerous nutrients and hence are not found to be free living in nature. Another trait of Mycoplasma, seen in their growth using artificial media, is the requirement for sterols which are supplied by blood serum. Sterols are integral building blocks that make up the tri-layered cell membrane of Mycoplasma and helps in amplifying structural durability to its otherwise delicate nature.[6] *M. pneumoniae* also possess very limited biosynthetic activities for cellular events as compared to the typical bacteria.[4]

EPIDEMOLOGY

M. pneumoniae is known to occur in both higher and lower lung infections and is known to cause both endemic as well as epidemic manifestations worldwide. Even though tracheobronchitis is viewed as a more prevalent clinical feature, pneumonia is the most significant illness associated with *M. pneumoniae* infections. *M. pneumoniae* is recognised to cause about 4 to 8% of community-acquired bacterial pneumonias (CABP) especially during endemic periods. However, during epidemics, this agent can create a rise in CABP by 20 to 40% in the normal population, even growing to around 70% in close well knitted population.[9]

Along with community-acquired pneumonia, which produces principally lung infections, *M. pneumoniae* may also lead to various complications such as autoimmune haemolytic anaemia as well as other blood infections, circulatory system, intestinal tract and skin. It may lead to various other complications like pericarditis, myocarditis, nephritis and meningitis as well.[8] Spread of the disease to other systems of body excluding the lungs can occur and may be mainly due to autoimmune activation or leaking of infection into the bloodstream causing septicemia. Neurologic manifestations are also of importance as it can lead to diseases such as Guillain-Barré syndrome and acute encephalomyelitis. In some individuals, a syndrome of that involves the cutaneous mucosa and which closely resembles Stevens-Johnson syndrome is seen.[10]

When there is a marked dissimilarity in the original integration of the P1 adhesin it can be interpreted as a major cause of *M. pneumoniae* disease. The two variants of *M. pneumoniae* that are most often isolated from samples have certain alteration in their nucleotide sequencing and coding of P1 adhesin, although multiple subtypes have been distinguished over the years. The extensive growth period, fairly low rate of transmission along with the existence of the organism in the lung as well as the upper respiratory tract for long periods after being exposed are few of the reasons for the long prevalence of *M. pneumoniae* infections.[6]

PATHOGENESIS

M. pneumoniae binds to specialised ciliated cells seen along the epithelium of respiratory tract through inhalation route, with the help of an organelle especially for attachment through adherence. This property of cytadherence is known to help in gaining access to nutrients as well as to evade the immune response of the host. The adherence of *M. pneumoniae* to the surface of the host cell mainly is due to the sialic acid containing proteins and sulphated glycolipids. The gliding motility of *M. pneumoniae* which is essentially a function required for cell multiplication and extent of spread of infection is also a key factor in adherence onto the cell surface.[9] Along with this, the lack of a cell wall enables local interaction between the host cell and *M. pneumoniae*, thereby causing significant interchange of nutrients essential for the development and survival. Community-acquired respiratory distress syndrome (CARDS) toxin is an Adenosine diphosphate-ribosyl transferase, which acts similar to the pertussis toxin, causes binding of the organism to surfactant protein and causes entry into the cells by endocytosis (clathrin-mediated). The CARDS toxin then induces fragmentation of the nucleus and cilia

damage that activates release of inflammatory mediators such as cytokines and interleukins thereby precipitating an acute inflammatory response which leads to respiratory impairment.[10] The increase in chemokine mediators such as Interleukin-1-b, Interleukin-8, tumour necrosis factor-a (TNF-a) by alveolar type II pneumocytes in cases infected with *M. pneumoniae* supports the knowledge that the attachment to cells of respiratory epithelium leads to stimulation of cytokines which further leads to the release of inflammatory cells such as macrophages, lymphocytes and plasma cells which are modulated under the control of these cytokines.[11]

M. pneumoniae further causes stimulation of T and B lymphocytes that promotes production of antibodies against the antigen by forming antigen-antibody complex with host tissues. Most of the symptoms manifested of an acute inflammation that progresses to complications directed towards other systems are as a result of exacerbated inflammatory reaction and activation of immunopathogenic response by the host cell rather than the microbe.[10] Host cells due to attack by antibodies have damage to their cilia, seem vacuolated, and decrease their oxygen utilization as well as other cellular events such as glucose consumption, uptake of amino acid and protein biosynthesis which eventually results in apoptosis. Some of the persistent clinical symptoms of the respiratory tract infections such as dry, brassy cough are as a result of these occurrences.[12]

The different mechanisms of pathogenesis cannot be pointed towards one factor alone as it involves multiple aspects such as adhesion causing damage to the host cells, membrane fusion damage, depletion of nutrition, invasion into host cells, toxic damage, immune cells and excessive inflammatory cells activation. As recent efforts have focused more into looking into gene structure and sequencing of *M. pneumoniae*, there has been greater investigation at a molecular on the virulent factors of the membranous and adhesive proteins This development is not only helpful for assistance with the management course of infections of *M. pneumoniae*, but it can also provide better progression in the development of *Mycoplasma* vaccines that can further aid prevention of infection among high-risk population consisting of school going children and elderly.[8]

CLINICAL FEATURES IN CHILDREN

The clinical features of *M. pneumoniae* infection differs extensively among children. The most profound presentation is tracheobronchitis, that persists with dry or mucoid sputum containing cough. Numerous patients also present with nonspecific symptoms such as sore throat, headache, general malaise and rarely otitis media that ambiguously resembles that of mild upper respiratory tract infection. No lymphadenopathy or discharge is seen in patients with complaints of patients complaining of sore throat.[9] Children less than five years demonstrate symptoms such as wheezing and coryza wherein development into pneumonia is quite rare, while older children of five to fifteen years of age are most probable to form bronchopneumonia, usually involving more than one lobe that on progression might require hospitalization.[4] The most common manifestations such as fever and cough were seen in more than 96% children hospitalized with *M. pneumoniae* pneumonia.

The 65% tachypnoea and 11% hypoxia were found in children admitted to the ICU in a study based in Taiwan, China.[13] It was also found in a study conducted in Belgrade that symptoms such as cough, fever, headache and wheezing were more recurrent in children with *M. pneumoniae* infections when differentiated between children with non- *M. pneumoniae* infections.[14] In another study, *M. pneumoniae* pneumonia classically caused extended bouts of cough that persisted for a duration of 3 to 4 weeks in children and typically around 54 days in grown-ups.[15] Haemolytic anaemia is seen as a uncommon but uncompromising manifestation of mycoplasmal infection, that occurs more frequently in children as compared to adults and the reason to its severity is attributed to formation of cross-reacting cold agglutinins.[4] Occurrences of fatal cases of *M. pneumoniae* are uncommon and due to the pathogenesis, that is incompletely understood, onset of prolonged illness may lead to an exacerbated response manifesting in the lungs as due to an already weakened immune system due to exposure to prior infections. Eradication of the organism from the lungs proves to be difficult task due to the prolonged duration of infection which further activates the immune system finally leading to the macrophages and lymphocytes going into overdrive which will adversely affect the immunity response.[16]

PREVALENCY IN CHILDREN

In recent times there has been an awareness that children below the age of three years including infants are more vulnerable than usual and more prone to *M. pneumoniae* infection. In a study conducted in England and Wales there was a greater incidence in children between five to fourteen years of age and *M. pneumoniae* infection detected through polymerase chain reaction technique was found in children between four to fourteen years and was seen negative in children under four years.

During the study period of 2011-12, about 14.3% of children belonging to this age group were infected signifying that a minimum of one in seven children with pulmonary symptoms were infected with *M. pneumoniae*.[17] In another study based off in Lyon, France, the cases of *M. pneumoniae* with polymerase chain reaction test positive had ascended from 7.1% in 2009 to 14.8% during 2010 and 2011 in children aged five to fifteen years.[18] The proportion of *M. pneumoniae*-positive cases was correlating to a study conducted in Denmark, where there was a rapid rise in polymerase chain reaction positive tests from 3% to 15% in the year 2010.[19] Similar evidence seen in Finland showed 8-17% positive cases for

M. pneumoniae in the year 2010 and 2011 which mainly used serology methods for detection.[20] A percentage of 23% in 2006 and 2010 showed that the proportion of detection of *M. pneumoniae* by polymerase chain reaction was seen to be maximum in Sweden.[21] A spike in the rates in Denmark demanded a study to be conducted wherein around 18% of the children tested positive out of which the highest rate of *M. pneumoniae* infections were seen in school going children (65%), notably increased in preschool children (30%) and slightly increased in infants (4%).[22] A one year study was conducted in All India Institute of Medical Sciences(AIIMS) to understand the incidence of *M. pneumoniae* on 62 children admitted with community acquired pneumonia after serological detection showed seventeen (27.4%) positive cases indicating that *M. pneumoniae* has a substantial role in causing community acquired pneumonia in children and infants.[23]

ROLE IN ASTHMA

A leading cause of exacerbation of already existing respiratory diseases such as asthma following exposure of *M. pneumoniae* is the release of proinflammatory chemical mediators such as cytokines.[4] In a study conducted in 1973 to assess the corelation, it was first seen that infection with M. pneumoniae can be a possible pathogenesis for asthma.[24] The queries raised are whether *M. pneumoniae* is a principal source of asthma or does mycoplasma infection act as a predisposing factor by having a role to play as a cofactor in its development. *M. pneumoniae* is seen to be detected more often by polymerase chain reaction and culture methods from the samples of patients with long, steady asthma than from the patients that act as control group. Detection of *M. pneumoniae* was seen by polymerase chain reaction method in sputum samples of about ten out of eighteen stable adult patients with asthma while only one case was detected out of eleven healthy controls. In an alternative study observed, throat swabs sent for culture showed positive results of *M. pneumoniae* for about 24.7 % of individuals when compared to the 5.7% positives seen in healthy controls.[4] Various tests such as nucleic acid amplification tests (NAATs) and antigen capture assays for the CARDS toxin have been used in various studies and have helped in establishing the incidence of *M. pneumoniae* in chronic asthma.[10] Even though there has been various studies and experiments conducted that supports this speculation regarding an undetected link between M. pneumoniae and asthma there needs to be more controlled studies and evidence conducted to substantially solidate this matter.

TREATMENT

The guidance behind the treatment of *M. pneumoniae* infections that varies from one individual to another relies heavily on the established and dependable susceptibilities to certain drugs that belongs to the chemotherapeutic classes such as macrolides, tetracyclines and fluoroquinolones that are usually used in the form of oral administration.

Macrolides are ideally relied to be the drug of choice for *M. pneumoniae* infections in children.[4] Management of organ infiltrated infections caused by *M. pneumoniae* that have extra pulmonary manifestations by using antimicrobials can be quite tough, especially in individuals who are immunocompromised or have certain antibody deficits.[6] Due to the sudden rise in resistance against macrolide antibiotics by *M. pneumoniae* there has been lookout for alternative drugs. Tetracyclines and fluoroquinolones show certain clinical advantages such as decreasing the duration of symptoms exhibited as well as faster recovery and has been of significance in numerous reports. However, due to the toxicity damage, it raises safety issues and hence the ideal regimen of treatment should be chosen by weighing the pros and cons systematically.[25] It has been found that azithromycin in combination with glucocorticoids may be a good treatment option for children with macrolide-resistant *M. pneumoniae* pneumonia.[26]

CONCLUSION

As reviewed above there's been a clear establishment that *M. pneumoniae* is a leading causative agent in causing community acquired pneumonia in children and can lead to exacerbating symptoms if it is not diagnosed at an early stage. There have been various advancements in understanding the mechanisms and its role in affecting children due to technological progression. Therefore, the fact remains that even though there are various techniques that has evolved in diagnosing the diseases such as PCR, serology and cultures but the underlying pathogenesis is still deemed as complex and elucidating. The signs and symptoms appear as quite similar to a typical pneumonia that makes it difficult to distinguish from this particular pathogen. There is a need to perform more controlled studies and discussions so as to rely on more conclusive evidence. The treatment of *M. pneumoniae* causing pneumonia also requires more advancements as there has been increased resistance shown by the organism against macrolide antibiotics. Hence development of vaccines especially for high-risk population of children and elderly is in dire need.

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