

Physiologic abnormalities in the paranasal sinuses during experimental rhinovirus colds

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Six (18%) of 34 healthy, asymptomatic young adults had mucosal thickening or fluid in the paranasal sinuses on screening magnetic resonance imaging (MRI) examination. When 19 of these subjects were challenged with rhinovirus, 18 became infected. Twelve of the 18 infected subjects had technically satisfactory serial MRI examinations, and four (33%) of these developed MRI abnormalities of the ethmoid or antral sinuses that were temporally associated with the acute infection. The mean total nasal secretion weights were 22 gm/5 days in the four subjects whose MRI abnormalities were associated with the acute infection compared with 5.5 gm/5 days in the eight subjects who had normal MRI examinations during the acute infection ($p = 0.06$). Abnormalities of the paranasal sinuses, which were associated with increased volumes of nasal secretion, were detected by MRI examination during rhinovirus infection. These abnormalities may have a role in the pathogenesis of acute sinusitis associated with colds. (J ALLERGY CLIN IMMUNOL 1992;90:474-8.)

Key words: Acute sinusitis, rhinovirus, common cold, acute respiratory disease

Epidemiologic evidence suggests that acute viral respiratory infection is the major predisposing cause of acute community-acquired bacterial sinusitis. Also, respiratory viruses have been isolated alone or in combination with bacteria from sinus aspirates of patients with acute sinusitis.¹ Nevertheless, little attention has been paid to the role of viral infections in the pathogenesis of acute sinusitis. The frequency of the appearance of sinus abnormalities during respiratory virus infection is of particular interest as a starting point for study. Because conventional roentgenograms do not clearly outline the ethmoidal sinuses,² it has not been possible previously to determine the frequency of abnormalities in the ethmoid sinuses during common colds. However, the development of MRI has provided a sensitive and safe means for observing abnormalities in all of the paranasal sinuses.

Abbreviation used

MRI: Magnetic resonance imaging

In the present study, serial MRI scans of the paranasal sinuses were performed in volunteers who were given an experimental rhinovirus infection. The MRI abnormalities that were detected in these subjects were then correlated with their subjective symptom scores, duration of viral shedding, and nasal mucous weights. In addition, single MRI examinations were performed in 20 asymptomatic young adults to determine the frequency of baseline MRI sinus abnormalities.

MATERIAL AND METHODS

Volunteers

Rhinovirus infection. Nineteen healthy young adults who gave no history of chronic sinus disease, sinus surgery, or recent colds were recruited from the general University of Virginia population. The volunteers were 18 to 40 years old and included both males and females. All subjects had preinfection serum neutralizing antibody titers to the challenge virus of $\leq 1:2$.

Asymptomatic controls. Twenty asymptomatic, young adults, who also gave no history of sinus disease or recent colds, had single MRI scans of the paranasal sinuses. This group was not challenged with rhinovirus and had no nasal

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washings performed. Both experimental protocols were approved by the University of Virginia Human Investigation Committee, and all volunteers gave written consent to participate in the study.

MRI

MRI was carried out with a 1.0 Tesla Siemens Magnetom (Iselin, N.J.). Contiguous 4 mm thick, transverse sections were obtained through the paranasal sinuses by a spin-echo technique with TR 2500 msec and TE 28/80 msec. Fluid within a sinus appeared as uniform high-signal intensity filling an air cell. When the air cell was only partially filled, an air-fluid level was observed.

Viral challenge

The virus used to infect the volunteers was a strain of rhinovirus type 39 that had been passaged twice in WI-38 human embryonic lung fibroblasts and safety tested by previously described methods.³ After a nasal wash with normal saline solution (5 ml per nostril), the viral inoculum was introduced into the nose in coarse drops (0.25 ml per nostril), given twice, 10 minutes apart, while the volunteers were in the supine position. After viral challenge, volunteers were kept isolated in separate hotel rooms for 5 days.

Measurement of infection

The duration of virus shedding was evaluated by daily nasal washes for viral culture. Specimens were tested for rhinovirus in cell cultures of human embryonic lung (WI-38) by a standard method.⁴ One viral isolate from each subject was identified as type 39 rhinovirus by a neutralization test.⁴ Neutralizing antibody titers were measured in prechallenge and 3 weeks postchallenge serum specimens.⁴ The criteria used for the determination of infection with the experimental rhinovirus were a positive virus culture on 1 or more days and/or a fourfold rise in homotypic serum neutralizing antibody titer to the challenge virus.

Measurement of illness

A modification of criteria developed by Jackson et al. was used to evaluate symptoms scores.^{5,6} The severity of symptoms was graded on a scale from 0 (absent) to 4 (very severe). Eight symptoms (nasal obstruction, nasal discharge, sneezing, sore or scratchy throat, cough, headache, chilliness, and malaise) were evaluated. A total score of 6 or more for 5 days plus nasal discharge on at least 3 of these days and/or the subjective impression of having had a cold were the criteria used for judging the occurrence of illness. Also, daily expelled nasal secretion weights were determined by a previously described method.⁷ Differences in nasal secretion weights were evaluated for significance by the *t* test.

Experimental design

This study was conducted as part of an experiment to determine the therapeutic efficacy of a combination of atropine and pseudoephedrine in treating volunteers with experimental rhinovirus colds. Subjects were randomly assigned to the treatment or control groups. Treatment con-

sisted of 0.3 mg of atropine and 60 mg of pseudoephedrine in capsules given by mouth at 7 AM, 12 noon, 5 PM, and 11 PM for 5 days beginning 32 hours after viral challenge. Matching placebo capsules were given to subjects in the control group.

RESULTS

MRI findings in asymptomatic volunteers

An MRI abnormality of paranasal sinus was observed in 3 (15%) of 20 asymptomatic subjects. The abnormalities noted were ethmoid mucosal thickening, an air-fluid level in middle ethmoid cells, and mucosal thickening of the sphenoid sinus. One subject had the incidental finding of a mucosal cyst of the sphenoid sinus. In the rhinovirus challenge study, prechallenge MRI scans were considered of insufficient technical quality to adequately evaluate the paranasal sinuses in five subjects. Of the 14 volunteers who had technically satisfactory scans, 3 (21%) had an abnormality of the sinuses; all consisted of mucosal thickening in an ethmoid sinus before virus challenge. These abnormalities persisted on repeat testings from 7 to 35 days. Incidental findings in the latter group were that two subjects had antral sinus cysts and one had a frontal sinus cyst.

MRI findings in the rhinovirus-challenged group

Eighteen of the 19 challenged volunteers were infected with rhinovirus type 39 (Table I). One volunteer was infected with a wild-type rhinovirus on the prechallenge viral culture. In addition to the unsatisfactory examinations at baseline in five subjects, the MRI scans obtained during the period of infection were also unsatisfactory in two volunteers.

Of the 10 infected subjects who had technically satisfactory, normal preinfection MRI examinations, two developed abnormalities that were seen on the examination performed during the period of acute infection. Two additional subjects whose prechallenge scans were technically unsatisfactory had MRI abnormalities that were seen during the period of acute infection, which resolved at the time of late reexamination. Thus 4 (33%) of 12 subjects had MRI abnormalities of the ethmoid or antral sinuses that were temporally related to the period of active rhinovirus infection. Sinus mucosal thickening was seen in three of these subjects and an air-fluid level in one. Three of these 4 subjects had a third MRI scan done 37 days after challenge, which showed that the sinuses had returned to normal. The remaining eight volunteers with type 39 rhinovirus infection and technically adequate prechallenge scans did not develop MRI abnormalities of the paranasal sinuses during acute infection.

TABLE I. MRI findings in infected volunteers with T-39 experimental rhinovirus infection ranked by severity of illness based on total symptom score

Volunteer	Virus shedding (days)	Serum neutralizing antibody (pre/post)	Ill	Total symptom score	Nasal secretion wt (gm)	MRI			Active or placebo
						1st, Oct. 9, 13, or 14	2nd, Oct. 21 or 23	3rd, Nov. 21 or 24	
A.A.	4	<2/<2	Yes	45	55	N	R antral fluid	N	P
A.C.	4	<2/8	Yes	38	15	N	N	—	A
F.E.	5	2/<2	Yes	35	16	*	R ethmoid thickening	N	A
V.M.	5	2/4	Yes	30	1	N	N	—	A
J.S.	5	<2/8	Yes	27	7	*	*	—	A
R.D.	†	<2/2	Yes	23	6	N	N	—	P
P.M.	4	<2/32	Yes	22	35	R ethmoid thickening	No change	No change	A
M.K.	6	<2/4	Yes	20	3	N	N	—	A
B.S.	6	<2/8	Yes	19	8	N	N	—	P
A.R.	6	<2/8	Yes	18	8	R ethmoid thickening	No change	—	P
K.T.	6	2/64	Yes	16	4	N	N	—	A
N.G.	2	<2/<2	No	15	5	N	N	—	P
E.D.	5	<2/<2	Yes	12	4	N	Bilateral ethmoid thickening	—	A
E.P.	2	2/8	Yes	11	13	*	R antral thickening	N	P
R.B.	5	<2/32	No	10	5	*	N	—	A
P.L.	4	<2/<2	Yes	9	4	N	N	—	P
A.K.	1	<2/16	No	9	4	N	N	—	A
J.Z.	3	<2/<2	No	4	8	*	*	—	A
T.C.	1	<2/<2	No	3	3	R ethmoid thickening	No change	—	P

N, Normal.

*Technically inadequate for evaluation.

The characteristics of illness in the group showing MRI abnormalities were compared with those in the group without MRI changes (Table II). The mean nasal secretion weight was 22 gm/5 days in subjects who developed MRI abnormalities compared with 5.5 mg/5 days in those who did not ($p = 0.06$). This was confirmed by the mean ($\pm$ SEM) rhinorrhea scores, which were 5.75 (± 2.06) and 1.9 (± 0.7) in the groups with and without sinus MRI abnormalities, respectively ($p = 0.04$). Scores for the other symptoms showed no significant differences between the two groups. All four subjects with abnormalities met the criteria of illness compared with six of eight subjects with no abnormality. The length of virus shedding, serum neutralizing antibody responses, and mean total symptom scores were similar in the two groups.

DISCUSSION

The goal of this study was to determine the frequency of the development of MRI scan abnormalities of the paranasal sinuses during experimental rhinovirus infection. One third of the 12 infected volunteers had ethmoid or antral sinus MRI scan abnormalities that were judged to be associated with the period of active infection. This conclusion was supported by a repeat MRI examination in three of these four subjects at a later date, at which time the findings had returned to normal. In addition, a substantial frequency of MRI abnormalities were seen on initial screening. With both groups combined, 6 (18%) of 34 evaluable subjects had mucosal thickening or fluid in the asymptomatic baseline state. Some of these abnormalities persisted on serial examinations.

Kennedy et al.⁸ have reported on the difficulties in

TABLE II. Infection and illness characteristics in volunteers with experimental rhinovirus infection with abnormal or normal sinus MRI scans

Volunteer	Virus shedding (days)	Serum neutralizing antibody (pre/post)	Ill	Total symptom score	Nasal secretion wt (gm)	MRI results	Active vs placebo
A.A.	4	<2/<2	Yes	45	55	R antral fluid	P
F.E.	4	<2/8	Yes	35	16	R ethmoid thickening	A
E.D.	5	<2/<2	Yes	12	4	Bilateral ethmoid thickening	A
E.P.	2	2/8	Yes	11	13	R antral thickening	P
Total	15	2/4*	4/4				
Mean (± SEM)	3.75 (± 0.6)			26 (± 8.5)	22 (± 11.3)		
A.C.	4	<2/8	Yes	38	15	Normal	A
V.M.	5	2/4	Yes	30	1	Normal	A
M.K.	6	<2/4	Yes	20	3	Normal	A
B.S.	6	<2/8	Yes	19	8	Normal	P
K.T.	6	2/64	Yes	16	4	Normal	A
N.G.	2	<2/<2	No	15	5	Normal	P
P.L.	4	<2/<2	Yes	9	4	Normal	P
A.K.	1	<2/16	No	9	4	Normal	A
Total	34	5/8*	6/8				
Mean (± SEM)	4.25 (± 0.7)			19.5 (± 3.5)	5.5 (± 1.5)		

*≥Fourfold antibody rises.

evaluating MRI findings within the nose and ethmoid sinuses because of the normal nasal cycle. The finding in the present study, that mean nasal secretion weights were fourfold higher in volunteers with MRI sinus abnormalities associated with the period of active infection than in those without such abnormalities, suggests that the MRI abnormalities had clinical relevance in some of the patients. Nasal secretion weights vary widely during experimental rhinovirus infection for as yet unexplained reasons.⁹ The association of higher nasal secretion weights in volunteers with sinus MRI abnormalities in the current study may in part offer an explanation for these variations. Although none of the volunteers in the present study were considered to have clinical sinusitis, the diagnosis is difficult, if not impossible, to establish on clinical grounds alone because the signs and symptoms of viral colds overlap those of acute sinusitis. Therefore the accepted standard of diagnosis of acute sinusitis depends on sinus puncture with the finding of positive bacterial ($\geq 10^4 \log_{10}$) or viral cultures and/or elevated counts of polymorphonuclear leukocytes in the sinus aspirate¹ or the observation of acute abnormalities on conventional radiographs, computerized axial tomographic scans, or MRI scans.

The MRI study was done in combination with a study to test the effectiveness of psuedoephedrine and atropine treatment of experimental rhinovirus colds. This treatment did not have a significant effect on the severity of illness as determined by subjective scoring of respiratory syptoms. In the group of four volunteers with MRI abnormalities, two received active treatment and two received placebo. In the group of eight volunteers without MRI abnormalities, five were given active treatment and three were given placebo. This trend might suggest that a beneficial effect occurred with the treatment relative to the observed MRI abnormalities, but because of the small numbers of subjects studied, no conclusion can be drawn.

The incidence of acute sinusitis after colds has not been well studied. The Cleveland Family Study, a prospective epidemiologic study of minor illness in the home, reported a 0.5% incidence based on clinical diagnosis by the study nurses.¹⁰ The current investigation suggests that sinus MRI abnormalities, which are reversible without antimicrobial therapy, occur commonly in young adults with rhinovirus infection. It is not known if these abnormalities significantly affect the clinical course of illness or in some instances become associated with secondary bacterial infection

of the sinus. However, if the association of increased nasal secretion production and sinus MRI abnormality observed in this study is confirmed, it indicates that these sinus abnormalities are of some clinical importance.

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Prospects for ancillary treatment of sinusitis in the 1990s

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The basis for ancillary therapy of sinusitis derives from anecdotal accounts and personal beliefs rather than definitive data. The recent appreciation that noninfectious inflammatory causes predispose to infectious sinusitis has stimulated renewed interest in developing and documenting efficacious ancillary therapies that could supplement or abrogate antibiotic use. Ancillary therapies of sinusitis could be directed toward (1) preventing viral upper respiratory tract infections (immunizations, virucidal-impregnated tissues, and proper hand-washing techniques); (2) blocking rhinoviral replication and suppressing mediator release with supraphysiologic nasal hyperthermia, although contradictory studies exist with regard to efficacy; (3) promoting sinus and nasal ventilation with both topical and oral α -agonists and exercise; (4) improving mucociliary clearance by reducing mucus viscosity and elasticity with saline solution irrigation, mucoregulators (N-acetylcysteine, S-carboxymethylcysteine, and iodinated glycerol), and ciliary stimulants (adenosine triphosphate); and (5) suppressing/modulating cellular inflammation (eosinophilic, basophilic, and neutrophilic) with topical nasal corticosteroid sprays and mediator antagonists. Recommendations are forwarded for future investigations of promising nonantibiotic ancillary therapies of chronic sinusitis. (J ALLERGY CLIN IMMUNOL 1992;90:478-95.)

Key words: Sinusitis, hyperthermia, α -agonists, mucoregulators, mucociliary clearance, N-acetylcysteine, iodinated glycerol, adenosine triphosphate, topical corticosteroids, mediator antagonists

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Chronic sinusitis may originate from either infectious or inflammatory causes. Infectious sinusitis, which may be suppurative or nonsuppurative and classified as acute, subacute, or chronic, represents infective inflammation of the mucosa of the sinuses with frequent concomitant involvement of the nasal phar-