Chronic sinusitis refractory to standard management in patients with humoral immunodeficiencies

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SUMMARY

Chronic refractory sinusitis is a common feature in patients with primary immunodeficiencies. The efficacy of standard therapeutic strategies is questionable. In an open trial we evaluated the efficacy of azithromycin, N-acetylcysteine and topical intranasal beclomethasone ($100\,\mu$g twice daily for 6 weeks) in 16 patients with primary immunodeficiencies (median age $13 \cdot 5$ years, range 5–32 years). All patients suffered from chronic sinusitis despite regular immunoglobulin replacement therapy every 3 weeks. Magnetic resonance imaging (MRI) scans were performed before and after 6 weeks of treatment to evaluate morphological changes in the paranasal sinuses. Nasal swabs and washings were taken for microbial analysis and measurement of inflammatory mediators (IL-8, tumour necrosis factor-alpha (TNF-α), eosinophilic cationic protein (ECP)) before and post therapy. Inflammatory mediators in nasal secretions were significantly elevated in patients: IL-8 median 2436 pg/ml (range 441–5435 pg/ml), TNF-α $37 \cdot 3$ pg/ml ($3 \cdot 75$–524 pg/ml) and ECP 33 ng/ml ($1 \cdot 5$–250 ng/ml) *versus* age-matched healthy controls: IL-8 median 212 pg/ml (99–825 pg/ml), TNF-α $3 \cdot 77$ pg/ml ($2 \cdot 8$–$10 \cdot 2$ pg/ml) and ECP $1 \cdot 5$ ng/ml ($1 \cdot 5$–$14 \cdot 8$ ng/ml) ($P < 0 \cdot 0001$). Inflammation of the maxillary sinuses was confirmed by MRI scans in all patients, additionally infection of the ethmoidal and frontal sinuses was recorded in five patients. Bacterial growth appeared in 11 out of 16 cultures. In spite of therapy, no improvement in sinal inflammation visualized by MRI was achieved. Moreover, no significant decrease in pathogens and levels of inflammatory mediators could be detected (IL-8 1141 pg/ml, 426–4556 pg/ml; TNF-α $13 \cdot 9$ pg/ml, $4 \cdot 1$–$291 \cdot 6$ pg/ml; ECP $32 \cdot 3$ ng/ml, $3 \cdot 7$–$58 \cdot 4$ ng/ml). Our results demonstrate that conventional management of sinusitis is of little benefit in patients with chronic refractory sinusitis with an underlying immunodeficiency. More studies are needed to test antibiotic regimens, probably combined with surgical drainage and anti-inflammatory agents.

Keywords   immunodeficiency   chronic sinusitis   inflammatory mediators   cytokines   MRI scan

INTRODUCTION

The beneficial effect of intravenous immunoglobulin (IVIG) replacement in patients with humoral immunodeficiencies has been well documented [1,2]. Although with IgG levels of > 500 mg/dl the incidence of severe infections, in particular pneumonia, has been reduced, recurrent and chronic infection of the paranasal sinuses remains a common problem. If chronic sinusitis is present, nasal symptoms like discharge and cough are predominant [3]. The clinical management of sinusitis in the immunodeficient patient is controversial. Some authors recommend the same as for the non-immunodeficient patient. Nasal decongestants and steroids, either topically or systemically applied, are thought to be helpful [4]. The choice of antibiotics and their duration and dosage is currently under discussion [5,6]. Moreover, the role of sinus surgery in these patients has not been well defined. Many immunodeficient patients have been treated by sinus surgery without benefit before the diagnosis of their immunodeficiency was established [7].

However, clinical trials to evaluate effective treatment of chronic sinusitis in patients with humoral immunodeficiencies are rare. Therapeutic recommendations rely more on individual experience and practicability rather than on controlled clinical trials.

We attempted to evaluate the effect of antimicrobial treatment in combination with nasal decongestants and beclomethasone on chronic sinusitis in patients with primary immunodeficiencies monitored by magnetic resonance imaging (MRI) and measurement of inflammatory mediators in nasal secretions.

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Table 1. Clinical characteristics of patients

Patient	Age (years)	Sex (M/F)	Diagnosis	IgG	IgM	IgA	IgE (U/ml)	IgG trough (g/l)	MRI (%)	
				At diagnosis (g/l)					Pre-therapy	Post-therapy
A.A.	5	M	CVID	0·15	0·2	<0·05	<0·1	9·2	77	74
K.A.	9	M	CVID	1·7	0·2	0·8	<0·1	12·0	73	67
H.P.	13	M	CVID	0·4	0·2	<0·05	<0·1	9·7	75	84
R.K.	14	M	CVID	2·5	0·3	<0·05	<0·1	8·45	54	32
M.P.	15	F	CVID	0·7	0·3	<0·05	<0·1	5·1	25	50
G.O.	16	M	CVID	<0·5	<0·1	<0·2	<0·1	11·2	43	49
K.D.	16	M	CVID	2·9	0·2	0·7	<0·1	7·0	81	74
H.P.	19	F	CVID	3·5	0·2	0·08	<0·1	13·7	42	48
K.A.	24	M	CVID	4·0	0·1	1·2	<0·1	7·5	83	80
W.S.	32	M	CVID	0·9	<0·2	<0·05	<0·1	3·7	82	80
P.D.	7	M	AT	15·3	2·1	<0·05	<0·01	15·8	ND	ND
F.T.	11	M	AT	6·2	1·51	0·09	0·8	12·3	93	93
E.S.	13	F	AT	9·9	3·1	2·5	6·0	10·3	75	61
B.M.	5	M	XLA	<0·1	<0·2	<0·05	<0·1	9·0	43	49
B.J.	23	M	XLA	<0·01	<0·02	<0·05	<0·1	8·7	66	68
E.A.	9	M	XLP	0·1	0·3	<0·05	0·2	8·4	65	82

CVID, Common variable immunodeficiency; AT, ataxia telangiectasia; XLA, X-linked agammaglobulinaemia; XLP, X-linked proliferative syndrome.

Clinical characteristics of patients and results of MRI scan planimetry of three slices through both left and right maxillary sinuses pre- and post-therapy, given in percent. (q = area of changes of the sinal lining/area of maxillary sinuses × 100).

PATIENTS AND METHODS

Patients

Sixteen of 18 patients with primary immunodeficiencies were selected for the study: 10 with common variable immuno-deficiency syndrome (CVID), three with ataxia telangiectasia, two with X-linked agammaglobulinaemia and one patient with X-linked proliferative syndrome. Median age was 13·5 years, range 5–32 years, sex distribution M:F 13:3.

All 16 patients met the criteria for chronic sinusitis proposed by Shapiro & Rachelefsky [8] (presence of two of the three major clinical signs, rhinorrhoea, postnasal drip and cough for at least 3 months). None of the patients had signs or a history of allergy (IgE median 0·1 U/ml, range 0·1–6·0 U/ml). There were no signs of acute infection and all patients received regular immunoglobulin replacement therapy at a dosage of 400–500 mg/kg body weight every 3 weeks. Levels of IgG, IgM, IgA and IgE at diagnosis and current IgG trough levels are given in Table 1. All patients received adequate doses of IVIG and trough levels did not fall below 0·5 g/l, except for one patient.

Study design

After initial clinical evaluation, MRI scan was performed and nasal lavage fluid was obtained for determination of inflammatory mediators. Additionally, nasal swabs were taken for culture. Sub-sequently all patients were treated with azithromycin (10 mg/kg) for 5 days, the dose being given twice on the first day. This dosing regimen is expected to produce drug concentrations in target tissues above the minimum inhibitory concentration for target pathogens for a period of up to 10 days [9]. Patients also received *N*-acetylcysteine (10 mg/kg) for 3 weeks, decongestant (xylome-tazolin) for 1 week, and topical intranasal beclomethasone, 100 mg per nostril, twice daily for 6 weeks. Follow-up evaluation, where MRI scan, nasal wash and cultures were repeated, was performed 6 weeks after the first evaluation.

The study was approved by the local Human Committee of Ethics and informed consent was obtained from patients and parents before entering the study.

Monitor parameter

MRI scan. MRI scan was performed on each patient before and after therapy to evaluate morphological changes of the sinal lining. It was chosen for the following advantages. MRI is the best way to assess soft tissue contrast resolution, and images are obtained without exposure to ionizing radiation. Images can be standardized and are examiner-independent [10,11].

Transversal T2 weighted turbo-spin-echo (TSE) (TR = 3800 ms, TE = 20 ms) and proton density weighted (TR = 3800 ms, TE = 20 ms) sequences as well as sagittal and coronal T1 weighted spin-echo sequences (TR = 450 ms, TE = 12 ms) were performed (Siemens Magneton Vision; 1·5 T).

Transversal T2 weighted TSE sequences (scan time 2 min) provided the best images regarding the patterns of inflammatory sinus disease. First, all the paranasal sinuses were compared by two radiologists both pre- and post-therapy. The severity of sinus mucosa abnormality in both maxillary sinuses was then given as a percentage of the total area of both left and right maxillary sinuses. This required three representative slices through the maxillary sinuses in all patients. In these three slices total sinal areas and aeriferous areas were determined by computer-assisted planimetry (program: Siemens sienet). The differences between the two parameters was defined as morphological changes of the sinal lining (mucosal sinal swelling, secretion of mucus, retention cysts or polyps). In one patient only was evaluation of MRI scan by planimetry not possible, due to technical reasons (motion arte-facts). The results of the subjective judgement of all sinuses and planimetry (Table 1) were comparable and equivalent.

Nasal secretions. Nasal secretions were obtained by instilling 5 ml of phosphate buffer into each nostril while the head was tilted

backwards at ≈ 45°. Due to this difficult manoeuvre, which requires a high degree of patient collaboration, nasal secretions could only be obtained in nine of the 16 patients.

Measurement of inflammatory cytokines

Inflammatory cytokines IL-8 and tumour necrosis factor-alpha (TNF-α) were measured in nasal secretions using commercially available ELISA kits (DPC, Bad Nauheim, Germany). Eosinophilic cation protein (ECP) was measured by radioimmunoassay (Cap-System, Pharmacia, Freiburg).

As there are no normal ranges for inflammatory cytokines in nasal secretions, results in our patients were compared with levels of inflammatory mediators found in 14 healthy age-matched controls.

Cultures

Cultures were taken by deep nasal swabs and processed immediately. Swab material was transferred to an agar base containing 5% sheep blood and to chocolate agar to allow growth of *Haemophilus influenzae*. The substrate haemin and NAD, together with the Bacitracin test, were used for further bacterial classification. Typing was performed using a slide agglutination test with polyclonal antisera (Wellcome).

Only accepted pathogenic organisms were considered, organisms of the residual flora (*Corynebacterium* spp., *Staphylococcus epidermidis*, *Streptococcus viridans*, and *Neisseria* spp. other than *N. meningiditis* and *M. catarrhalis*) were not listed. All strains identified were sensitive to azithromycin.

Statistical analysis

Results are expressed as median and range. Data were analysed by use of the Mann–Whitney *U*-test

RESULTS

MRI scan

MRI before therapy revealed chronic infection of the maxillary sinuses in all patients. Moreover, mucosal swelling in the ethmoidal and frontal sinuses was recorded in five patients.

The evaluation post-therapy showed no improvement of sinal inflammation. Moreover, mucosal swelling in the maxillary sinuses increased by more than 20% in two patients. The degree of mucosal swelling measured by planimetry for each individual patient pre- and post-therapy is presented in Table 1.

Inflammatory mediators

At initial evaluation, levels of inflammatory mediators in nasal secretions were significantly elevated in patients compared with healthy controls: IL-8 levels in patients before therapy, median 2436 pg/ml, range 441–5435 pg/ml; IL-8 in healthy controls, median 212 pg/ml, range 99–824 pg/ml ($P < 0.0001$) (Fig. 1).

TNF-α in nasal secretions of patients before therapy were: median 37·3 pg/ml, range 3·75–524 pg/ml; healthy controls, median 3·77 pg/ml, range 2·8–10·2 pg/ml ($P < 0.0001$) (Fig. 2).

ECP levels in patients before therapy were: median 33 ng/ml, range 1·5–250 ng/ml; ECP in healthy controls, median 1·5 ng/ml, range 1·5–14·8 ng/ml ($P < 0.0001$) (Fig. 3).

Evaluation post-therapy showed slight reduction in IL-8 (median 1141 pg/ml, range 426–4556 pg/ml, NS, Fig. 1) and TNF-α (median 13·9 pg/ml, range 4·1–291·6 pg/ml, NS, Fig. 2)
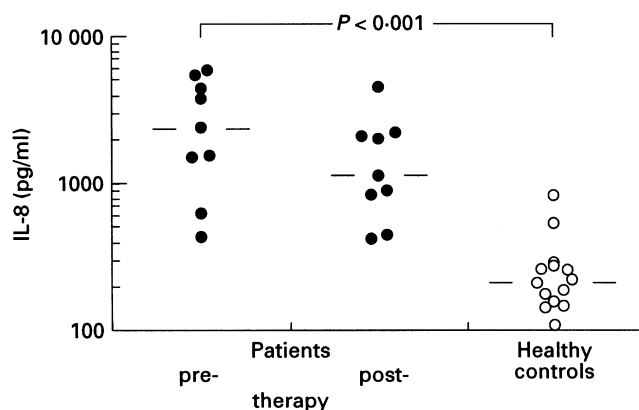

Fig. 1. IL-8 (pg/ml) measured in nasal lavage fluid pre- and post-therapy of patients with chronic sinusitis and healthy controls. IL-8 levels in patients are significantly higher compared with healthy controls. The slight reduction of IL-8 after therapy does not reach statistical significance.

and no change in ECP levels (median 32·3 ng/ml, range 3·7–58·4 ng/ml, Fig. 3).

Cultures

Initially, bacterial growth was seen in 11 of 16 cultures (nasal swabs) and was not significantly changed by therapy. (For detailed results see Table 2.)

DISCUSSION

Although the respiratory tract is the primary area of infection in patients with humoral immunodeficiency, it is surprising that only a few studies have investigated the treatment of chronic sinusitis in such patients. As anticipated by clinical signs, sinusitis was confirmed radiographically and by the measurement of significantly increased levels of locally produced inflammatory cytokines and mediators in all our patients. In addition, in most nasal cultures pathogens were detected. Although the use of cultures from deep nasal swabs for the microbiological assessment of sinusitis is questionable, cultures of material directly aspirated were not done for ethical reasons.
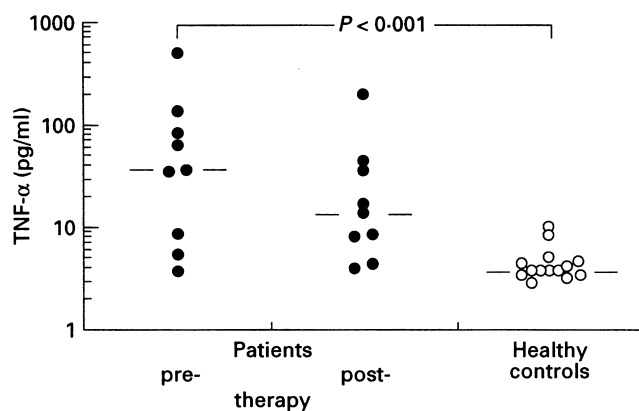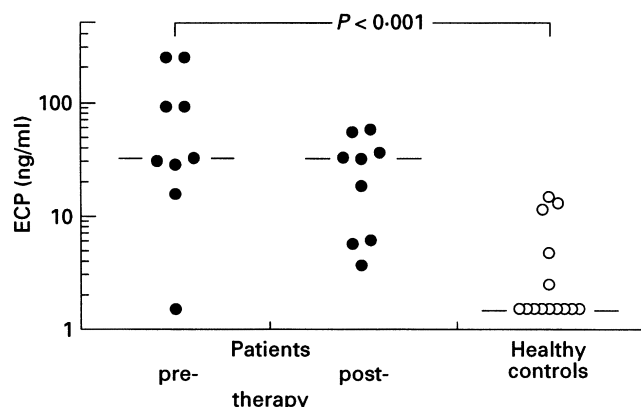

Fig. 2. Tumour necrosis factor-alpha (TNF-α) (pg/ml) measured in nasal lavage fluid pre- and post-therapy of patients with chronic sinusitis and healthy controls. TNF-α in patients is elevated compared with healthy controls ($P < 0.0001$) and not significantly influenced by therapy.

Fig. 3. Eosinophilic cationic protein (ECP) (ng/ml) measured in nasal lavage fluid pre- and post-therapy of patients with chronic sinusitis and healthy controls. ECP is elevated compared with healthy controls ($P < 0.0001$) and not influenced by therapy.

There has been debate on the interpretation of abnormalities seen in the sinuses with computed tomography (CT) and MRI, since there have been reports of a high incidence of incidentally found sinus opacifications in asymptomatic children, in some series up to 30–50% [12,13]. However, ostial obstruction in children with upper respiratory tract infection usually resolves within 2 weeks after disappearance of symptoms [14]. This has also been shown in adults [15].

In our patients, oedema and mucosal thickening of the sinal lining were paralleled by high levels of TNF-α, IL-8 and ECP, reflecting a high activity of neutrophilic, monocytic as well as eosinophilic inflammation. It has been shown by others that proinflammatory cytokines in nasal lavage fluid are significantly elevated during both allergic inflammation and acute upper respiratory infection, with normalization 2–4 weeks later [16,17].

Besides the elevation of proinflammatory cytokines, a high

Table 2. Results of cultures

Patient	Age (years)	Culture pre-therapy	Culture post-therapy
A.A.	5	*H. influenzae* non-b	Negative
K.A.	9	*H. influenzae* non-b	Negative
H.P.	13	*H. influenzae* non-b	*H. influenzae* non-b
R.K.	14	*H. influenzae* non-b	*S. pneumoniae*
		Staph. aureus	*Staph. aureus*
M.P.	15	*H. influenzae* non-b	*H. influenzae* non-b
G.O.	16	*Staph. aureus*	*Staph. aureus*
K.D.	16	Negative	*S. pneumoniae*
H.P.	19	Negative	*H. influenzae* non-b
K.A.	24	*H. influenzae* non-b	*H. influenzae* non-b
W.S.	32	*H. influenzae* non-b	*H. influenzae* non-b
P.D.	7	*S. pneumoniae*	Negative
F.T.	11	Negative	*Staph. aureus*
E.S.	13	Negative	*Serratia liquefac.*
B.M.	5	*H. influenzae* non-b	Negative
B.J.	23	Negative	*H. influenzae* non-b
E.A.	9	*S. pneumoniae*	*S. pneumoniae*
		H. influenzae non-b	*H. influenzae* non-b
			Staph. aureus

degree of eosinophilic inflammation was also observed, as demonstrated by high levels of ECP in nasal secretions. This finding is in contrast to previous studies, which revealed a high degree of eosinophilic infiltration in patients with both chronic sinusitis and allergy and/or asthma, but not in patients with chronic sinusitis alone [18]. Our finding of high ECP concentrations in nasal secretions in the absence of asthma or allergies, demonstrated by normal or undetectable IgE levels in our patients, challenges this generally accepted concept. Alternatively, high levels of ECP may support the view that recurrent infections trigger an asthma-like hyper-responsiveness of the sinal mucosa which makes chronic sinusitis in patients with an underlying predisposing condition not a matter of infection alone.

In patients with primary immunodeficiencies, immunoglobulin replacement therapy has proved effective in preventing recurrent infections and chronic sinusitis [19,20]. However, in our patients, who were all under high-dose IVIG when participating in this study, this therapeutic approach seems to have failed. The reason for this discrepancy is unclear, but may be related to the failure of immunoglobulin therapy to restore antibody concentrations at the mucosal surface to compensate for absent secretory IgA and IgM. However, other issues also need to be addressed, like choice of antibiotics, duration of treatment, doses of anti-inflammatory steroids and sufficient sinal drainage.

We chose azithromycin since it is known to achieve high local tissue concentrations at the site of infection, and has an excellent activity against Gram-positive and Gram-negative pathogens. It is taken up by macrophages, which serve as a vehicle for transport to more distant disease foci, leading to tissue levels exceeding concurrent serum concentrations [21,22]. In addition, azithromycin also possesses activity against intracellular pathogens such as *Mycoplasma pneumoniae*, which may frequently cause respiratory infections in patients with antibody deficiency syndromes [23]. The fact that a relatively short 5-day schedule of azithromycin treatment achieves antimicrobial activity for at least 10 days makes compliance and completion of treatment more likely [9]. Nevertheless, we noted no change of microbial load during therapy.

The need for antimicrobials in the treatment of subacute sinusitis in children has been challenged by some authors [6]. This further raises the question whether findings of mucosal oedema or opacification of the sinuses on radiographic examination are indicators of inflammation due to infection. Nevertheless, many authors recommend antibiotics combined with decongestants and intranasal steroids to diminish the inflammatory response and improve drainage of the sinuses. Although we used topical beclomethasone in an appropriate dosage, we found no effect on proinflammatory cytokines and ECP levels in nasal secretions. This suggests that either higher doses of anti-inflammatory steroid treatment or endoscopic surgery to ensure adequate sinal drainage in chronic sinusitis may be necessary. However, whereas surgery for chronic sinusitis has proved to be effective in otherwise healthy children, failures occur in patients with underlying immunodeficiencies, cystic fibrosis and immotile cilia syndrome [7].

To treat effectively patients with humoral immunodeficiencies and chronic sinusitis, a combined therapeutic concept is probably necessary. Management of chronic sinusitis has to be directed at clearing bacterial infection, restoring mucus integrity and mucocilliary clearance for prevention of renewed infection of the sinuses. Surgical procedures in immunodeficient patients might be necessary in some cases, but should be considered carefully. Whether normal IgG levels in nasal secretions, achieved by

increased doses of IVIG therapy, can prevent bacterial colonization of the sinuses is currently not known. Future studies will have to be directed at evaluating the effect of long-term antibiotic treatment, high doses of anti-inflammatory medication and the benefit of increased local immunoglobulins, which might be achieved by increasing the dose given intravenously or even by local application.

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