Acta Pædiatr Scand 80: 413–417, 1991

Mixed Infection Is Common in Children with Respiratory Adenovirus Infection

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ABSTRACT. Korppi, M., Leinonen, M., Mäkelä, P. H. and Launiala, K. (Department of Paediatrics, University Central Hospital, Kuopio, and National Public Health Institute, Helsinki, Finland). Mixed infection is common in children with respiratory adenovirus infection. Acta Paediatr Scand 80: 413, 1991.

The presence of concomitant viral or bacterial infection was evaluated in 20 patients hospitalized for adenovirus infection of the middle or lower airways by using new serological methods for detection of both antigens and antibodies. Adenovirus infection was identified by measurement of antibodies with complement fixation test or by direct detection of viral antigen in nasopharyngeal aspirates. Mixed infection was present in 11 (55%) of the 20 patients. Viral coinfection was demonstrated in five (25%) and bacterial in nine (45%) patients. Bacterial coinfection was common, 67%, in children with an infection focus, pneumonia or acute otitis media, but rare, 13%, in those without it. Seroconversion to nontypable *Haemophilus influenzae* was indicated in six children; four of them were infants, four had pneumonia and three acute otitis media. Pneumococcal infection was indicated in two patients with pneumonia, both aged over two years. *Chlamydia trachomatis* was involved in one case. The results indicate that bacterial coinfection is common in respiratory adenovirus infection affecting lower airways, especially if pneumonia is present. *Key words: adenovirus, respiratory tract infection, bacterial serology, bacterial coinfection, mixed infection.*

Adenoviruses (AV) are associated with a large variety of upper or lower respiratory tract infections in children (1, 2). In hospitalized children, the most common manifestation of AV infection is acute febrile tonsillitis (1). Pneumonia occurs in less than 10% of children with AV infection (1, 2). Chronic pulmonary complications, such as bronchiectasia, have been frequently reported in children with AV disease of lower airways (3, 4). Acute otitis media (AOM) is also frequently associated with AV infection (1, 2, 5). C-reactive protein (CRP) concentration, frequently used to differentiate between viral and bacterial infection, is often elevated in AV infection (6, 7). These observations raise the question of the role of secondary bacterial infection in patients with AV infection.

The importance of bacterial involvement in viral respiratory tract infection is difficult to assess because of the frequent carriage of common respiratory bacteria, including *Streptococcus pneumoniae* (PNC), *Haemophilus influenzae* and *Branhamella catarrhalis,* by healthy children (8). Recently, serologic methods have been introduced for the evaluation of the role of such bacteria in respiratory tract infections (9–13). By these methods, a high rate of bacterial coinfection has been indicated in children with respiratory syncytial virus (RSV) or parainfluenza virus (PV) infection of the lower airways (14, 15).

The aim of the present study was to evaluate the frequency of mixed infection, either viral or bacterial, in children with a verified AV infection of the middle or lower airways. Pharyngeal or other upper respiratory tract infections were not included.

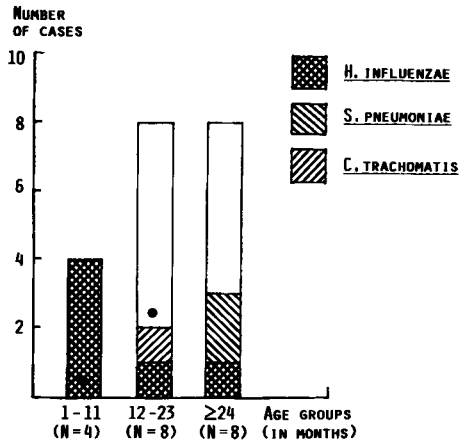

Fig. 1. Age distribution of 20 children with adenovirus infection in relation to bacterial coinfection. Two patients with a positive *H. influenzae* culture from the middle ear effusion are marked with shaded circles (●).

PATIENTS AND METHODS

Twenty children with AV infection affecting the middle or lower airways were treated during a prospective study in 1981–1982 (14, 16) in the Department of Paediatrics, Kuopio University Central Hospital. They constituted 5% of all 449 patients hospitalized with middle or lower respiratory tract infection within the 12-month study period. Four of these 20 patients (20%) were infants and 12 (60%) were aged less than two years (see Fig. 1).

The diagnosis of AV infection was based on a 4-fold or greater rise between paired sera in the antibody titre measured by the complement fixation assay (17 cases) and/or on direct detection of AV antigen in nasopharyngeal secretions by radioimmunoassay (17) (seven cases). A corresponding diagnostic set for detection of antigens and antibodies was used to identify RSV, PV types 1, 2 and 3, or influenza A and B viruses (16, 17). Mumps virus, herpes simplex virus, cytomegalovirus, enteroviruses and coronaviruses were studied by complement fixation assay alone (16).

Chest radiographs were taken from 16 patients in whom pneumonia was clinically suspected. Pneumonia was diagnosed in 11 of them (see Table 1) based on a pulmonary infiltration as evaluated independently by two radiologists without knowledge of the clinical findings. AOM was diagnosed in five patients; four of them had also pneumonia (see Table 1). Myringotomy was made and purulent effusion obtained in all five cases.

Enzyme immunoassay was used for measuring antibodies to pneumococcal C-polysaccharide and type-specific polysaccharides, to nontypable *H. influenzae, B. catarrhalis,* and *Chlamydia* sp. as described in detail earlier (10–13). A 3-fold or greater rise in antibody titres between the paired sera was considered diagnostic (14). Complement fixation assay was used for measuring antibodies to *Mycoplasma pneumoniae* and to the chlamydial group antigen; a 4-fold or greater rise in titer was considered diagnostic. The capsular polysaccharide antigens of PNC and *H. influenzae* type b were looked for in acute phase serum by latex agglutination (14, 15) and PNC antigens also in 10-fold concentrated urine by counterimmunoelectrophoresis and latex agglutination as described (9, 14, 15). The concentration of CRP in the acute phase serum of 19 patients was measured immunonephelometrically (18).

Fisher's exact probability test was used in statistical analysis of the data.

RESULTS

Mixed infection, either viral or bacterial, was present in 11 (55%) of the 20 children hospitalized with AV infection of the middle or lower airways (Table 1). Viral coinfection was indicated in five (25%) and bacterial in nine (45%) patients. Viral coinfection was equally common in children with or without an infection focus (pneumonia or AOM). Bacterial coinfection, however, was common (67%), only in patients with pneumonia and/or AOM.

H. influenzae was indicated in six children, and it was the most common organism associated with AV infection (Table 1). The identification was based on an antibody response to nontypable *H. influenzae*; all acute sera were negative for type b antigen. RSV, PV and PNC were each found in two patients. RSV infection was diagnosed by antigen detection in nasopharyngeal secretion, PV infection by antibody response and pneumococcal infection by antigen detection in acute serum or by antibody response to the type-specific antigen. *C. trachomatis* infection was diagnosed by demonstrating an antibody response both in enzyme immunoassay and micro-immunofluorescence test (19).

All the four infants had bacterial coinfection caused by *H. influenzae* (Fig. 1). After infancy, bacterial involvement was present in 31% of the cases, and *H. influenzae* was found in only two cases. PNC was found in two children, who both were older than two years.

CRP was over 20 mg/l in 50%, and over 40 mg/l in 25%, of the children with AV infection, without any correlation to the presence of bacterial coinfection. Similarly, no correlation was seen between CRP concentration and the presence of pneumonia or AOM.

AOM was diagnosed in four patients with pneumonia, but only in one patient without pneumonia (Table 1). There was serological evidence of bacterial infection in four of the five AOM cases (Table 1). *H. influenzae* was involved in three cases, and PNC in none. Thus, three of six children with *H. influenzae* infection had AOM. Unencapsulated *H. influenzae* was cultured from middle ear effusion in two patients, one with and one without seroconversion. PNC was not found by culture.

Seven of the patients had pneumonia without AOM. Four of them (57%) had bacterial coinfection, two caused by PNC and two by *H. influenzae*. Thus, bacterial involvement was associated with AV pneumonia irrespective of the presence of AOM.

Table 1. *Viral and bacterial coinfection in 20 children with respiratory adenovirus infection in relation to the presence of an infection focus*

	Infection focus present			Infection focus not present ($n=8$)
	Pneumonia ($n=11$)	AOM ($n=5$)	Pneumonia and/or AOM ($n=12$)	
Viral coinfection[a] ($n=5$)	2	1	3 (25%)	2[b] (25%)
RSV	2	0	2	0
PV	1	1	1	1
Bacterial coinfection[a] ($n=9$)	7	4	8 (67%)*	1 (13%)
H. influenzae	4[c]	3[c]	5[c]	1
S. pneumoniae	2	0	2	0
C. trachomatis	1	1	1	0

[a] Three patients with viral and bacterial coinfection; RSV was present in two cases, PV in one case, *H. influenzae* in two cases and *S. pneumoniae* in one case.
[b] One patient with a seroresponse to herpes simplex virus.
[c] One patient with a seroresponse to *Mycoplasma pneumoniae*.
* $p<0.05$.

DISCUSSION

The frequency and clinical importance of secondary bacterial infection in children with viral respiratory infection is still unresolved. By applying serological methods to indicate antibody responses to bacteria and to detect bacterial antigens in serum or urine we have observed a high rate, 39% and 31%, of bacterial coinfection in children hospitalized with lower respiratory tract infection caused by RSV or PV, respectively (14, 15). There is only one previous study in which bacterial serology has been applied to children with respiratory AV infection (20); bacterial coinfection was present in 42% of the 19 patients.

In the present study, bacterial coinfection was common only in patients with pneumonia and/or AOM. CRP, which has been used as an unspecific means to differentiate viral and bacterial infections (6, 7), was equally often elevated regardless of the presence of bacterial coinfection or an infection focus, AOM or pneumonia. CRP values over 40 mg/l, a screening limit considered to indicate bacterial infection, have been frequently found in AV infections in which the presence of concomitant bacterial involvement has not been studied (7).

H. influenzae was the organism most often associated with AV infection (20), in contrast to the findings in our earlier studies which have shown that PNC is the most common bacterial finding in RSV and PV infections (14, 15). Two-thirds of the patients with *H. influenzae* involvement had pneumonia, and a half had AOM. PNC involvement was only seen in association with pneumonia. Both pneumonia and AOM were also seen without serological evidence of bacterial infection, which argues for the less than ideal sensitivity of the serological methods used.

In the present study we used antibody assay to PNC polysaccharide antigens for the aetiological diagnosis, and this method has been shown to be rather insensitive for diagnosing PNC pneumonia (13) and AOM (11, 21). Poor antibody responses have also been demonstrated in children under two years of age receiving PNC vaccine (21, 22), who constituted the majority of our patients. Measurement of antibodies to a protein antigen, pneumolysin, seems to be a more sensitive indicator of pneumococcal infection in adults, but the experience in children is so far limited (23), and the method was not used in the present study.

Even while probably some bacterial infections were missed because of the limitations of available methods, the rate of bacterial coinfection in AV infections detected was high, 45%, and even higher, 67%, if an infection focus, pneumonia or AOM, was present. Bacterial coinfection therefore seems to be common in AV infection of the lower airways, just as in similar infections caused by RSV or PV (14, 15). Bacterial coinfection may be partly responsible for the later pulmonary complications associated with AV infection of the lower airways (3, 4). The data presented show that the establishment of a viral aetiology does not exclude bacterial involvement. We conclude that bacterial infection should be actively looked for and antibiotic treatment considered in children with AV infection affecting the lower airways.

ACKNOWLEDGEMENTS

This work was financially supported by the Academy of Finland (M. K. and M. L.). We thank Manu Munter, MSc (Orion, Diagnostica, Espoo, Finland) for the CRP assays, and Seppo Soimakallio, MD, and Seppo Tanska, MD, for the interpretation of radiological findings.

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Submitted Jan 8, 1990. Accepted April 6, 1990

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