Rhinology, 42, 131-136, 2004

The pathogenicity and antibiotic resistance of coagulase-negative *Staphylococci* isolated from the maxillary and ethmoid sinuses*

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SUMMARY

***Aim of the study**: To investigate the pathogenicity and antibiotic resistance of coagulase-negative staphylococci (CNS) isolated from the maxillary and ethmoid sinuses of patients undergoing endoscopic sinus surgery for chronic sinusitis.*

Patients and methods: *Ninety-three patients (63 males, 30 females) aged between 19 - 68 years, who had undergone functional endoscopic sinus surgery (FESS) for chronic sinusitis, were included in the study. Nasal mucosa, skin and adjacent structures were cleansed with povidone-iodine solution before surgery to prevent a probable contamination. In all patients, nasal swabs were taken before and after the application of povidone-iodine solution.*

Colonies isolated and identified as Staphylococci in cultures were further investigated for pathogenicity and antibiotic susceptibility. Slime test was used to determine the pathogenicity of CNS. The relationship between antibiotic resistance of pathogenic and non-pathogenic CNS was compared by χ^2 analysis.

***Results**: While bacterial growth rate was 62.3% in nasal swab cultures taken before the application of povidone-iodine solution, it decreased to 12.9% after the application of solution. Microorganisms were isolated in 95.6% of cultures taken from maxillary sinuses and in 91.3% of cultures obtained from ethmoid sinuses during the FESS. The most frequently isolated microorganism in each of the sinuses was CNS. Slime test was carried out in 30 CNS isolated. Twelve of these were slime positive and 18 were slime negative. While 83.3% of CNS isolated was resistant to penicilin, all of CNS were sensitive to vancomycin and teikoplanine. The difference between slime positive and slime negative CNS for gentamicin and ciprofloxacin resistance was statistically significant ($p<0.05$).*

***Conclusion**: We consider that the pathogenicity tests like slime production and antimicrobial susceptibilities of CNS frequently isolated from the patients with chronic sinusitis should be investigated and also these microorganisms should be kept in mind in the selection of empiric treatment.*

Key words: chronic sinusitis, CNS, pathogenicity, antibiotic resistance

INTRODUCTION

Sinusitis is defined as an inflammatory process of the mucous membranes of the paranasal sinuses. Chronic sinusitis is any inflammatory state that lasts longer than 12 weeks. The incidence of sinusitis varies widely in the general population, but it is estimated that about 0.5% of all "common colds" progress to sinusitis (Vining et al., 1993; Sobol et al., 2003). Sinuses are air-filled spaces lined with the pseudostratified, ciliated columnar epithelium. This feature suggests existence of a defence system eliminating bacterial particles from the sinuses. For a long time, paranasal sinuses were considered to be sterile cavities, but, research by Brook in 1981 changed this opinion. He found anaerobic bacteria in 100% of aspirates taken from healthy maxillary sinuses and aerobic bacteria in 58% of the cases

*Received for publication: October 13, 2003; accepted: April 6, 2004

(Brook, 1981a). The microbiology of the paranasal sinuses has long been a subject of interest.

The microorganisms isolated in chronic sinusitis are different from the ones isolated in acute sinusitis. *H. influenzae, Str. viridance* and other streptococci together with anaerobes including Bacteroide*s, Veillonella, Rhinobacterium* and other anaerobes lead to chronic sinusitis (Benninger et al., 1997; Brook, 2002). Most frequently encountered bacterial pathogens leading to sinusitis are streptococci (alpha and beta haemolytic), *H. influenzae* and *Staphylococcus aureus*. Despite a rarely encountered entity, sinus infections secondary to fungi should also be kept in mind, especially in recurrent cases (Schubert, 2001).

Coagulase-negative staphylococcus (CNS) has been regarded as either a member of normal flora or contamination even though it has been, until now, the most frequently isolated microorganism in cultures prepared from the aspirates and / or biopsy materials of the sinuses of the patients with chronic sinusitis (Almadori et al., 1986; Doyle and Woodham, 1991; Hasçelik et al., 1996). In recent years, however, CNS has been gradually gaining importance as a potential pathogen, especially in nasocomial infections, because it's both resistant to most of the antibiotics and also more frequently encountered. CNS has been observed in many of the infections (e.g., immune deficiency, neutropenia, malignancy, premature labour, infections following a surgical intervention or prosthetic operation). CNS has also been found as a pathogenic agent in cardiac valve endocarditis in nonnasocomial infections, tricuspit endocarditis in heroin addicts and in urinary system infections secondary to *S. saprophyticus* in sexually active young women (Mirrett et al., 2001).

When these microorganisms found in the normal flora of the skin and mucous membranes are isolated clinically, it is rather difficult to decide as to whether they are the real pathogens or not. Real pathogenicity can only be determined after a series of laboratory tests besides clinical findings (Arciola et al., 2002a).

It has been shown that CNS adheres to the surfaces of medical devices used during medical intervention, with the aid of an extracellular mucoid substance known as "slime". In most of the epidemiologic studies, an association between the production of slime and the virulance of CNS has been observed. Besides mediating the adherence of CNS to the surface of biomaterials, "slime" factor also protects these microorganisms against antibiotics, phagocytosis, degranulation and chemotaxis (Christensen et al., 1985; Arciola et al., 2002b).

Today, in the management of chronic sinusitis, medical therapies are given initially, and then surgical treatment is carried out if the medical treatment fails. Medical therapies include antibiotics, agents decreasing mucosal oedema and other supportive drugs. Generally, empiric antibiotics are recommended to the patients with chronic sinusitis, since taking cultures from sinuses requires invasive procedures. On the other hand, in the selection of this empiric treatment, studies on sinus microbiology of the patients with chronic sinusitis will guide us.

With the advent of endoscopic instruments, our knowledge about sinus infections has rapidly increased and endoscopes have allowed us to examine the nasal cavity in detail. In this way, taking samples with the minimal probability of contamination to determine the microbiology of each sinus has been possible.

In this study, we investigated the pathogenicity and antibiotic susceptibility of CNS isolated from the maxillary and ethmoid sinuses of patients undergoing endoscopic sinus surgery for chronic sinusitis.

MATERIAL AND METHODS

Ninety-three patients aged between 19 to 68 years (mean age 36 ± 17.4), who had undergone functional endoscopic sinus surgery (FESS) for chronic sinusitis, were included in the study. Of the patients, 63 were males and 30 were females. Patients with chronic sinusitis were included in the study. The criteria for chronic sinusitis were as follows: a) disease lasting for more than 12 weeks with no response to medical treatment, or b) recurrent sinusitis with more than 4 episodes in one year. On conventional radiographs and / or computed tomography, patients had either complete opacification in the maxillary or ethmoidal sinuses or mucosal thickening of more than 5 mm. Patients with acute infection or those who were given local or systemic antibiotic therapy in the last week were excluded from the study. All the patients were examined by using a Karl Storz endoscopy and endovision system. The nasal mucosa, skin and adjacent structures were cleansed with povidone-iodine solution before surgery to prevent probable contamination. Nasal swabs were taken before and after cleansing the nasal and facial skin with povidone-iodine solution in all of the patients. Samples were taken under general anesthesia from all the patients during FESS. Purulent material directly from the sinus was taken to a collector tube with a sterile disposable aspiration set (Xomed Surgical Products, Jacksonville, FL, USA) just at the time of opening ethmoid and maxillary sinus ostia during the surgery. While carrying out these procedures, we paid utmost attention not to touch the adjacent structures. Aspiration materials were taken to coal amies transport broth and enriched thioglycolate broth by sterile swabs. Samples were transported to the microbiology laboratory by coal amies transport broth within two hours and inoculated onto 5% sheep blood agar, chocolate agar and EMB agar for aerobic bacteria and incubated at 35°C, 5% CO_2 for 24-48 hours. Samples were inoculated onto anaerobic blood agar, pre-reduced vitK1 enriched Brucella blood agar, blood agar with kanamycin and thioglycolate broth during the surgery for anaerobic culture and incubated at 35°C in Gas-Pak anaerobic jars for 48-72 hours. Samples obtained from the sinuses were also inoculated onto Saboraud-Dextrose agar for fungi and left at room temperature for 20 days. Samples taken during the surgery onto the enriched thioglycolate agar were incubated in the Gas-Pak anaerobic jar at 35°C for 4-7 days to increase the proliferation of anaerobic bacteria. Gram stain preparations

were performed immediately from the anaerobic material sent to the laboratory for cultivation to prevent wasting of the anaerobic bacteria during collection and transport. OXOID An-Ident Discs were used for identification of the anaerobes (Oxoid Ltd., England). Aerobic microorganisms were identified and isolated by standard methods. Also, Vitek automation system (BioMerieux, Inc. MI, USA) was used for aerobic identification. Colonies identified as *Staphylococci* after incubation (colony appearance, pigment, hemolyse, etc.) were further investigated.

Coagulase Experiment

The tube method was used. One ml plasma was diluted 1:5 with H_2O within the tube and was used for the experiment. A sample taken with an applicator from Staphylococcal colonies was homogenized within the diluted plasma. Clot formation was examined at 1, 2, 4, 8 and 24 hours after incubation at 37°C. It was regarded as coagulase positive if the clot was observed and as coagulative negative otherwise.

Slime test

The Congo red agar method was used for the slime test. Growth medium and Congo red were separately dissolved within distilled water. Growth medium was autoclaved in a sterilizer for 15 minutes at 121°C. Growth medium was cooled. As soon as the temperature of the growth medium decreased to 55°C, Congo red dye was added. Growth medium was poured in sterile petri dish. One colony of CNS isolates was inoculated onto this dish and was incubated at 37°C for 24 hours in an anaerobic environment.

The slime test was carried out for 30 CNS strains which were isolated in the specimens taken intraoperatively from maxillary and ethmoidal sinuses of patients with chronic sinusitis, and which were further investigated (coagulase, colony appearance, pigment, hemolyse, catalase, etc.).

Evaluation

After incubation, dry and black colonies were accepted as slime positive and pink colonies as slime negative.

Antibiotic susceptibility tests

Antibiotic susceptibilities of all the *Staphylococci* identified were investigated by the disc diffusion method (Kirby-Bauer). The disc diffusion experiment followed the NCCLS M2-A6 criteria: wide inoculation from a colony suspension adjusted to 0.5 Mc Farland in distilled water, which is subsequently spread over 4 mm thick Mueller Hinton broth. After drying for 15-20 minutes, the discs (Oxoid) were incubated at 37°C for 16-18 hours. After incubation, they were regarded as susceptible (S) or resistant (R) by measuring the zone diameter. In the disc diffusion experiment, *Staphylococcus aureus* ATCC 25923 was used as the control strain.

Antibiotic susceptibility tests were carried out in 30 samples identified as CNS.

Statistics

The $\chi 2$-test was used for statistical analysis.

RESULTS

In preoperative nasal swab cultures, in 58 (62.3%) of the patients, the total aeroob bacteria count isolated from cultures taken before the application of povidone-iodine solution was 72, while in 12 (12.9%) of the patients, the number isolated from cultures taken after the application of povidone-iodine solution was 16 (Table 1).

No bacterial growth was observed in 4 (4.3%) of the patients whose cultures were taken from the maxillary sinus and in 8 (8.6%) of the patients whose cultures were taken from the ethmoid sinuses. Among bacterial cultures showing bacterial

Table 1. Microorganisms isolated in the nasal swab cultures taken before and after the application of povidone-iodine solution.

Nasal Flora	Before the application of povidone-iodine solution (%)	After the application of povidone-iodine solution (%)
AEROOB		
Coagulase (-) *staphylococcus*	36 (50.0%)	7 (43.7%)
Coagulase (+) *staphylococcus*	27 (37.5%)	4 (25.0%)
Viridans streptococcus	6 (8.3%)	2 (12.5%)
Streptococcus peumoniae	2 (2.7%)	1 (6.2%)
Klebsiella pneumoniae	1 (1.3%)	1 (6.2%)
Pseudomonas aeruginosa	-	1 (6.2%)
ANAEROBE	-	-
TOTAL	**72 (100%)**	**16 (100%)**

Table 2. Microorganisms isolated in the cultures obtained intraoperatively from maxillary and ethmoid sinuses.

Microorganisms	**Maxillary sinus (%) n=89**	**Ethmoid sinus (%) n=85**
AEROBE		
Coagulase *(-) staphylococcus*	18 (20.0%)	12 (33.3%)
Viridans streptococcus	12 (13.3%)	9 (25.0%)
Coagulase *(+) staphylococcus*	9 (10.0%)	4 (11.1%)
Streptococcus pnömoniae	9 (10.0%)	3 (8.3%)
Klebsiella pnömoniae	4 (4.4%)	2 (5.5%)
A grubu β-hemolytic *Streptococus*	2 (2.2%)	2 (5.5%)
Enterecoccus gallinorum	3 (3.3%)	-
Haemophilus parainfluenza	3 (3.3%)	1 (2.7%)
Haemophilus influenza	3 (3.3%)	2 (5.5%)
Klebsiella oxytoca	3 (3.3%)	1 (2.7%)
Streptococcus bovis (Group D nonenterococci)	3 (3.3%)	-
Pseudomonas aeruginosa	3 (3.3%)	-
ANAEROBE		
Bacteroides fragilis	12 (13.3%)	-
Gram positive coccus	6 (6.6%)	-
Total	**90 (100%)**	**36 (100%)**

Table 3. The distribution of resistant and susceptible CNS strains according to antibiotics.

Antibiotic	Total resistant strain		Total susceptible strain	
	n	%	n	%
Penisilin	25	83.3	5	16.7
Vankomisin	0	0	30	100
Teikoplanin	0	0	30	100
Klindamisin	13	43.3	17	56.6
Azitromisin	12	40	18	60
Metisilin	15	50	15	50
Siprofloksasin	12	40	18	60
TMP/ SMX	16	53.3	14	46.7
Gentamisin	15	50	15	50

growth, 6 (6.45%) had both aerobic and anaerobic bacteria which proliferated together; 21 (22.5%) had more than one aerobic bacteria (two or three) together; 54 (58.0%) had only aerobic bacteria and 12 (12.9%) had only anaerobic bacteria isolated. Table 2 shows the distribution of bacterial growth in the specimens taken during FESS from maxillary and ethmoidal sinuses.

Of 30 CNS strains which underwent the slime test, 12 were slime positive and 18 were slime negative. The distribution of resistant and susceptible strains according to antibiotics are shown in Table 3. The antibiotic resistance of slime positive and slime negative CNS strains are shown in Table 4. All of the CNS strains were found to be sensitive to vancomycin and teikoplanine. The difference between slime positive and slime negative CNS for gentamicin and ciprofloxacin resistance was statistically significant ($p<0.05$).

DISCUSSION

Because of the close association between the upper respiratory tract and sinuses, inflammatory conditions affecting the nasal cavity and nasopharynx may easily influence the sinuses as well. Hence, a detailed knowledge of the normal nasal and paranasal flora is required for the evaluation of acute and chronic sinusitis microbiology (Kremer et al., 2001). Because it is easy to reach, maxillary sinus has long been a target sinus to determine the microbiology of acute and chronic sinusitis, and contamination does not occur frequently while taking cultures from maxillary sinuses. On the other hand, it is difficult to take cultures from ethmoid sinuses without contamination even under operating room conditions. We cleansed the nasal pasage and facial skin preoperatively with povidine-iodine solution to minimize the risk of contamination. CNS, which is present in 40-100% of the normal nasal flora, has been isolated in 50.0% of the cultures taken before the application of the povidone-iodine solution. Coagulase positive *Staphylococcus* (CPS) is present in 25-40% of the nasal flora. On the other hand, CPS is a highly virulant bacteria and may cause infections (Doyle and Woodham, 1991; Brook et al., 1994; van Cauwenberge and Ingels, 1996; Biel et al., 1998). In our study, CPS has been isolated in 37.5% of the cultures taken before the application of the povidone-iodine solution. While bacterial growth occured in 62.3% of nasal swab cultures taken before application of the povidone-iodine solution, it decreased to 12.9% after application of the solution. There was also no diphteroidal growth in our study, which is present in 90-100% of the normal flora of the nasal cavity. Both results show that contamination had been prevented significantly.

The studies investigating the microbiologic etiology of chronic sinusitis revealed variable results. Many researchers reported that the most frequently isolated microorganisms in cultures obtained from mucosal biopsy specimens and / or aspiration samples of maxillary and etmoid sinuses were CNS, *Staphylococcus aureus, Str. pneumonia, Str. viridance, diphteroids* (Brook, 1981b; Almadori et al., 1986; Doyle and Woodham, 1991; Hasçelik et al., 1996). In our study, CNS (32.2%) was the most frequently isolated bacterium, followed by *Str. viridance* (22.5%).

The reported frequency of anaerobic bacteria isolated in chronic sinusitis changes from 0% to 100% (Doyle and Woodham, 1991; van Cauwenberge and Ingels, 1996; Jiang et al., 1997; Biel et al., 1998). These variable results may be related to sample collection techniques, patient's age, duration of the disease, preoperative antibiotic usage, the origin of the culture taken, culture transport methods and the time between the collection and cultivation of the sample. However, the difference in sampling techniques may only partly explain the differences in the ratio of the microorganisms reported in various

Table 4. The antibiotic resistance of slime positive and slime negative CNS strains.

Antibiotics	Resistant slime positive strain		Resistant slime negative strain		Statistical significance
	n=12	%	n=18	%	(p)
Penisilin	11	90.6	14	77.7	$p>0.05$
Vankomisin	0	0	0	0	$p>0.05$
Teikoplanin	0	0	0	0	$p>0.05$
Klindamisin	6	50	7	38.8	$p>0.05$
Azitromisin	5	41.6	7	38.8	$p>0.05$
Metisilin	7	58.3	8	44.4	$p>0.05$
Siprofloksasin	8	66.6	4	22.2	$p<0.05$
TMP/ SMX	8	66.6	8	44.4	$p>0.05$
Gentamisin	11	90.6	4	22.2	$p<0.05$

studies. Anaerobic bacteria have been reported to be 88% by Brook (1989), 6% by Almadori et al. (1986), and 0% by Doyle and Woodham (1991). Most frequently isolated anaerobes were Gram-positive cocci and Bacteroides species in order of frequency. In our study, the ratio of anaerobic bacteria in cultures taken from maxillary sinuses was 20%, existing of *Bacteroides fragilis* (13.3%) and *Gram-positive coccus* (6.6%), while no anaerobic bacteria were seen in the ethmoid sinuses. Doyle and Woodham (1991) claimed that the generally lower isolation rate of anaerobic bacteria in cultures taken from the ethmoid sinuses may be due to a lower likelihood of obstruction in this sinus and more oxygen exposure while breathing when compared to other sinuses.

The use of the term "pathogen" for some microorganisms like CNS, *Str. viridance*, etc. and also for anaerobes in the pathogenesis of chronic sinusitis still remains a controversy. However, Brook (1989) and Karma et al. (1979) accepted these agents as pathogens in the pathogenesis of chronic sinusitis. According to the study of Biel et al. (1998), *Staphylococci* have been considered as common pathogens in chronic supurative sinusitis. In that study, 35% of CNS isolated was found to be resistant to the oral antibiotics used.

In our study, we investigated the relationship between antibiotic resistance and slime production by the "Congo red agar method" in 30 CNS strains isolated from maxillary and ethmoid sinuses. In various studies, slime production has been reported to be correlated with increasing resistance of CNS strains and also it has been claimed that slime factor contributes to the formation of resistance against antibiotics, constituting a barier surrounding the microorganisms (Kotilainen et al., 1991; Boussard et al., 1993).

In this study, slime production which is an important pathogenicity criterion has been found to exist in 40% of the 30 CNS strains isolated from maxillary and ethmoid sinuses. For antimicrobial resistance, we observed a statistically significant difference between slime positive and slime negative CNS strains for gentamicin and ciprofloxacin resistance ($p<0.05$).

Today, in the management of patients with chronic sinusitis, empirical antibiotic treatments directed against the frequently encountered bacteria are used. However, formation of resistant bacteria and the variability of the etiologic spectrum make identification of the infectious agents necessary. There has also been a number of studies that have shown middle meatal aspirates reflect the bacteriology of the maxillary sinuses. Therefore, it is a current accepted treament to do a middle meatus aspirate or swab and to identify the bacteria microorganism that may be playing a role in the chronic sinusitis and directing the anti-microbial therapy appropriately (Jiang et al., 2002; Tantilipikorn et al., 2002). We consider that the antimicrobial susceptibilities and pathogenicity tests like slime production of CNS frequently isolated from sinus cultures of patients with chronic sinusitis should be investigated and also CNS should be kept in mind in the selection of empiric treatment. We hope this study can be helpful in clarifying sinus microbiology and guiding the treatment of patients with chronic sinusitis.

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