

Leading Article

***Mycoplasma pneumoniae* infection in Sri Lanka**

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Introduction

Mycoplasma pneumoniae is the smallest organism that can be free living in nature. It is about 125-250 nm in size. About 60 species of mycoplasma have been identified but only *M pneumoniae*, *M hominis*, *M fermentans* and *M ovale* infect man. Of these *M pneumoniae* is the commonest.

M pneumoniae is a causative agent of community acquired pneumonia in children and adults^{1,2}. It was originally known as the Eaton agent, named after Monroe A. Eaton (1944) who described the organism as a filterable agent isolated from the sputum and lungs of patients with primary atypical pneumonia. In Sri Lanka, several cases of atypical pneumonia, reported by Prof. C. C. de Silva in 1953, had features compatible with mycoplasma pneumonia.

M pneumoniae infection is worldwide. Yearly about one per 1000 people in the United States experience mycoplasma pneumonia. The incidence of other upper and lower respiratory infections due to *M pneumoniae* is probably 10 times that of pneumonia. In some countries such as the United Kingdom and Denmark epidemics have been observed about every 4 years. In Sri Lanka it was found that this infection has a seasonal pattern, incidence being higher from November to April.

Mycoplasma infection commonly affects the respiratory tract. Other systems involved include central nervous system (CNS), cardiovascular system (CVS), locomotor system and urogenital system. It also gives rise to haematological manifestations. Several systems can be affected simultaneously. Uncommon manifestations include gastroenteritis, conjunctivitis, uveitis, hepatitis, Steven Johnson syndrome and acute urticaria.

No clinical studies on this infection have been carried out previously in Sri Lanka probably due to

an assumption by clinicians that the burden to the community due to mycoplasma infection was not significant. However, over the past few years the author has shown the high incidence of this infection by prospective analysis of respiratory infections and their complications in children. If clinicians are aware of these different presentations, it will be possible to prevent under diagnosis, prolonged hospital stay and even some of the lethal complications in children and adults infected with *M pneumoniae*.

Isolation of mycoplasma by culture is difficult and is not done routinely. *M pneumoniae* takes about 3 weeks to grow in a culture medium and hence it is not of much clinical use. Estimation of mycoplasma antibody levels is the currently accepted method of diagnosing this infection in most centres. Seroconversion occurs within 12-15 days of infection and peak antibody titre ranges from 1256 to 11,240. The confirmation of the presence of IgM by ELISA technique is diagnostic of infection. Estimation of both IgM and IgA is necessary for maximum detection of current infection³. Microparticle agglutination test, the commercially available serological test carried out in most laboratories, has 100% sensitivity and 96% specificity⁴. Gene probe test, which has 95% sensitivity and 85% specificity, is the best available test for the rapid diagnosis of *M pneumoniae* infection⁵.

Cold antibody formation is a known feature following mycoplasma infection. Anti-I formation is seen in *M pneumoniae* and *Listeria monocytogenes* infections and in systemic leishmaniasis⁶. Cold agglutinin test could be used in the diagnosis of acute infections with *M pneumoniae*. Positive predictive value of rapid cold agglutinin test was found to be 70%⁷. Cold agglutinin test can be done at any blood bank in this country and could be used as a screening test for *M pneumoniae* since serological tests are not freely available in most hospital laboratories in Sri Lanka. However, cold agglutinin formation is not found in every patient with mycoplasma infection and the latency of its appearance will hinder its value

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in acute infection. Presence of elevated cold agglutinin with the specific antibodies to mycoplasma almost certainly makes the diagnosis of acute infection.

Respiratory tract manifestations

M pneumoniae infection often has an insidious onset with malaise, myalgia, sore throat and headache followed by cough and other chest symptoms. A prolonged paroxysmal cough simulating whooping cough may be a feature in children. Respiratory tract manifestations include pharyngitis, sinusitis, otitis media, bronchitis, laryngotracheobronchitis, pneumonia (broncho, lobar & interstitial), lung abscess, adult respiratory distress syndrome, pleural effusion and necrotizing pneumonitis.

LRTI due to *M pneumoniae* are not uncommon in Sri Lanka. A study done by the author in children with respiratory tract infections presenting to the outpatient clinic during a 3 year period starting from November 1999 has shown that 23% of LRTI were due to *M pneumoniae*. Most of them were clinically diagnosed as having bronchopneumonia or acute bronchitis. Majority of mycoplasma positive children were above 4 years of age and presented from November to April showing a seasonal pattern in contrast to other countries. Insidious onset of cough, fever, headache, myalgia and malaise was a common feature. Lung signs such as crepitations, rhonchi and diminished air entry were not seen in most of the children. Chest x-ray showed features of typical interstitial pneumonia.

Pleural effusions due to *M pneumoniae* have been described in Sri Lanka. In a study by the author 4 of 19 patients with lobar pneumonia due to *M pneumoniae* had pleural effusions⁸. In these patients pleural aspirates were exudates. Pleural effusions are usually self limiting and resolve with anti-mycoplasma therapy. Nagayama et al found 56 patients with pleural effusions among 775 patients with mycoplasma infection⁹. Polymerase chain reaction (PCR) seems to be the best way to diagnose mycoplasma pneumonia pleural effusion¹⁰. However, in the absence of this facility, diagnosis could be made if the effusion is associated with high mycoplasma antibody titre.

Lung abscess formation¹¹ and adult respiratory distress syndrome¹² are rare complications of respiratory tract infection caused by *M pneumoniae*.

Neurological manifestations

M pneumoniae infection in the CNS is not uncommon and can give rise to a wide range of manifestations. CNS manifestations¹³ occur in one per 1000 patients with *M pneumoniae* infection including meningoencephalitis, aseptic meningitis, encephalitis, encephalomyelitis, acute cerebellitis, Guillain-Barre syndrome, acute hemiplegia, acute transverse myelitis, choreoathetosis, Hopkin syndrome (flaccid paralysis of limbs), Bell palsy, reversible parkinsonism and dystonia, and acute sensory neural deafness. Early diagnosis of some of these conditions would prevent serious consequences¹³.

Fever, headache, vomiting, photophobia, neck stiffness, positive Kernig sign and alteration of level of consciousness are the main clinical features of CNS infections due to *M pneumoniae*. The onset of symptoms is more insidious in mycoplasma infection than in bacterial infection.

Encephalitis is the most frequent manifestation but meningitis, polyradiculitis, acute cerebellitis and Guillain-Barre syndrome have also been reported. Very rarely, brainstem encephalitis is also caused by this infection¹⁴. CSF findings of children with *M pneumoniae* meningitis or meningoencephalitis are indistinguishable from that of viral infections and diagnosis is based on serological tests.

From January to December 2001, children presenting with features of CNS infection admitted to the university paediatric unit were investigated for the presence of acute *M pneumoniae* infection by particle agglutination test¹⁵. Eight of 35 children with CNS infection were due to *M pneumoniae*. Five of these children had meningoencephalitis while 3 had meningitis. Mycoplasma antibody titres of these 8 children ranged from 160 to 5120¹⁵.

Haematological manifestations

Haematological manifestations of *M pneumoniae* infection include autoimmune haemolytic anaemia, autoimmune thrombocytopenia and disseminated intravascular coagulation. Autoimmune haemolytic anaemia is due to cold antibody mediated immune haemolysis. Cold antibody formation is a well known feature following *M pneumoniae* infection. The predominant type of cold antibody seen following this infection is anti-I. Corticosteroids are used in the treatment of severe haemolytic anaemia due to *M pneumoniae*. Blood transfusions too will be required rarely.

Severe haemolytic anaemia due to this infection has been observed by the author in a 6 year old boy who presented with fever and cough of 25 days duration. On examination, the child was febrile, pale and dyspnoeic. He had pneumonia in the upper lobe of right lung.

Cardiovascular manifestations

Cardiovascular manifestations of *M pneumoniae* infection include myocarditis, pericarditis, pericardial effusion¹⁶, heart block¹⁷, vascular thrombosis and acute hypertrophic cardiomyopathy.

Joint and locomotor system manifestations

M pneumoniae infection is associated with polyarthritis, polyarthralgia and polymyositis¹⁸. Polyarthritis of mycoplasma origin could mimic acute rheumatic fever¹⁹. These patients commonly present from 5-12 years of age with fever and polyarthritis which may be migratory. Unlike in rheumatic fever, polyarthritis of mycoplasma origin is usually associated with a moderately high ESR and there is no neutrophil leucocytosis.

Renal manifestations

M pneumoniae can affect the kidneys and related structures as an isolated disease or as a part of multisystem infection. Clinical manifestations may be due to acute infection of the kidney and related structures or due to an immunological process. Renal manifestations include progressive glomerulonephritis, nephrotic syndrome, transient massive proteinuria, chronic renal failure due to cold agglutinin, acute interstitial nephritis, acute renal failure due to acute nephritis, haemoglobinuria or haemolytic uraemic syndrome, isolated haematuria, cystitis or urethritis.

Glomerulonephritis due to *M pneumoniae* could be due to an immunological process. It could lead to progressive glomerulonephritis²⁰. Patients may present with fever, oedema, oliguria and hypertension. This condition should be differentiated from acute post streptococcal glomerulonephritis which is the commonest cause of glomerulonephritis in children between 3-10 years of age seen in this country. Acute glomerulonephritis may be an isolated presentation of this infection or could be a part of systemic disease. Author published a case report of a five year old child presenting with acute glomerulonephritis, pneumonia and hepatitis due to *M pneumoniae*²¹.

Hepato-biliary manifestations

Mild hepatitis is not uncommon in mycoplasma infection. Acute acalculous cholecystitis complicating mycoplasma infection has been reported by Sugimota et al in 1997. According to Arav-Bogert (1995) cholestatic hepatitis could be the main manifestation of mycoplasma infection. Acute fulminant hepatic failure due to mycoplasma is a rare manifestation. Author reported a case of a 4 year old girl with acute fulminant hepatic failure due to *M pneumoniae*. She presented with fever 2 days and vomiting and developed hepatic encephalopathy the following day.

Treatment

M pneumoniae is a unicellular organism without a cell wall and drugs acting on cell wall such as penicillin have no place in management. Macrolide antibiotics are the drugs of first choice in the treatment of mycoplasma infection. Erythromycin, the first introduced macrolide antibiotic, is still being used in the treatment. With the introduction of new macrolide antibiotics such as clarithromycin, roxithromycin and azithromycin the choice has been changed to one of the newer drugs. Erythromycin seems to be as effective as clarithromycin since the minimum inhibitory dose required in both drugs was <0.008mg/L²² but according to Ishidak et al the minimum inhibitory concentration value for clarithromycin, roxithromycin and azithromycin was significantly lower than for erythromycin²³. Roxithromycin has an additional advantage because it gives very high tissue and blood levels after oral ingestion and has a long half life²⁴. Anti-mycoplasma activities of the new quinolones have been extensively studied in the past. Fifty strains of mycoplasma were tested for susceptibility to new quinolones and macrolides. Ciprofloxacin possessed most mycoplasmacidal activity, MBC 50 to MIC 50 ratios for macrolides were higher than that of the quinolones²⁵.

Author suggests the following guidelines for the management of mycoplasma infection.

- Mild mycoplasma infections should be managed with oral erythromycin.
- Patients with severe mycoplasma pneumonia such as lobar pneumonia with or without effusion should be treated with intravenous (IV) or oral clarithromycin. IV clarithromycin is known to cause thrombophlebitis. Thus, it has to

be given as an infusion after dilution or should be given into a central venous line.

- Ciprofloxacin is a better alternative to clarithromycin when IV therapy is required.
- Duration of therapy depends on the severity of disease. An average of 10 days is required to eradicate mycoplasma infection especially when systemic involvement is present.

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