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Mycoplasma pneumoniae infections in children

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SUMMARY Details are given of all serologically confirmed *Mycoplasma pneumoniae* infections in children referred to Bristol hospitals during an epidemic lasting 18 months. 44 children, many below school age, had lower respiratory infections. The majority had cough and malaise which had failed to respond to antibiotics given before referral. Chest *x*-rays showed no pathognomonic features: segmental or patchy consolidation was common; 3 cases had lobar consolidation. Cold agglutinins were raised in 9 out of 12 cases. In the majority of cases the total leucocyte count was normal and the absolute neutrophil count raised. Mean duration of symptoms was 4·2 weeks (range 1–16). Treatment with erythromycin or tetracycline appeared to have little effect in most cases. Seven nonrespiratory manifestations were seen in 6 children. These were meningitis (2 cases), Stevens-Johnson syndrome (4 cases, 1 case complicated by toxic epidermal necrolysis), and acute haemolytic anaemia (1 case).

Mycoplasma pneumoniae infections affect both the upper and lower respiratory tract and occur most frequently between the ages of 5 and 30 years (Couch, 1973). *M. pneumoniae* has been found to be an uncommon cause of pneumonia before school age (Foy *et al.*, 1970) and infections in this age group are usually mild (Fernald *et al.*, 1975). This paper gives details of all serologically confirmed *M. pneumoniae* infections in children, many below school age, referred to Bristol hospitals during a recent epidemic.

Manifestations of *M. pneumoniae* outside the respiratory tract are uncommon. Acute haemolytic anaemia (Barret-Connor, 1972), arthritis (Lambert, 1968), Stevens-Johnson syndrome (Cherry *et al.*, 1975), pericarditis (Grayston *et al.*, 1965), myocarditis (Grayston *et al.*, 1967), hepatitis (Murray *et al.*, 1975), meningitis, and other neurological disorders (Lerer and Kalavsky, 1973) have been described. Details of some of these unusual but serious manifestations are presented.

Patients and methods

Between September 1974 and March 1976, 45 children with *M. pneumoniae* infections were seen in Bristol hospitals. Diagnosis of *M. pneumoniae* infection was made if there was a single complement-fixing (CF) antibody titre to *M. pneumoniae* >1/256 together with clinical features of an *M. pneumoniae* infection, or if there was a more than fourfold rise in titre, or a falling titre in late convalescence. All serology is performed in the same laboratory, so we were able to obtain details of all *M. pneumoniae* infections in children referred to outpatient clinics or admitted to hospitals in Bristol. The population under 15 years directly served by these hospitals is approximately 168 000. No attempt was made to screen all children with lower respiratory tract infection and there was no surveillance of cases not referred to hospital.

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Forty-four children had *lower* respiratory tract infections; 40 had pneumonia confirmed by radiology, and the remaining 4 had bronchitis. 5 of the children with lower respiratory tract infections had significant nonrespiratory manifestations and one child had Stevens-Johnson syndrome and no pulmonary illness. Ages ranged from 16 months to 14 years. 18 children were aged under 5 years and 27 between 5 and 13 years. There were 28 males and 17 females (ratio 1·6:1).

Cases with lower respiratory tract involvement. Symptoms and signs of the 44 children with lower respiratory tract infections are shown in the Fig. Onset was usually insidious with cough, fever, and malaise. In some children symptoms began abruptly; with delirium in 3, acute breathlessness in 2, and pleuritic pain in 1. 6 children had an erythematous macular skin rash on the trunk and limbs, but this

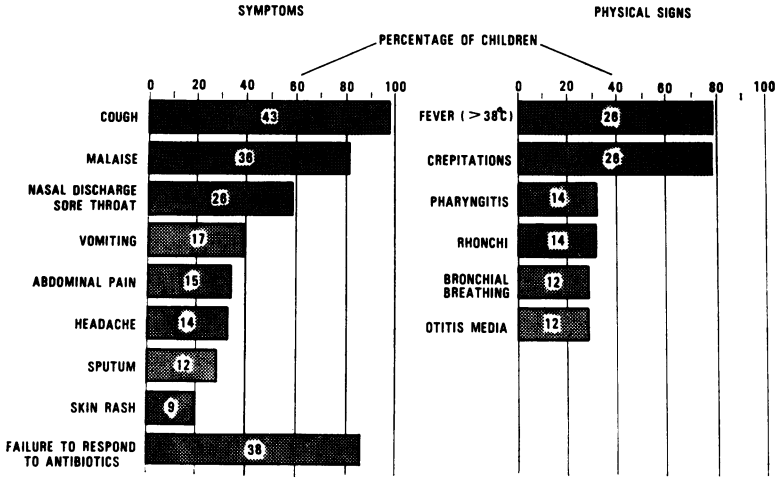

Fig. *Clinical features of 44 children with lower respiratory tract infections due to Mycoplasma pneumoniae.*

was usually fading at the time of referral. 36 children had been given antibiotics before referral, and 18 of those who failed to improve had been changed to a second antibiotic. In most children cough and malaise were the predominant symptoms. 12 older children produced sputum, which was yellow in 7 and white in the remainder. One child, aged 8, had a paroxysmal cough, whooping, and vomiting, consistent with pertussis syndrome, but bacterial culture was negative. A history of fever was common and the axillary temperature was more than 38°C in 26 children at referral. Comparison between older and younger children with lower respiratory tract involvement showed no difference in the severity, duration of the illness, or symptoms; except that nasal discharge and pharyngitis were commoner in the younger children and productive cough commoner in the older children. 9 children had otitis media and 1 a haemorrhagic myringitis. Crepitations were the commonest auscultatory finding. Bronchial breathing and rhonchi were less common. A pleural rub was heard in the case presenting with pleuritic pain.

Cases with nonrespiratory manifestations. 7 nonrespiratory manifestations were seen in 6 children: meningitis 2 cases, Stevens-Johnson syndrome 4 cases, and acute haemolytic anaemia 1 case. Details of these cases are summarised in Table 1.

Table 1 *Details of children with nonrespiratory manifestations*

Case no.	*Age (years)*	*Sex*	*Diagnosis*	*Clinical features*	*CF antibody M. pneumoniae*	*Progress*
1	5	M	Pneumonia, meningitis	Confusion, photophobia, fever and stiff neck 4 d; (CSF 0·073 lymphocytes $\times 10^9$/l; protein 0·3 g/l; glucose 3·5 mmol/l; bacterial and viral culture neg); chest *x*-ray consolidation	>1/4000	No antibiotics; recovered in 1 w
2	8	M	Pneumonia, meningitis	Cough 10 d, headache, fever, stiff neck 24 h; (CSF 0·076 lymphocytes and 0·002 polys $\times 10^9$/l; protein 0·45 g/l; glucose 3·5 mmol/l; bacterial and viral culture neg); chest *x*-ray consolidation	>1/16000	Tetracycline; headache better and CSF normal in 10 d
3	11	M	Bronchitis, Stevens-Johnson syndrome, haemolytic anaemia	Cough 7 d, erythema multiforme, mouth and genital ulcers 12 h; rhonchi; haemolysis Hb drop 12·6–10·4 g/dl; retic 23%, spherocytes, haemosiderinuria, direct antiglobulin test neg, cold agglutinins 1/512 4°C and 20°C and neg 37°C; chest *x*-ray normal	1/512	IV fluids, corticosteroids; lesions healed in 3 w; haemolysis for 2 m
4	8	M	Pneumonia, Stevens-Johnson syndrome	Malaise, cough, fever, erythema multiforme, mouth and genital ulcers; rhonchi; cold agglutinins 1/512 4°C and 20°C and neg 37°C; chest *x*-ray consolidation	1/4000; after 1m 1/2000	IV fluids, corticosteroids; recovered in 3 w
5	11	F	Bronchitis, Stevens-Johnson syndrome	Cough, erythema multiforme, mouth and genital ulcers; rhonchi; chest *x*-ray peribronchial thickening	1/16; after 10 d 1/512	IV fluids, corticosteroids; recovered in 2 w
6	8	F	Stevens-Johnson syndrome, toxic epidermal necrolysis	Sore eyes 2 d, mouth and genital ulcers 24 h, severe blistering arms and trunk for a few hours (Nikolsky's sign positive); chest *x*-ray normal	1/1024; after 7 d 1/512	IV fluids; severely ill 4 d; finger nails lost and regrown; conjunctival shrinkage

Investigations. A chest *x*-ray was taken in every case. Consolidation varied greatly in extent and was usually patchy and segmental but in 3 cases there was dense consolidation confined to one lobe. 2 cases had marked hilar lymphadenopathy, and 1 had a moderate sized pleural effusion. One case of bronchitis had a normal chest *x*-ray, whereas the remaining 3 had changes of peribronchial thickening.

Leucocyte counts were performed in every case (Table 2), and no consistent pattern was seen. The commonest finding was a normal total leucocyte count with the differential count showing an absolute neutrophilia. Cold agglutinins were looked for in 12 cases; a cold agglutinin titre was estimated in 9 and a rapid test (Garrow, 1958) used in the other 3. All the rapid tests were positive and 6 of the cold agglutinin titres were >1/64 at 4°C and all showed anti-I specificity. Red cell autoagglutination was seen on blood film examination in 6 cases. Erythrocyte sedimentation rate (Westergren) was performed in 31 cases and was >20 mm/h in 20 (range 3–130 mm).

Table 2 *White blood cell counts* in 45 children with M. pneumoniae infections*

Leucocytosis	15 (33%)
Normal leucocyte count	29 (64%)
Leucopenia	1 (2%)
Neutrophilia (absolute values)	30 (67%)
Normal neutrophil count	14 (31%)
Neutropenia	1 (2%)

*Normal values from Black and Barkhan (1974).

CF antibody titre to *M. pneumoniae* was measured in every case and in the same laboratory. 20 had an initial titre >1/256 but <1/1000; 5 were between 1/1000 and 1/4000; and 20 were >1/4000. In 12 there was a more than fourfold rise in titre or a falling titre in late convalescence. There was little or no CF antibody to respiratory syncytial virus, adenovirus, influenza A and B and parainfluenza 1 and 3 viruses, and psittacosis and Q fever antigens, in any case with lower respiratory tract infection. There was little or no CF antibody to *Herpes simplex* and Coxsackie B viruses in those cases with Stevens-Johnson syndrome. The cases with meningitis had little or no CF antibody in the serum to Coxsackie B, lymphocytic choriomeningitis, or leptospiral antigens; and no CF antibody in the cerebrospinal fluid to *Herpes simplex* virus.

Treatment and progress. One child had been given erythromycin, and 1 tetracycline, before hospital referral. 25 children were subsequently given erythromycin, 2 older children given tetracycline, 9 other antibiotics, and 9 were not given any antibiotic. Erythromycin or tetracycline was given if *M. pneumoniae* infection was suspected on clinical features, or delayed until the diagnosis was confirmed by serology.

The mean duration of symptoms of the 43 cases seen at follow-up was 4·2 weeks (range 1–16). During the acute stage, all 4 cases of Stevens-Johnson syndrome required intravenous fluids and intensive nursing care, and 2 received systemic cortiocosteroids. The skin and mucous membrane lesions resolved completely in 3 cases but one child (Case 6) was left with a severe conjunctival shrinkage syndrome which required a mucous membrane graft. Both cases of meningitis resolved quickly with no sequelae. The acute haemolytic anaemia was present for 2 weeks after which there was a compensated haemolysis for a further 2 months.

Discussion

Studies of families in outpatient practice have shown that *M. pneumoniae* is the principal nonbacterial pathogen causing pneumonia in school age children (Foy *et al.*, 1970). Below the age of 5 years, infections are often asymptomatic or cause mild coryza or cough (Fernald *et al.*, 1975), but studies of infections within families with several children have shown that pneumonia can occur before school age (Grayston *et al.*, 1967). This suggests that intensity of exposure is important for pneumonia to develop in young children, and cases in this age group might be expected to be commoner in epidemics.

In a report of a large number of cases of *M. pneumoniae* infections, the ratio of males to females was 1·1 to 1 (Foy *et al.*, 1970). The male predominance was said to be greater in children but figures were not quoted. Our findings suggest that lower respiratory infection is commoner in boys but this may hold true only for more severe disease, as all our cases had been referred to hospital. *M. pneumoniae* tends to cause smouldering epidemics lasting 1 to 2 years and does not show any marked seasonal variation (Foy *et al.*, 1970). The epidemic in Bristol followed this pattern and lasted 18 months.

Symptomatology was similar in most respects to the illness in adults (Murray *et al.*, 1975). Cough was almost always present and malaise common. We found no important differences in the severity, duration of illness, or clinical features of younger and older children with lower respiratory tract infection. Respiratory distress is said to be rare (Couch, 1973), but was present in 2 of our cases. One of our cases had a clinical picture similar to whooping cough; a presentation which has been noted before (Lambert, 1969). The majority of children were referred with a history of failure to respond to antibiotics. Crepitations are the commonest auscultatory finding

(Mufson *et al.*, 1961); signs of consolidation were also present in about one-quarter of our cases.

The radiological signs of *M. pneumoniae* have been reviewed (Foy *et al.*, 1973). There are no pathognomonic features although segmental or patchy consolidation and central dense infiltrates are common. These were the commonest findings in our series but in 3 cases there was dense lobar consolidation, indistinguishable from typical pneumococcal pneumonia. Large effusions are rare but small effusions were found in 3 out of 20 cases described by Lambert (1969).

Experimental infection with *M. pneumoniae* in volunteers (Smith *et al.*, 1967) showed that total leucocyte counts are frequently normal, or slightly raised, with differential counts showing a neutrophilia. We have found similar changes in children. It is clear that leucocyte counts cannot be relied on to discriminate between bacterial and *M. pneumoniae* pneumonia. However, a normal leucocyte count may help to support a clinical suspicion of *M. pneumoniae* pneumonia. Cold agglutinin titres are raised in 33–76% of *M. pneumoniae* pneumonias (Chanock, 1965) and the antibody usually shows anti-I specificity (Barret-Connor, 1972). Cold agglutinins may occasionally be raised in other pneumonias (Jansson *et al.*, 1964). The rise in cold agglutinin titre precedes the rise in CF antibody (Couch, 1973). The laboratory procedure for demonstrating cold agglutinins is time-consuming, so a positive rapid screening test (Garrow, 1958) which suggests a raised cold agglutinin titre, is a suitable screening test.

Laboratory diagnosis of *M. pneumoniae* infection depends on either isolation of the organism by culture or on serological methods. Culture of the organism takes 10 days or more and is presumptive evidence of infection. A more than fourfold rise of complement-fixing or growth-inhibiting antibody in paired samples of sera is confirmation of infection. A rising titre is not always possible to show because the rise has frequently taken place before the child is first seen (Foy *et al.*, 1970). A falling titre in late convalescence is confirmatory evidence, but additional venepunctures are difficult to justify in children who are recovering.

The growth of *M. pneumoniae* is inhibited *in vitro* by both tetracycline and erythromycin (Denny *et al.*, 1971) and trials in adults have shown that the illness is shortened by these drugs (Kingston *et al.*, 1961; Rasch and Mogabgab, 1965). However, the efficacy of these drugs remains to be proven in children, and symptomatic treatment only has been recommended (Eichenwald and McCracken, 1975). If antibiotic therapy is used, erythromycin is preferable to tetracycline because it has fewer and less severe side effects in children. These drugs appeared to have little effect on the course of the illness in our cases and symptoms persisted for long periods. In most cases, the interval between the onset of symptoms and start of treatment was more than 48 hours, and it is possible that earlier treatment might have been more effective. However, recovery was complete in all cases who attended follow-up.

Nonrespiratory manifestations of *M. pneumoniae* are uncommon. Haemorrhagic or bullous myringitis was first described in experimental infection in volunteers (Rifkind *et al.*, 1962) but has been infrequent in naturally occurring infection (Grayston *et al.*, 1967). Only one of our cases showed this sign, although otitis media, described previously in *M. pneumoniae* infections (Grayston *et al.*, 1967), occurred quite frequently.

Lerer and Kalavsky (1973) reviewed neurological manifestations which included 10 reported cases of meningitis. The CSF usually showed a lymphocytic predominance. Pulmonary disease was not always present. Most cases made a complete recovery. Other neurological disorders described included the Guillain-Barré syndrome, encephalitis, and cerebellar ataxia. A few cases of encephalitis were left with residual neurological deficit.

Arthritis is an uncommon but well recognised complication (Lambert, 1968). Large rather than small joints are affected and complete recovery can be expected. In this epidemic one case of arthropathy with significant CF antibody to *M. pneumoniae* was seen, but there was also a raised antistreptolysin O titre. The case was therefore excluded from this series.

About 50 cases of acute autoimmune haemolytic anaemia due to *M. pneumoniae* were reviewed by Barret-Connor (1972). Cold agglutinins are usually but not invariably raised. The antibody is complement-binding and the direct antiglobulin test should be performed using a reagent with anticomplement activity. A 'broad spectrum' antiglobulin reagent was used in our case of haemolytic anaemia but the negative result could have been due to low anticomplement activity in the reagent. Haemolysis usually begins late in the illness as the pneumonia begins to resolve. Haemolysis may be severe, resulting in haemoglobinuria and profound anaemia; but death is rare. Spontaneous recovery occurs and no treatment is necessary, except for blood transfusion for severe anaemia. It is probably wise to avoid cooling the patient since this could increase the haemolysis.

Skin rashes have been found in 9–30% of cases of *M. pneumoniae* infection (Cherry *et al.*, 1975). The rash can be erythematous maculopapular, vesicular, bullous, petechial, urticarial, or pruritic. The commonest skin rash in our cases was a transient

erythematous macular rash which was often fading at the time of hospital referral. In a review, Cherry *et al.* (1975) analysed 7 reported cases of Stevens-Johnson syndrome. They could find no reports of bullous or vesicular lesions occurring in females. Drugs, including penicillin, can cause Stevens-Johnson syndrome. One of our cases had been given penicillin but there was good serological evidence of *M. pneumoniae* infection. Case 6, with severe toxic epidermal necrolysis and permanent ocular sequelae, appears to have had a unique and very serious complication of *M. pneumoniae*.

It is clear that *M. pneumoniae* infections evoke a number of different host responses. Antibody confirmation of infection should certainly be sought in infants and children with lower respiratory infections associated with persistent cough and malaise, or in children with Stevens-Johnson syndrome. Complete recovery, often after several weeks of illness, can be expected in nearly all cases of childhood *M. pneumoniae* infection. Therapy with erythromycin or tetracycline appears to have little or no effect in most cases. Trials of early therapy will probably have to await more reliable and convenient methods of early diagnosis.

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