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Serological Evidence of Viral or *Mycoplasma pneumoniae* Infection in Acute Maxillary Sinusitis

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Evidence for the involvement of viruses, *Mycoplasma pneumoniae*, and *Chlamydia* spp. was studied by the complement fixation test in paired sera from 310 young adults (297 men and 13 women) with acute maxillary sinusitis. The diagnosis of acute sinusitis was confirmed by radiography and sinus puncture. Elevated antibody titres were found in 102 patients (33%). A four fold or greater titre rise was detected in 21.5%, and a high stable titre suggestive of recent viral infection was present in a further 11.5%. Adenovirus, influenza A and B viruses, and *Mycoplasma pneumoniae* accounted for most of the elevated antibody titres. Elevated titres were found in 79 (32%) of the 245 patients with purulent maxillary sinusitis (pathogenic bacteria isolated in sinus secretion) and in 23 (35%) of the 65 patients with non-purulent sinusitis (no pathogenic bacteria isolated). About 90% of the fourfold or greater titre rises in bacteriologically negative cases were due to adeno- or influenza viruses. A fourfold rise in antibody titre was also found in 7 of 101 control patients (7%). The results of this study suggest that respiratory viruses and *Mycoplasma pneumoniae* may be potential etiological agents in acute maxillary sinusitis, either alone or in combination with the common bacterial pathogens of sinusitis.

Acute sinusitis usually follows a viral infection of the upper respiratory tract. The mucosal response to viral attack causes a disturbance in maxillary ostial function, which in turn leads to impaired sinus ventilation and drainage and, eventually, to the establishment of clinical maxillary sinusitis (1, 2). A viral infection is thought to impair several local and general defence mechanisms (3, 4). Thus, deterioration of ciliary motility (5, 6), damage to ciliated cells and, at a later stage, massive destruction of the epithelium may occur as a result of viral insult (7, 8). These adverse effects may also be caused by *Mycoplasma pneumoniae* (9), although mycoplasmas have not been isolated from sinus secretions (10). The impairment of the host defences facilitates bacterial establishment and secondary colonization of the maxillary sinuses. However, results of bacteriological culture of the aspirated sinus secretion are negative in a considerable percentage of sinusitis cases, varying from 18 to 50% in different studies (11–15), and it seems plausible that at least part of these sinus infections could be due to respiratory viruses, *Mycoplasma pneumoniae* and *Chlamydia* spp.

We therefore decided to study the possible etiological role of viruses, *Mycoplasma pneumoniae* and *Chlamydia* spp. which commonly cause acute upper respiratory infections, in acute maxillary sinusitis. Paired sera from acute maxillary sinusitis patients and controls were tested for changes in complement-fixing titres of antibodies to the above-mentioned microorganisms.

Materials and Methods

Patients. The sinusitis series consisted of 310 young adults (297 men and 13 women) aged 18–28 years (mean 20.5 years) who were referred to the otolaryngological outpatient clinic of the Central Military Hospital for examination between 1 September 1983 and 31 December 1987 because of suspected acute maxillary sinusitis. The duration of symptoms was less than three weeks in all the patients included in the study. None of the patients had received antimicrobial treatment for the present infection or for any other illness during the two weeks prior to inclusion in the study. The clinical diagnosis of acute maxillary sinusitis was confirmed by radiological evidence of sinus infection and by sinus puncture.

Bacteriological Examinations. At the clinical examination, sinus secretion aspirates or injection-aspirates were obtained from all maxillary sinuses with radiologically verified infection. The aspirates were studied for aerobic and anaerobic bacteria as described previously (15).

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Serological Tests. Paired sera for the determination of antibodies were collected at the initial clinical examination and after an interval of about two weeks. The sera were tested by the complement fixation (CF) test for antibodies to the following organisms: adenovirus group, influenza A and B viruses, parainfluenza 1, 2 and 3 viruses, respiratory syncytial virus, herpes simplex virus, cytomegalovirus, coxsackie B 5 virus (as a representative of enteroviruses), *Mycoplasma pneumoniae* and *Chlamydia* spp. (using a group-specific antigen, Behringwerke AG, FRG). Fourfold titre changes were considered significant and an antibody titre above the following values was considered suggestive of a recent infection: ≥ 512 for antibodies to adenovirus, ≥ 256 for antibodies to parainfluenza 1, 2 and 3, coxsackie B 5, *Mycoplasma pneumoniae*, influenza A and B, herpes simplex and cytomegalovirus, ≥ 128 for antibodies to respiratory syncytial virus, and ≥ 64 for antibodies to *Chlamydia* spp. antigen (Table 2).

Control Group. Paired sera were also tested for antibodies as described above in a control group of 101 army conscripts who were admitted to the ear, nose and throat ward of the Central Military Hospital because of acute acoustic trauma between 1 January and 31 December 1986 and who had no clinical or radiological symptoms or signs of maxillary sinusitis.

Statistical Analysis. The chi-square test was used to determine the significance of differences between groups. P values below 0.05 were considered statistically significant.

Results

Clinical Examination

All 310 patients had a history of acute respiratory infection with onset of symptoms 1 to 20 days before inclusion in the present study. None of the 101 controls had radiological evidence of sinusitis, but six of them had subjective and clinical symptoms of respiratory infection.

Antibody Titres

Sixty-six or 21.5% of the patients showed a fourfold or greater rise of antibodies to one or several microorganisms tested (Table 1). In the control group, a corresponding rise in antibody titre was seen in seven patients (7%), three of whom had acute respiratory symptoms at the time of sampling (acute adenovirus tonsillitis, influenza A respiratory infection, and influenza A cough). The difference between the groups is statistically significant ($p < 0.01$). In the sinusitis patients the most commonly seen antibody rises were to influenza A or B virus in 27 cases (difference from the control group, $p < 0.025$), to adenovirus in 25 cases ($p < 0.05$) and to *Mycoplasma pneumoniae* in 11 cases ($p > 0.05$ = not significant). Fourfold or greater rises to other organisms were detected only occasionally (Table 1).

Table 1: Occurrence of fourfold or greater rises in complement-fixing titres of antibodies to respiratory viruses, *Mycoplasma pneumoniae* and *Chlamydia* spp. in patients and controls.

	Acute maxillary sinusitis patients n = 310	Control group n = 101
Adenovirus	25 ^a	1 ^b < p 0.025
Influenza A or B virus	27 ^c	2 ^d < p 0.05
<i>Mycoplasma pneumoniae</i>	11	1 > p. 0.05
Respiratory syncytial virus	3	—
Herpes simplex virus	1	—
<i>Chlamydia</i> spp.	2	2
Parainfluenza virus	1	—
Enteroviruses	—	—
Cytomegalovirus	—	1
Total no. of patients with a four fold or greater rise in titre	66	7 < p. 0.01

^aOne patient with concomitant fourfold titre rise to influenza A virus and two to *Mycoplasma pneumoniae*.

^bControl group patient with signs of acute respiratory infection at the time of sampling.

^cOne patient with concomitant fourfold titre rise to both influenza viruses.

^dBoth controls had signs of acute respiratory infection.

Table 2 shows the distribution of antibody titre values of ≥ 64 in those patients and controls who had a high antibody titre without a significant rise. According to the criteria used here, 36 patients had antibody titres that were suggestive of a recent infection: 13 to *Mycoplasma pneumoniae*, seven to respiratory syncytial virus, seven to adenovirus, five to influenza A or B virus, three to *Chlamydia* spp. and one to parainfluenza 1 virus (Table 2). Among the controls, one had a high titre to *Chlamydia* spp.; he also had rhinitis. Although the difference between the number of *Mycoplasma pneumoniae* infections among the patients and controls was not statistically significant when based on a fourfold antibody rise, it became significant when those individuals with a steady high titre (13 cases) were also included (24 versus 1, $p < 0.025$).

Bacteriological Findings

In 79% of the patients, the bacteriological culture of the sinus aspirate grew a bacterium considered to be pathogenic in this location: *Haemophilus influenzae* in 56%, *Streptococcus pneumoniae* in 18%, *Streptococcus pyogenes* in 4.5%, *Branhamella catarrhalis* in < 1%, and mixed anaerobic flora in one case. In the remainder (21%), the culture was negative or showed nonpathogenic bacteria.

Table 2: Values of complement-fixing titres ≥ 64 in 244 patients with acute maxillary sinusitis and 94 controls (values in parenthesis) who did not have a fourfold or greater rise of virus, *Mycoplasma pneumoniae* and *Chlamydia* specific antibody titres between paired sera.

Microorganisms	Number with given antibody titre			
	64	128	256	≥ 512
Adenovirus	39 (17)	4 (12)	3 (2)	7 (-)
Parainfluenza 1 virus	7 (4)	2 (2) ^a		1 (-)
Parainfluenza 2 virus	- (-)	- (-)	(-)	
Parainfluenza 3 virus	26 (10)	5 (3)	(-)	
Enteroviruses	13 (5)	2 (2)		
<i>Mycoplasma pneumoniae</i>	7 (7)	6 (1) ^b	6 (-)	7 (-)
Influenza A virus	7 (1)	5 (1)	2 (-)	
Influenza B virus	1 (-)	- (-)	3 (-)	
Herpes simplex virus	10 (10)	2 (-)	(-)	
Cytomegalovirus	3 (2)	1 (-)		
Respiratory syncytial virus	2 (-)	5 (-)	2 (-)	
<i>Chlamydia</i> spp.	1 (1) ^c	2 (-)		
Total	116 (57)	34 (21)	16 (2)	15 (-)

^aHistory of recent pneumonia in one of the controls.

^bControl group patient with acute cough.

^cControl group patient with rhinitis.

Correlations between Bacteriological Findings and Complement-Fixing Titres of Antibodies

Significant titres (at least a fourfold rise or a stable high titre) of viral antibodies were most frequent among patients with *Streptococcus pyogenes*-positive cultures and least frequent in patients with *Haemophilus influenzae*-infection, but the differences between the groups were not significant. Among the patients with significant titres of antibodies to adenovirus, 72% had a pathogen-positive sinus culture. Among those with influenza virus infection, the proportion was 78.5%, among those with *Mycoplasma pneumoniae* infection, 83%, and among those with respiratory syncytial virus infection, 90%. The differences were not statistically significant. Of the 65 patients in whom no bacterial pathogens were detected in the sinus aspirate, 23 (35%) had significant antibody titres, mostly to adenovirus or influenza viruses. A fourfold or greater rise in antibody titre was seen in 18 of the patients.

Discussion

It is generally thought that viruses, *Mycoplasma pneumoniae* and *Chlamydia* spp. are responsible for over 90% of all upper respiratory infections (16-19). Rhinovirus colds are apparently the most common, accounting for one-third of all cases. About 10% are thought to be due to coronaviruses, 15% to infections with adeno-, influenza, parainfluenza or respiratory syncytial virus, and 5% to infections with entero-

viruses or other (smaller) groups (19). The remaining 30-40% are also believed to be caused by viruses, although conclusive evidence of this has not been presented (19).

The test most commonly used in routine virological diagnostics is the CF test (20, 21). One drawback of the CF technique is that it is not suitable for detection of rhino- and coronaviruses. These organisms can only be detected by direct culture or antigen demonstration methods, which were not employed in the present study. Thus, the involvement of these two important groups of respiratory viruses was not recognized in the present series of patients with acute maxillary sinusitis. Antibodies measurable by the CF technique develop only after a latency period of one to two weeks, and a rise in antibody titre is therefore usually detectable when the patient seeks medical advice three to seven days after the onset of symptoms. A fourfold or greater rise in antibody titre between paired sera is commonly used as indicative of a recent viral infection (20, 21). In the present study, the proportion of patients with such a rise in antibody titre was 21.5% in the patient group and 7% in the control group. The difference between the groups was statistically significant ($p < 0.01$).

Sinusitis is usually regarded as a complication of a viral infection of the upper respiratory tract. In the present study, part of the patients had respiratory symptoms for almost three weeks when the first serum sample was collected, and thus it may be assumed that a significant rise in serum antibodies had already occurred and a further fourfold rise could no longer be demonstrated. Comparison with

Table 3: Previously reported virological studies in sinusitis patients.

Reference	No. of patients	Detection method		Findings	
		Isolation	CF test	Organism	No. of strains
Spector et al. 1973 (25)	22	x		adenovirus	1
Evans et al. 1975 (24)	13 23	x	x	rhinovirus no organism	2
Gwaltney et al. 1981 (26)	113	x		rhinovirus influenza A parainfluenza	7 3 2
Wald et al. 1981 (27)	30	x		adenovirus rhinovirus	1 1
Oehling et al. 1981 (23)	37		x	respiratory syncytial virus coxsackie B3 or B5 <i>Mycoplasma pneumoniae</i> ^a	4 2 1
Saito et al. 1981 (22)	31		x	parainfluenza	18

^aIncluded by authors (23), although not a virus.

antibody titre values in the control group indicated that high titres above certain values could be considered suggestive of a recent viral infection in the patients with acute maxillary sinusitis (Table 2), although the requirement of a fourfold rise was not met. In all, significant antibody titres were thus recorded in 102 or 33% of all patients, consisting of a fourfold or greater rise in 21.5% and a high stable antibody titre in 11.5%.

Reports on the involvement of viruses in acute maxillary sinusitis in the literature are not very informative (Table 3). The number of studies is few and the patient series have usually been small. The series have included exacerbations of chronic sinusitis (22), or antibody titres have been measured in patients with acute exacerbation of asthma in association with sinusitis (23). A rise of antibody titres has been reported in 0–58% of patients (22–24; Table 3). A fourfold titre rise was usually used as indication of viral infection, but in the study by Saito et al. (22), for instance, antibodies were measured in a single serum sample in most of the patients and a titre of ≥ 128 was considered indicative of a recent infection by parainfluenza viruses. Virus isolation in tissue cultures has been reported in a few studies; viruses have been detected in 4.5–15% of the cases (24–27). In a part of these cases pathogenic bacteria were also isolated from the affected sinus (26, 27).

In the present study, cultures of aspirated sinus secretion were negative or showed a flora of non-pathogenic organisms in 21% of the patients with acute maxillary sinusitis. A fourfold or greater rise

in serum antibodies between paired sera occurred in 28%, and the titres in both sera were elevated in another 7%. Almost 90% of the fourfold rises were due to adeno- or influenza viruses, suggesting that these virus groups may be specially associated with acute maxillary sinusitis.

About 80% of the infections with influenza viruses were double infections, the influenza virus occurring concomitantly with another virus (Table 1) or a pathogenic bacterium. This finding is concordant with previous observations that the influenza virus can enhance the adhesion of bacteria to pharyngeal cells (28, 29) and so facilitate colonization of the mucosa by bacteria already present in the nose or nasopharynx (30). *Mycoplasma pneumoniae* has not been cultured from sinus secretions (10, 24). In the literature there is only one report of *Mycoplasma pneumoniae* antibodies in a patient with acute maxillary sinusitis (23). In the present study, 10.5% of the patients had a fourfold titre rise or a high titre of serum antibodies to *Mycoplasma pneumoniae*, suggesting that this organism may be a more common etiological agent in acute sinusitis than previously thought. As a rule, both *Mycoplasma pneumoniae* and respiratory syncytial viruses occurred in combination with another microbe. Comparison of bacteriological findings and antibody titres did not indicate that any given bacterial pathogen was more frequently associated with a viral or mycoplasmal infection than other pathogens, nor was there any indication that a certain virus or mycoplasma had a tendency to occur in combination with a particular bacterium.

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