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International Consensus Conference

on

NASAL POLYPOSIS

&

9th Croato-Italian Rhinosurgical Advanced School

CIRAS

Zagreb, Croatia, 2002.

Introduction

Two years ago I was invited to Siena as a speaker to the IFOS International Consensus Conference on Nasal Polyposis. This conference was organized by Desiderio Passali. Both scientific and social aspects of the conference were excellent as they are always when this knight of Italian rhinology organizes meetings.

Just at that time I agreed with Desiderio and a group of international friends to organize the second conference on nasal polyposis within the frames of the traditional Croato-Italian Rhinosurgical Advanced School (CIRAS), which otherwise is held on annual basis, most frequently in Zagreb, Croatia.

The International Faculty members here in Zagreb are as follows: Bachert C. (Gent, Belgium), Castelnuovo P. (Varese, Italy), Clement P.A.R. (Brussels, Belgium), Kawauchi H. (Izumo, Japan), Kern E. (Mayo, Rochester,USA), Klapan I. (Zagreb, Croatia), Kozlov V. (Yaroslavl, Russia), Lacroix S. (Geneva, Switzerland), Lopatin A. (Moscow, Russia), Lund V. (London, UK), Mann W. (Mainz, Germany), Mladina R. (Zagreb, Croatia), Nicolai P. (Brescia, Italy), Onerci M. (Ankara, Turkey), Pawankar R. (Tokyo, Japan), Ponikau J. (Mayo, Rochester, USA), Scadding G. (London, UK), Setliff R. (Sioux Falls, SD, USA), Sood V.P. (New Delhi, India), Stierna P. (Stockholm, Sweden), van Cauwenberge P. (Gent, Belgium).

Most of the speakers present today in Zagreb were also speakers in Siena at that time. I find this fact very important since the general knowledge about the ethiopathogenesis of nasal polyps obviously rises quickly. To again get together almost the same group of people who are considered to be the experts for the problem of nasal polyposis on biennal basis seems therefore an excellent idea.

I sincerely hope it will help in approaching the final goals: to completely understand the polyps, remove them from the list of surgical diseases, and to treat them definitely. This sounds like a science fiction, I know, but it is not like that. I will give you just three supportive arguments:

First, nobody believed in Jules Verne's visions. Still, one hundred years after he wrote his books, the first man was on the Moon.

Second, hardly five years ago the so-called forefinger human civilization begun to change into "thumb generation": the strongest and the most adroit finger of the man's hand is not any more a forefinger, but the thumb. The reason: mobile phones, SMS messages sent through the mobile phones, play-stations etc. Ten years ago probably nobody could believe it would happen. But it happened. Almost at once.

Third, the most recent results in human genome researches suggest the possible revolution. Big changes appeared at the horizon.

Are we ready?

I believe we are.

Ranko Mladina
Zagreb, May 2002.

About the book

This book is a result of big efforts of every single author. It consists of two parts: first, which presents the results of investigations, enthusiastic clinical work and the experience of every single of them. The authors, all of them speakers to this Consensus Conference in Zagreb, wrote their attitudes and opinions as journal articles which are the up to date statements about the particular problems concerning nasal polyposis.

The second part consists of 600 various answers to the 30 standardized Consensus questions, given by 20 speakers.

The reader will certainly find interesting controversies about most important points of the ethiopathogenesis and the treatment of nasal polyposis. These controversies give the outstanding value to this conference itself and to this book as well.

This book will serve as a precise document about the state of the art in the year 2002 when nasal polyposis is concerned.

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LONG TERM RESULTS OF ENDOSCOPIC SINUS SURGERY IN CYSTIC FIBROSIS

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Cystic fibrosis is the most common substantially lethal hereditary disease among young Caucasians (Vaughan and McKay 1975). That infectious and polypoid degeneration of the nasal mucosa is part of this condition had not been recognized by the otolaryngologist until 1959 (Lurie 1959). The frequency of nasal polyposis in children is extremely low, about 0.1 % (Lannof et al 1973). Schwachmann et al (1962) found nasal polyposis in 6.7 %, Cepero et al (1987) in 10 %, Neely et al (1972) in 24 % and Stern et al (1982) in 26 % of the patients with cystic fibrosis. Settipane (1984) stated that any child of 16 years or younger with nasal polyps should be evaluated for cystic fibrosis. He found in cystic fibrosis the prevalence of nasal polyps to be 20 %. Later the prevalence was estimated to be 32 % in children and 40 to 48 % in adults with cystic fibrosis (Deane et al 1997), but at the same time these authors state that the detection of nasal polyps may be limited by the ability of the young child to tolerate nasal examination.

With the introduction of modern examination techniques (nasal endoscopy and CT scanning), it was to be expected that the prevalence of nasal polyposis in cystic fibrosis was higher than estimated ever before. Brihaye et al (1994) found in a prospective clinical study of 84 patients during careful endoscopic examination after decongestion, topical anaesthesia and aspiration of the secretions, the presence of inflammatory polyps coming out of the middle meatus in 45 % of the cases (mean age 15 years : range 5-34 years). The same authors performed a CT scan in 28 patients with cystic fibrosis and found in all cases a partial or complete opacification of the anterior complex (anterior ethmoid, maxillary sinus and when developed frontal sinus). In 42 % of the patients the posterior complex was free of disease (posterior ethmoid, and -when developed- sphenoid sinus).

Initially, radical surgery for nasal polyposis in cystic fibrosis was estimated to be necessary and it was advised to remove the polyps as they appeared (Lurie 1959). When nasal obstruction occurred polypectomy was the rule (Schwachman et al 1962). Regrowth, however, was sometimes observed within 3 weeks and many patients had multiple polypectomies going from 1 up to 12 procedures per child (Schwachmann et al 1962, Stern et al 1982, Reilly et al 1985). Crockett et al (1987) was the first to stress the importance of a long term follow-up (average 5 years) and showed that when intranasal ethmoidectomy and Caldwell-Luc procedures are combined with polypectomy, fewer recurrences and longer symptom-free intervals result. Cepero et al (1987) also advocated Caldwell-Luc procedure in conjunction with polypectomy. Unfortunately as a sublabial antrostomy is contra-indicated in children less than 10 years (Shurin 1983), a Caldwell-Luc procedure can only be performed in older children and adults.

Since the introduction of endoscopic sinus surgery (Wigand 1981, Stammberger 1986, Kennedy 1985), a sublabial antrostomy is not needed any longer to achieve radical surgery. With endoscopic sinus surgery (ESS), because of the optic control, not only more radical surgery can be achieved, but also the morbidity has decreased and the safety increased, all major advantages in pediatric surgery. The first results of this technique in children were reported by Lusk et al (1990). Duplechin et al (1991) reported for the first time the result of this kind of surgery in cystic fibrosis children and afterwards this type of surgery was used more or less successfully by many other authors (Cuyler et al 1989, 1992, Duplechin et al 1991, Triglia et al 1992, Jones et al 1993, Tunkel et al 1994, Moss et al 1995, Davidson et al 1995, Nishioka et al 1995, Rowe-Jones et al 1996, Marks et al 1997). Many of these articles dealing with cystic fibrosis show one or more flaws, such as: no follow-up time mentioned (Cuyler et al 1984, Duplechin et al 1991, Davidson et al 1995), mixed patient population (cystic fibrosis, isolated polyposis, Woakes syndrome : Triglia et al 1992, cystic fibrosis patient with lung transplantation and sinonasal disease or only sinonasal disease), long term follow-up which is not long term for this disease (3 years: Cuyler 1992, Parson 1992, Nishioka et al 1995; 2 years : Moss et al 1995, Rowe-Jones et al 1996, 9 months : Marks et al 1997), inadequate follow-up (by phone : Jones et al 1993; by questionnaire Nishioka et al 1995), retrospective studies (Moss et al 1995), majority of patients not children (Moss et al 1995, Davidson et al 1995, Rowe-Jones et al 1996) or different surgical procedures had been performed (mostly endoscopic antrostomy with or without irrigation catheters, frontal trephination, transantral ethmoidectomy : Moss et al 1995) and the number of patients and average age not mentioned (Parson 1992).

The aim of this study was to evaluate (subjective and objective evaluation done by one single ENT specialist) in a prospective way the long-term results (average follow-up time 8 years) of extensive sinus procedures from sinonasal polyposis in a pediatric population of cystic fibrosis patients in a pediatric population of cystic fibrosis patients only suffering from sinonasal polyposis.

Material and Methods

A. *Patients*

All patients were seen before surgery and followed after surgery by one staff member of the ENT department who did not perform the surgery himself, but assisted all the surgical procedures. In all children a careful ENT history was taken as well as an endoscopic nasal examination and a CT scan before surgery. Thirty-five endoscopic ethmoidectomies were performed in 21 patients (mainly children). The average age was 8.7 years (3 months to 27 years) at the time of the first surgery.

All patients belong to a population of ± 100 cystic fibrosis patients who are followed continuously by the pneumologist in the pediatric department (life-time follow-up). The diagnoses of cystic fibrosis were confirmed in all cases by a positive sweat test. In all children endoscopic total sphenoidectomy was performed under general hypotensive anaesthesia. All operations were performed by one experienced ESS surgeon.

The number of recurrences was determined by history and nasal endoscopy. This prospective study was started in 1977 and ended in 1995.

B. *Indications for surgery*

Indications for surgery were based mainly on history (referred to the ENT department by the paediatricians, because of medical therapy-resistant complaints, signs and symptoms), ENT examination and CT scan of the sinuses. All patients showed a satisfactory respiratory and nutritional status. An extensive nasal endoscopy was performed with a rigid 2.8 mm or 4 mm Panoview Wolf endoscope just prior to surgery, while the patient was already under general anaesthesia.

C. Postoperative care

The postoperative care consisted in frequent cleansing of the nasal cavity after surgery, nasal lavage and antibiotic therapy. All the postoperative care was carried out again by the staff member, who did not perform the surgery.

Results

A. *Complaints before surgery*

The most common complaints (n=21) at first consultation and ranked according to the frequency of occurrence were : nasal obstruction (94 %), recurrent spells of acute rhinosinusitis (85 %), rhinorrhea (75 %), headache (69 %) and poor quality of sleep (62 %). The youngest patient was referred at the age of 3 months because of a failure to thrive caused by poor nutrition due to complete nasal obstruction which was not present at birth but occurred later, and at the time of surgery was accompanied by stridor.

In the older children it was the discomfort caused by the above mentioned complaints that resulted in chronic fatigue, decreased ability to concentrate and poor school results.

B. *Signs and symptoms before surgery*

Again ranked according to frequency of occurrence, the sign that was always present was mouth breathing (100 %), broadened nasal dorsum (72 %), high arched palate and hypertrophy of the gum (22 %).

During endoscopy nasal obstruction after decongestion was still present in 86 %. The nasal obstruction was due to massive polyposis in 72 % of the cases and to medialisation of the nasal lateral wall of the remaining 28% of the cases. Purulent secretions were seen in 67 % and concomitant septal deviation in 44 %. One case showed the presence of a unilateral antrochoanal polyp.

Main indications for surgery: recurrent spells of rhinosinusitis, rhinorrhea and sleep disturbances due to nasal obstructions.

In two older patients the indications for surgery had been headache caused by localised recurrence of polyps due to compartmentalisation of the frontal recess region and one case of acute dacrycystitis due to a huge ethmoidal pyocoele, compressing the nasolacrimal duct on one side.

C. *Associated procedures*

Apart from the complete spheno-ethmoidectomy, 3 septoplasties were performed because of severe septal deviation, obstructing one nasal cavity (if this septal deviation was not corrected it would continue to impair nasal breathing and it would make postoperative care on that side impossible) and three partial medial conchotomies were performed because of severe polypous degeneration of the middle turbinate.

D. *Results of the surgery*

Three to six months after surgery : there was a 100 % decrease of the nasal obstruction (main preoperative complaint). The quality of sleep and the day-time somnolence was also improved in 60 %. The complaints of headache had mostly disappeared in 80 % but some patients still complained of partial or total anosmia (20 %), rhinorrhea (40 %) and recurrent spells of rhinosinusitis (65 %). Rhinoscopy showed persistent purulent secretions in practically all children. Two patients didn't show any recurrence of polyps during that period, 12 showed limited recurrence. In 3 cases a massive recurrence was seen at 6 months after surgery, again resulting in severe nasal obstruction.

Long term follow-up (Table I)

The average follow-up was 7 years (9 months to 10 years). In that period surgery was performed 35 times in 21 children. Massive recurrence justifying repeated surgery was seen in 42 % of the cases. Therefore, the number of operations for each child averaged 1.6 (1 to 4 operations). Twelve patients (58 %) were completely free of recurrence and needed no further surgery. Six children (29 %) all younger than 10 years a the time of the first surgery showed recurrent massive polyposis. Three of these (14 %) had more than one recurrence. The duration between the first and the second surgery (average 1.5 years, 6 months to 4 years) was always shorter than between the second and third surgery (average 4 years, in three cases only), or between the 3rd and the 4rd surgery (4 years, in one case). Two older patients (10 %) aged 12 and 15 years respectively at the time of the first surgery, showed localised recurrence in the frontal recess as mentioned before 3 and 7 years after the initial surgery.

Discussion

Stern et al (1982) claimed that in 31 % of the patients with massive polyposis in cystic fibrosis spontaneous and permanent disappearance of polyps occurs. In view of this statement one can wonder if surgery in these children is necessary at all, as

spontaneous and permanent disappearance seems to be the natural evolution of the disease. This statement highlights the necessity to know more about the natural history of massive polyposis in cystic fibrosis children. The authors (Brihaye et al 1994) endoscopically studied a population of 84 cystic fibrosis patients. They found medial bulging of lateral nasal wall in 10 children (12 %, 6 males and 4 females, mean age 5 years, range : 3 months to 8 years), inflammatory polyps coming out of the middle meatus in 30 patients (45 %, 28 males and 10 females, mean age 15 years, range 5-34 years). These observations on the prevalence of the disease related to the age tell something about the natural history of the disease. It seems that the disease starts at early age (0-10 years) with a medialisation of the lateral nasal wall due to a mucopyosinusitis of the maxillary sinus, followed by nasal polyposis at later age (5-20 years), protruding from the middle meatus (mean age 15 years). The authors had seen CT evidence that at later age some patients show a kind of spontaneous ethmoidectomy with limited polyposis. So it seems that Stern et al. (1982) are right in their statement on spontaneous improvement of the nasal polyposis in adult age (spontaneous and permanent disappearance however was not observed by the authors). Therefore the remark of Marks (1996) on the article of Nishioka et al (1995) that asymptomatic and minimally symptomatic patients with CF should not undergo sinus surgery and that extreme caution should be used before electing to operate on symptomatic patients with cystic fibrosis, looks meaningful. When facial deformation occurs in children with complete nasal obstruction (broadening of the the nasal dorsum and development of high arched palate because of mouth breathing) resulting in a poor quality of life, surgery is the only option. In the infant with respiratory distress and feeding disturbance, even the most conservative ENT surgeon or paediatrician will agree that surgery is the only alternative. One can of course argue that maybe a simple polypectomy is sufficient and complete sphenoidectomy is not necessary (Schwachmann et al 1962).

One sees, however, a very high recurrence rate of the polyposis in the series of patients treated only with polypectomy (61 % Cepero et al 1987, 72 % Schwachmann et al 1962, 87 % Reilly et al 1985). When combining intranasal ethmoidectomy with Caldwell-Luc the recurrence rate dropped dramatically (12 % Cepero et al 1987, 35 % Crockett et al 1987).

With the introduction of endoscopic sinus surgery, surgery became even more radical because of a better visualisation of the disease, and the morbidity decreased in such a way that the surgery can also be performed in children and young infants. The youngest patient ever operated upon in the literature (Tunkel et al 1994) was a 13 month-old girl. She was operated upon because of nasal obstruction caused by medial displacement of the lateral nasal wall. The same condition was seen by the authors of this article in a 3 month-old boy, resulting in total nasal obstruction and stridor. Tunkel et al (1994) called this condition maxillary sinus mucocoeles. It is our opinion, however, that this condition is not caused by mucocoeles, but by mucopyosinusitis. The mucosa of the maxillary sinus shows already polypous degeneration (not found in mucocoeles) and the lumen is filled with the typical puttylike purulent secretions. Because of ostial dysfunction the pressure in the maxillary sinus

increases and the nasal lateral wall is displaced medially. Parson (1992) stated that the extent of intranasal surgery of polyposis was found to be inversely proportional to the recurrence rate. Even with a total sphenoidectomy, the recurrence rate will still be high if the follow-up time is long enough. Those articles that deal with long-term results (average of 2-3 years) showed recurrence rates of ± 50 % (Parson 1992, Rowe Jones et al 1996, Nishioka et al 1995). The authors confirmed that the longer the follow-up is the higher the recurrence rate will be. In our series the patients with no recurrence had an average follow-up of 5 years, those with one recurrence 8 years, two recurrences 9 years and the only one with 3 recurrences had a 12 year follow-up period. Also important, however, for the recurrence rate is the age at which the first surgery took place. The average age of the 12 patients with no recurrence was 11 years, with 1 recurrence 8 years, with 2 recurrences 5 years, and the one with 3 recurrences was also 5 years of age at the time of the first surgery.

So, the younger the child is at the first surgery, the higher the odds are to have a recurrence. Two factors may be responsible for this observation. First it may be that an early nasal manifestation of cystic fibrosis represents a more aggressive type of the disease and/or secondly it may also be that the after care in these young children (average 5 years of age) is very difficult and not adequate to prevent early recurrence (several general anaesthesias are required for an adequate cleansing of the nasal cavity after surgery). The exception, however, confirms the rule. From Fig. 1 it is clear that some children were operated on at a very young age for nasal polyposis and they remained free of recurrence during a long follow-up time (one child was operated on for the first time at age 4 and was followed-up for 10 years).

Also in the authors' experience endoscopic sinus surgery for nasal polyposis in children with cystic fibrosis proved to be a safe technique. Two cases showed post-operative temperature that disappeared the day after surgery when the packing was removed. One case had an easy-to-control postoperative bleeding and another case showed a benign heart arrhythmia during the first postoperative day. Finally one patient showed a temporary ozaena for 6 months.

Due to the lower morbidity and better visualisation of the pathology during surgery, ESS is definitely a better (more radical and safer) technique than the headlight intranasal ethmoidectomy. Combined with hypotensive anaesthesia the safety is even higher (less bleeding results and better visualisation) and the blood loss can be limited on average to 130 ml (20-200 ml).

In conclusion one can state that in consideration of the good clinical results (major improvement of the quality of life) and the absence of major complications (in the hands of an experienced surgeon) ESS in children with cystic fibrosis seems to be a better option than repeated polypectomies and/or headlight intranasal ethmoidectomy with or without Caldwell-Luc.

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CLINICOPATHOLOGICAL CHARACTERISTICS OF INVASIVE-TYPE ASPERGILLOSIS IN PARANASAL SINUSES

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Invasive-type aspergillosis occurring in paranasal sinus is not a common disorder. We have experienced three cases of aspergillosis in paranasal sinuses invading to the orbit and skull base. These cases are presented and clinicopathological feature of this disease entity is discussed. Case-1: 70-year-old man with hypertension complained of headache. Fungal infection was located in frontal and ethmoidal sinuses and bone destruction was found at superior wall of frontal sinus and at medial wall of ethmoidal sinus. Case-2: 81-year-old man with dehydration suddenly complained of visual disturbance. Aspergillosis was found in ethmoidal sinus and sphenoidal sinuses, and bone destruction was seen at medial wall of the ethmoidal sinus. Case-3: 84-year-old man with diabetes mellitus complained of headache and sudden visual disturbance as well. The lesion of aspergillosis was located in the maxillary sinus,and bone destruction was found at posterior wall of maxillary sinus. For the diagnosis and treatment, CT scan and MRI was effective in making sure bone destruction and intracranial or intraorbital invasion of fungal infection. Serum level of α-D-glucan was an useful specific indicator of fungal infection and continuous monitoring of it reflects clinical outcome of aspergillosis in these patients. In three cases, the surgical intervention was performed together with a medication of anti-fungal drugs. Prognosis of these patients is individually different, but unfortunately two of them died of the intracranial complication (at 22nd and 93 rd postop day, respectively), because fungal infection was long-lasting due to immunocompromized aged-hosts. Therefore, much more intensive care should be paid for managing these patients, if aspergillosis in paranasal sinus is of an invasive type. Otherwise, these patients clinical course can easily become worse and fatal.

AMPHOTERICIN B MODIFIES THE BIOELECTRIC PROPERTIES OF HUMAN NASAL EPITHELIAL CELLS IN VITRO

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Chronic rhinosinusitis associated with nasal polyposis (NP) is a severe recurrent clinical condition. The etiology of NP remains not elucidated and has been debated for many years. Several theories have attributed nasal polyposis to a variety of causes including genetic predisposition, dysfunction of the autonomic nervous system of the nose and abnormalities of carbohydrate metabolism. The two most plausible, widely discussed theories involved allergy and inflammation (1). On the other hand, because nasal polyposis has been associated with increased bacterial and fungal infection, treatment with antibiotics and anti – fungus have been proposed. We have recently reported that nasal lavages with the fungicidal agent Amphotericin B (AmphoB) induce disappearance of polyposis in about 40 % of our patients.

AmphoB belongs to a class of cholesterol – binding agents known as the polyene antibiotics whose members also include nystatin and filipin. It has been shown to form channels in lipid membranes that are permeable to ions, water and electrolytes (2). A recent work has reported that AmphoB cause a redistribution of caveolin to endosmes and loss of caveolae (3). On the basis of these findings, we speculate that AmphoB might alter cell membrane stricture and thus affect the properties and/or cell surface statement of membrane ion channels/transporters, and as a consequence transepithelial ion transport. The aim of the present study was to investigate the possible effects of a short – and long – term treatment with AmphoB on ion transport across primary human nasal epithelial cells (HNEC). HNES were isolated from polyp and turbinate mucosa samples by protease despersion and cultured on collagen – coated Millicell polycarbonate filters. After 15 – 20 days of culture, the cells had achieved a polarized state and the bioelectric properties of epithelial cell monolayers were studied by placing the filters in Using chambers. These epithelial cell cultures exhibit dominant Na^+ absorption, and have a transepithelial potential (V1) of – 54 ± 7 mV/cm² and a transepithelial resistance (Rt) of 665 ± 65 */cm², corresponding to a short – circuit (Isc) of 62 ± 9 *A/cm² (n = 10). An apical Cl^- conductive pathway exists, but basal Cl^- secretion does not occur because Cl^- is near electrochemical equilibrium across the apical membrane. In the presence of amiloride, a specific blocker of the luminal Na^+ channel, the apical membrane hyperpolarizes, creating an electrochemical gradient favoring Cl^- secretion. Luminal application of amiloride effectively blocks the apical Na^+ conductance and yields an Isc that represents the induction of net Cl^- secretion. In untreated cells, the magnitude of the amiloride – sensitive current ($*isc_{amil}$), which represents the contribution of electrogenic Na^+

absorption to transepithelial transport, was 48 ± 10 *A/cm^2. Cells that had been treated with AmphoB (50 mM) for 4 h and then cultured for a further 18 h in the absence of AmphoB showed a 70 % decrease in Vt and Isc but no change in Rt. In addition, in these cells, Na^+ absorbtion was significantly reduced, as shown by a 70 % decrease in $*isc_{amil?}$, whereas Cl^- secretion in response to either forskolin (that increase cAMP) or ATP did not change. Chronic apical treatment with AmphoB (50 mM for 4 h per day for 5 days) resulted in a decrease in Rt by 60 %. The transepithelial potential and the amiloride – sensitive current were nearly completely abolished, but, surprisingly, ATP could still induce apical Cl- secretion. These cells were larger in size, and showed a loss in the distribution of the tight junction protein occludin and of the basolateral Na – K – ATPase pump. Neither a short – term nor a long – term treatment with AmphoB affect cell viability, as assessed by the activity of the mitochondrial enzyme succinat – dehydrogenase (MTT test).

In conclusion, our observations suggest that AmphoB significantly affects transepithelial ion transport. The most striking observation is that AmphoB decreased Na^+ absorption, without affecting Cl^- secretion. Because Na^+ hyperabsorbtion, that leads to water retention, may contribute to the development of nasal polyps, we suggest that the decrease in Na^+ absorption following AmphoB treatment might lead to decreased movement of water across the nasal epithelial cells and into the submucosal space. This may result in reduction of interstitial edema and contribute to the disappearance of polyps observed in the patients treated by AmphoB.

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POLYP SURGERY IN ANALGESIC INDUCED ASTHMATIC PATIENTS

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ABSTRACT

The aim of this survey was to disclose the clinical features of analgesic induced asthmatic patients and determine the rate of polyp surgery in these. Between January 1991 and June 2000, 247 patients have been diagnosed analgesic induced asthma in Hacettepe University Hospital Adult Allergy Unit and ENT department. The mean age of the patients were 41.2□12.4 and 179 (72.5%) of them were females. The rate of other accompanying diseases were as follows: perennial rhinosinusitis 78.1%, nasal polyp 34.4%, food allergy/intolerance 23.1%, antibiotic allergy/intolerance 15.8% and chronic urticaria 6.5%. The severity of asthma was mild in 32%, moderate in 51% and severe in 17%. The beginning ages for rhinosinusitis, asthma, nasal polyps and analgesic intolerance were 27.5□11.2, 31.5□12.3, 33.3□12.0 and 35.8□12.2, respectively. Analgesic intolerance spectrum by history was as follows: aspirin 68%, metamizole 51%, paracetamole 20.2%, naproxen 19.8% and other NSAIDs 10.5%. Skin prick tests with common aeroallergens were performed in 205 of the patients and were positive in 24.7% of them where allergen spectrum was as follows: mite sensitivity 14.6%, pollen sensitivity 10.1%, pet sensitivity 2.8% and fungus sensitivity 1.6%. The mean total IgE (log_{10}) level was 1.82□0.59. Oral provocation tests with various analgesics were performed in 135 (54.7%) patients and at least one safe analgesic was determined for these patients. 61(24.7%) of the patients were performed nasal and sinus surgery-29 patients extended surgery, 32 patients conservative surgery of the sinuses. Extended sinus surgery group yields better results than the conservative group.

INTRODUCTION

Nasal polyposis affects about 5 % of patients referred to otolaryngologists. There are different types of polyps ranging from symptompless isolated polyp to diffuse nasal polyposis as in Samter disease. The prevalence of analgesic intolerance (AI) is less than 1% in general population and much more common in certain risk group of patients who have bronchial asthma, chronic urticaria and nasal polyps, where it is 10% in asthmatic patients. The condition where AI and asthma are seen together is classically known as "Aspirin-Induced Asthma" or "Samter's Syndrome", and recently called as "Analgesic-Induced Asthma" (AIA). In the classical description of this syndrome rhinitis starts first and nasal polyp, asthma and AI accompany rhinitis later. In some cases AI may be the first disorder appearing (3,5,7).

The recurrence rate after surgery changes according to the type of polyp and surgical techniques. As a result of the high recurrence rate for nasal polyposis different surgical techniques advocated. Simple intranasal polypectomy with prolonged medical therapy may provide relief in some cases. Ethmoidectomy, internal or external, helped in some more advanced polyp cases. The traditional approaches of the maxillary sinus(Caldwell-Luc procedure), frontal sinus and sphenoid sinus have also been used for along time with different rates of success. The endoscopic surgical approach supplied the surgeons with improved visualization and enabled the surgeons to clean the polyps more effectively. The treatment with steroids increased the symptom free period after the surgery. Antibiotics, leukotrien blocking agents, furosemide have also been used with some efficacy at preventing polyp recurrence. Powered instrumentation and image guided surgery gave additional advantages in polyp surgery (1,2,4,6).

Nasal polyps themselves alone are not an indication for surgery. But it is necessary in patients with decreased quality of life despite appropriate medical therapy. Nasal polyp surgery is recommended to improve nasal airway, to prevent recurrent infections, to improve asthma and to decrease medication requirements. Surgery in nasal polyps should be accepted as an adjunct to medical therapy. Although we have more detailed information about the polyps and anatomical structure of the patient and more sophisticated technical advantages compared to previous surgeons, we still have problems in preventing recurrences in diffuse nasal polyposis. To decrease the incidence of recurrences and to lengthen the symptom free period in diffuse nasal polyposis requiring surgery, prospective studies comparing the efficacy of different types of surgeries are necessary.

MATERIAL AND METHODS

A total of 247 patients admitted to Hacettepe University Hospital Adult Allergy Unit who were diagnosed AIA between January 1991 and June 2000 were enrolled in this survey.A standard questionnaire was filled in for all the patients. Data collected by this questionnaire included age, gender, age of diagnosis for asthma, rhinosinusitis, analgesic intolerance, nasal polyps; features of AI (responsible analgesic(s), latent period between the drug ingestion and the beginning of the symptoms, the reactions or the symptoms emerged, duration of the symptoms), other accompanying allergic diseases (antibiotic and food allergy/intolerance, metal allergy, dermographism, chronic urticaria), the atopic status of the patient and of his/her family.

Routine skin prick tests were performed to all the patients except for the patients, who were pregnant, or had chronic urticaria and/or dermographism or used antihistaminic drugs at the time of the test. Twelve standard antigen solutions (dermatophagoides pteronyssinus, phleum pratense, olea europa, artemisia vulgaris, parieteria officinalis, hazelnut, betula verrucosa, cat, dog, horse, alterneria alternata and cladosporium herbarum) were used which were prepared by ALK (Denmark) and Greer (USA) companies. Skin testing was performed as described by Österballe et al. The standard antigen solutions were applied after pricking the skin of the volar

aspect of the forearm with a special lancet having 1 mm tip. Histamine and saline were used as positive and negative controls, respectively. A wheal with perpendicular diameters of 3x3 mm or more was considered as positive reaction. Atopy was defined as a positive reaction to any one of the allergens. A positive familial history of atopy was considered when the patient reported a first-degree family member with the symptoms of asthma, allergic rhinitis and/or atopic dermatitis. Serum total IgE levels were measured in all the patients except for those who refused blood drawing or in whom blood could not be drawn for some reason. The diagnosis of bronchial asthma was made by history depending the international guidelines or had been made in previous years in the same clinic.

The diagnosis of AI and AIA were made by history. Sufficient and reliable clinical history of at least 2 events was required for AI. The reaction should have occurred within 3 hours after the ingestion of the analgesic. If there was only one event, then confirmation by oral provocation test was required. Oral provocation tests were performed in the selected patients with the purpose of determining the analgesics that they could use safely. To perform these tests the requirements as follows should have been met: there should not have been a history of urticaria or angioedema attack in the last week; asthma should have been stable (FEV_1 at least 70 % of the predicted value or absolute value over 1.5L/min); continuing normal antiasthma treatment including steroids; betamimetics, methylxanthines and short acting antihistamines should have been stopped 10 hours, sodium cromoglycate and ketotifen 48 hours and long acting antihistamines 20 days, before the test. There should be at least a seven days interval between a positive test and the second one.

Tests were performed in the hospital, under conditions that the patients are observed closely and could be treated urgently. ASA, paracetamol, and codein prepared as pills in the pharmacy of our hospital; and sodium salicylate and nimesulide as marketed were used. All the patients were examined and their basal FEV_1 and blood pressure values were determined before the tests. Tests were ended when a reaction appeared or when the highest test dose was reached. After the highest dose the blood pressure and FEV_1 measurements were continued for 3 more hours in 1 hour intervals. All of the oral provocation tests were started with lactose as placebo. The drugs were applied in doses of 0.1, 1 and 10 mg for ASA; 50, 100, 250, 500 and 750 mg for paracetamol; 3, 5, 10 and 20 mg for codein, 500 mg of single dose for sodium salicylate. In addition, one quarter, one half, three quarters and whole of the 100mg, 7.5mg, and 12.5 mg tablets of nimesulide, meloxicam and rofecoxib were used for oral provocation, respectively. Bronchospasm (at least 15 % drop in FEV_1 or PEF value); nasoocular reaction (sneezing, nasal discharge, nasal obstruction and conjunctival irritation); urticaria (itching and erythematous lesions rised over the skin); angioedema (swelling in the skin and/or the external mucosa) and/or systemic anaphylaxis (in addition to urticaria and/or angioedema more 30 mmHg drop in blood pressure and/or upper airway obstruction) were considered as positive reaction.

Physical examination, chest radiography, pulmonary function testing was performed in all the patients. Bronchodilatation test, methacholine airway challenge, and serological test were also performed when indicated. SPSS statistical package

(SPSS, 7.0- 95 release) was used for the analysis of the data. The means and the standard deviations for the numerical variables were calculated. Ten-based logarithm of the serum total IgE level was determined to obtain a normal distribution.

61 patients underwent surgery. 56 patients had prior surgeries at other institutions such as sinonasal polypectomy, Caldwell-luc, intranasal ethmoidectomy, sphenoidotomy, external ethmoidectomy, frontal sinus trephination, frontal sinus obliteration with osteoplastic flap. 32 patients underwent conservative surgery and 29 patients underwent extended surgery.

RESULTS:

Results are shown in the tables. In table I, demographic, clinical and laboratory characteristics of the analgesic induced asthma patients are presented. In table II, data about the analgesic intolerance is listed.

During early postoperative period in all patients sinonasal symptoms improved. Asthma improved in all patients but one. The worsening of asthma after operation despite patent nasal airways in this patient might be explained by inspiration of unhumified, unfiltrated, unwarmed air into the lungs, or postnasal discharge, or sinopulmonary reflex. 27 patients required revision surgery.

The indications for revision surgery were :

- o Nasal obstruction
- o increased complaints of asthma posterior nasal discharge
- o recurrence of diffuse polyposis
- o recurrence of complaints after cessation of systemic corticosteroids.

In this group despite postop marked reduction of asthma, 82% required asthma treatment during postop follow up later. 29 patients underwent extended surgery. In this group five patients required revision surgery due to disease in the maxillary sinus or in the frontal recess. No worsening of asthma occurred. Only two patients required treatment of their asthma on the followup.

When we look for the reasons for failure in revision cases the following factors were found responsible :

- Insufficient ethmoidectomy
- Insufficient opening of anterior wall of sphenoid sinus
  -Decreased ventilation
  -Decreased drainage
  -insufficient drug concentration
  -Insufficient cleaning
- Insufficient surgery of the frontal sinus
  -Polyps at the frontal recess and frontal ostium area
  -Polyps and mucoceles in the frontal sinus

-Stenosis of frontal ostium
- Insufficient surgery of the maxillary sinus
  -Insufficient maxillary sinus ostium
  -Reclosure of the ostium
  -Decreased ventilation and drainage
  -Insufficient drainage due to thick secretions
  -Insufficient cleaning
- Insufficient removal of septa
  -Insufficient drug concentration behind the septa
  -Insufficient cleaning of the polypoid mucosa behind the septa
  -Pool for collection of secretions
  -May be the focus for polyp regeneration
- Free bony spicles, granulation tissue and polyp recurrence

CONCLUSIONS:

Analgesic induced asthma is more common in middle aged females and there are some diseases accompanying this condition like rhinosinusitis, nasal polyp, food allergy/intolerance, metal allergy and chronic urticaria as reported before with which our current results are in accordance. The beginning ages for rhinosinusitis, asthma, nasal polyps and analgesic intolerance were 27.5□11.2, 31.5□12.3, 33.3□12.0 and 35.8?12.2, respectively in which the order of appearence is also in accordance with the literature. Intolerance to aspirin, metamizole and paracetamole are most common which may be due to their common use. It's important to suggest alternative analgesics to the analgesic intolerant asthmatics most of whom are frightened to use any analgesic even when they have severe pain. Oral provocation tests should be performed before suggesting an analgesic to these patients. At least one alternative analgesic was found for the tested patients and the safety of nimesulide, meloxicam and rofecoxib are similar to that of codeine and paracetamole.

Operation on the sinuses and nasal airways reduce asthmatic medication requirements and frequency of hospitalization for asthma after the operation. Therapeutic intervention of sinonasal disease has an impact on lower airways. Extended approach appear to offer a significant advantage to the ASAI patients requiring surgical management for severe diffuse nasal polyposis over conservative treatment.

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Table I. Demographic, clinical and laboratory characteristics of the analgesic induced asthma patients.

	N=247
Age	41.2□12.4
Gender (Females)	179 (72.5%)
Beginning ages for (mean□SD) Rhinosinusitis Bronchial Asthma Nasal polyp Analgesic intolerance	 27.5□11.2 31.5□12.3 33.3□12.0 35.8□12.2
Asthma Severity Mild Moderate Severe	 79 (32%) 126 (51%) 34 (17%)
Accompanying disorders Rhinosinusitis Nasal polyps Food allergy/intolerance Antibiotic allergy/intolerance Metal allergy Dermographiasm Chronic urticaria	 193 (78.1%) 85 (34.4%) 57 (23.1) 39 (15.8) 27 (10.9) 26 (10.) 16 (6.5)
Familial history of atopy	148 (59.9%)
Familial history of analgesic intolerance	21 (8.5%)
Skin prick test performed Positive reaction among the patients tested Mite sensitivity Pollen sensitivity Animal dander sensitivity Fungus sensitivity	205 (83%) 61 (24.7 %) 36 (14.6%) 25 (10.1%) 7 (2.8%) 4 (1.6%)
Log_{10} of total serum IgE	1.82 □ 0.59
Keeping pets	24 (12.6%)
Smoking status (ever smoked)	59 (23.9%)

Table II. Data about the analgesic intolerance:

	N=247
Patients oral provocation tests performed	135 (34.7%)
No of tests with aspirin and no of positive ones	5 - 4 50 - 14
No of tests with paracetamole and no of positive ones	3 - 2 0 - 0
No of tests with metamizole and no of positive ones	86 - 7 14 - 4
No of tests with naproxen and no of positive ones	43 - 9 33 - 4
No of tests with codeine and no of positive ones	13 - 1
No of tests with sodium salicylate and no of positive ones	
No of tests with nimesulide and no of positive ones	
No of tests with meloxicam and no of positive ones	
No of tests with rofecoxib and no of positive ones	
Intolerance with history Aspirin Metamizole Paracetamole Naproxen Other	 168 (68%) 126 (51%) 50 (20.2) 49 (19.8) 26 (10.5)
Refractory period (from ingestion of the drug to the emergence of the reaction in minutes)	38.5 □ 42.8
Emergency room referrals in the last year due to analgesic intolerance	127 (51.4%)
Type of reaction (with clinical history) Bronchospasm Urticaria Angioedema Anaphylaxis Rhinitis Gastrointestinal symptoms	 166 (67.2%) 73 (29.6%) 65 (26.3%) 21 (8.5%) 15 (6.1%) 4 (1.6%)

BASIC IMMUNOLGY OF NASAL AND PARANASAL SINUS MUCOSA AND OUR TREATMENT STRATEGY WITH AN IMMUNOPHARMACOLOGICAL DRUG (SUPLATAST TOSILATE) OF CHRONIC INFECTIVE RHINOSINUSITIS COUPLED WITH NASAL ALLERGY

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Our ongoing research on basic immunology for nasal mucosa is briefly adressed for better understanding of immunological events in nasal and paranasal sinus mucosa. And then our clinical trial for the treatment of patients with chronic persistent rhinosinusitis with polyp formation is introduced in detail. As you already know, a long term per os administration of macrolide series of antibiotics has been widely used and settled down in Japan for the treatment of chronic infective rhinosinusitis or otitis media with effusion and its clinical efficacy is fairly accepted.

However, chronic rhinosinusitis coupled with nasal allergy is refractory even to this treatment. It is because that eosinophilic infiltration and activation in paranasal sinuses are considered to be a major contributing factor to the pathology, in addition to ostium blockade with polyp formation.

Therefore, we conducted a clinical trial and examined the clinical efficacy of Suplatast Tosilate together with macrolide series of antibiotics in the treatment of patients with chronic rhinosinusitis coupled with nasal allergy with or without polyposis , in order to target on the pathological contribution of eosinophils. Simultaneously, nasal lavage fluid and mucosal specimen of middle meatus were sampled as much before and after treatment and processed for analyses of eosinophil infiltrations, ECP levels, and the immunohistochemistry of Th2-type cytokine-producing cells and VCAM-1 expression of capillary venule. As results, the long term(more than 4 weeks) administration of Suplatast Tosilate together with macrolide series of antibiotic is fairly effective for the treatment of patients with chronic rhinosinusitis coupled with nasal allergy, even though a large polyp formation around ostium can be a prolonging factor of inflammation in maxillary sinus. In patients with good response to the treatment, eosinophil infiltration and ECP levels were both down-regulated.

Furthermore, in these cases, number of IL-4 producing cells and VCAM-1 expression in capillary epithelia were also decreased interestingly.

At the upcoming symposium, based on our data, we will discuss pathology of this disease entity and the treatment strategy employing macrolide series of antibiotics and cytokine-modulating immunopharmacological drug (Suplatast Tosilate).

CLINICOPATHOLOGICAL CHARACTERISTICS OF INVASIVE-TYPE ASPERGILLOSIS IN PARANASAL SINUSES

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Invasive-type aspergillosis occurring in paranasal sinus is not a common disorder. We have experienced three cases of aspergllosis in paranasal sinuses invading to the orbit and skull base. These cases are presented and clinicopathological feature of this disease entity is discussed. Case-1: 70-year-old man with hypertension complained of headache. Fungal infection was located in frontal and ethmoidal sinuses ,and bone destruction was found at superior wall of frontal sinus and at medial wall of ethmoidal sinus. Case-2: 81-year-old man with dehydration suddenly complained of visual disturbance. Aspergllosis was found in ethmoidal sinus and sphenoidal sinuses, and bone destruction was seen at medial wall of the ethmoidal sinus. Case-3: 84-year-old man with diabetes mellitus complained of headache and sudden visual disturbance as well. The lesion of aspergllosis was located in the maxillary sinus,and bone destruction was found at posterior wall of maxillary sinus. For the diagnosis and treatment, CT scan and MRI was effective in making sure bone destruction and intracranial or intraorbital invasion of fungal infection. Serum level of â-D-glucan was an useful specific indicator of fungal infection and continuous monitoring of it reflects clinical outcome of aspergillosis in these patients. In three cases, the surgical intervention was undergone together with a medication of anti-fungal drugs. Prognosis of these patients is individually different, but unfortunately two of them died of the intracranial complication ,respectively, at 22 days and 93 days after even an appropriate surgical intervention, because fungal infection was long-lasting due to immunocompromized aged-hosts. Therefore, much more intensive care should be paid for managing these patients, if aspergillosis in paranasal sinus is invasive type. Otherwise, these patient s clinical course can easily become worse and fatal.

ARACHIDONIC ACID METABOLITES AND SINONASAL POLYPOSIS

Possible Prognostic Value

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Introduction

Arachidonic acid metabolites (AAm) have an important regulatory function within several areas of otorhinolaryngology, such as modulation of immune[1] and allergic response,[2] inflammation,[3] and cancer.[4-7] Cyclooxygenase converts AA into prostaglandins (PGs) and thromboxanes (Txs), whereas lypooxigenase converts it to hydroxyeicosatetraenoic acids (HETEs) and leukotrienes (LTs).[8] Nonsteriodal anti-inflammatory drugs, like aspirin, inhibit the cyclooxygenase and stimulate the lipooxigenase pathway, resulting in increased production of HETEs and LTs, whereas corticosteroids inhibit the release of AA from membrane phospholipids, causing a decrease of both lipooxygenase and cyclooxygenase products.[8]

The etiology of sinonasal polyposis (SNp) is still obscure, and so are the possible mechanisms responsible for its formation and development. It has been shown that cell- mediated immune reactions[9] or their disturbances,[10] as well as basophils,[11] might play an important role in the pathogenesis of SNp. In the epithelium of nasal polyps, suppressor-cytotoxic T cells ($CD8^+$) were more frequently observed than helper-inducer T cells ($CD4^+$) and were not located close to mast cells[9]. On the other hand, $CD4^+$ cells were commonly observed in the submucosal layer and in the connective axis.[12] Also, evidence has been given that mast cells, displaying interleukin-2 (IL-2)-receptor, are very often related to $CD4^+$ and major histocompatibility complex (MHC) class II-positive T lymphocytes.[9] Furthermore, the increased number of mast cells and their degranulation, [12] caused by activated T-cell cytokines, play an important role in the development of edematous changes in Snpformation.[13] The capillaries in SNp appear small in number but have very high permeability.[14] Recent data suggest that transforming growth factor b 1 (TGF-b-1), synthesized by most prevalent inflammatory cells in SNp-eosinophils,[15] contributes to the structural abnormalities (eg. Stromal fibrosis and basement membrane thickening), characteristic of SNp.[16] Also, urokinase-type plasminogen activator (u-PA) in inflammatory tissue has been shown to be related to proliferative changes of the mucous membrane.[17] A significant decrease in nasal mucociliary clearance was also observed in patients with SNp.[18]

SNp was considered a manifestation of allergy in at least a part of patients. Recently, many investigators have shown that a number of patients with SNp have no obvious evidence of allergic disease per se [19,20] and that non-immunoglobulin E-mediated mechanism are responsible for triggering the release of histamine from nasal polyp mast cells.[21] Also, it has been shown that the increased number of metachromatic cells in the epithelium of SNp and adjacent nasal mucosa is not allergy-dependent.[22] On the other hand, allergic rhinitis, asthma, chronic sinusitis, and aspirin sensitivity are frequently associated with SNp.[23] However, it has been shown that they are not under the allergic influence and the both prostaglandins and leukotriens contribute to the formation of edema.[24]

Although AAm have been described as products synthesized by human SNp tissue,[8] no prospective study on AAm metabolism in either SNp or adjacent SN "polypoid" mucosa, or in normal mucosa, has been performed so far. Thus, the aim of this study was to highlight this problem. The AAm used for this analysis were chosen because: A) leukotriene was reported to has important role in the pathogenesis of nasal polyps[8]; B) using PGE2 and PGI_2 as potent vasodilators; PGI_2 could block formation of LTs over AAm system; and C) TxA2 could be used as vasoconstrictive AAm.

Materials and Methods

Production of Eicosanoids

Samples of SNp (adjacent sinus or nasal polypoid) and normal mucosa were obtained at the time of surgery and processed essentially as described before.[25] Briefly, the samples were kept on ice in phospate-buffered saline (PBS) and within 30 minutes minced and processed for measuring the AAm production. Tissue was minced into small fragments (1 to 3 mm^3) in cold PBS and washed 3 times more in fresh PBS by sedimentation at unitgravity for 2 to 3 minutes. The fragments were transferred, sedimented, and resuspended in Minimum Essential Medium (1 mg tissue/5-10 mL MEM) and incubated for 1 hour in waterbath at 37°C. Following centrifugation at 300g for 2 minutes, supernatants were pipetted and stored at –70°C until determination of eicosanoid concentrations.

Radioimmunoassays for Eicosanoids

The level of PGE2, PGI2, TxA2, and LTC4 were determined by radioimunoassay (RIA) procedure, using appropriate kits (Amersham, UK). The procedure of manufacturer was followed strictly. The following kits were used: RIA PGE2, PGI2, TxA2, and LTC4. The determination of PGE2 is based on the conversion of the major PGE2 metabolite (13,14-dehydro-15-keto-PGE2) to a stabile bicyclic compound (11-deoxy 13,14-dehydro-15-keto-11 b, 16E-cyclo PGE2) using sodium carbonate. The amount of free tracer in the supernatant was determined by counting in a beta scintillation counter. The level of unlabeled bicyclic PGE2 was determined from a linear standard

curveusing log-logit graph paper. All assays were performed in triplicate, and each sample was tested twice.

The assays for the detection of 6-keto-prostaglandin F1-alpha (a stabile metabolite of PGI2) and TxB2 (a stabile metabolite of TxA2) or LTC4are based on the competition between unlabeled eicosanoide and a fixed amount of the (^{3}H) labeled compound for specific antibody. Separation of the protein-bound 6-keto-PGF1-alpha, TxB2, or LTC4 from the unbound ligand is achieved by adsorptionof the free component onto dextran-coated charcoal, followed by centrifugation. Measurement of the radioactivity in the supernatant and determination of the concentration of unlabeled 6-keto-prostaglandin F1-a were performed as for PGE2.

Patients

AAm production was analyzed in SNp and in control tissue samples of 37 patients undergoing functional endoscopic sinus surgery at the ENT Department, School of Medicine University of Zagreb, Croatia. Initialy, 63 patients surgically treated for SNp were included in the study. Twenty-six of them were excluded for various reasons: 4 patients have no follow-up data, 8 patients had been treated with corticosteroids and 6 with antiallergic medication before the operation, and 8 had sniffed an upper-respiratory illness 2 weeks before the surgery. All patients underwent a complete otolaryngologic examination. Computerized tomography (CT) echocardiograms , diagrams, and pathological reports were done routinely in each case. There were 22 man and 15 women, aged 37 to 66 years (mean age 58). CT-diagrams showed almost all sinuses and noses tunnels completely occupied with no evidence of the main landmarks of the lateral wall in almost all patients who underwent classical technique surgery more than one (Group 4). On the contrary, Groups 1 and 2 showed relatively clear anatomic landmarks in sinuses and nose and polyp tissue, which were relatively isolated in the above- mentioned areas.

All patients were followed-up for 18 months and periodically examined (at least twice a year) for recurrence of the main disease. One control group included 10 patients treated at the ENT Department for various non-SNp-related diseases. They were treated for otitis media (n=3), nodulus plicae vocalis (n=3), and septal deformities (n=4). There were 7 man and 3 women age 20 to 61 years (mean age 41,7 years). Control mucosa tissue was taken from their noses in the superior part of middle turbinates. This was performed with patient's consent. Another control group consisted of 5 patients previously treated for SNp pathology who still suffered from the mentioned disease. These patients were age 31 to 53 years (mean age, 39,1 years). This group was chosen to be a second control group, because in the hypothesis was made before the study that polyposis recurrences in these patients could be different from "normal" SNp in untreated patients. The differences in CT diagrams between the groups were the other reason for such creation of the study. We expected to find the difference in AAm production between previously untreated patients (Group 1/ Group 2) and patients who had had no response of both maximal medical and surgical therapy.

Statistics

The tissue AAm production was presented as mean ±SD, and statistical comparisons were done by Mann-Whitney-U test and Kruskal-Wallis oneway Anova test. The normality of data distribution was estimated by Kolmogorov-Smirnov Goodness fit test. Post hoc miltiple comparisons were done with Tukey-HSD for unequal sample sizes test modified according to Spjotvoll and Stoline.

Results

Since the production of eicosanoides differed greatly between the patients who had undergone surgery for SNp and have no disease recurrence within 18 months, and those who had disease recurrence during the same period, data for these two groups of patients are shown separately.

As shown in Table 1, the mucosa of the surgically treated patients with no recurrence produced less PGE2 (Group 1; 0.52 ± 0.27 pg/mL) then the mucosa of the patients with disease recurrence (Group 2; 1.24 ± 0.72 pg/mL). It was also lower then the PGE2 production of healthy mucosa (Group 3; 0.79 ± 0.72 pg/mL) or of mucosa of the patients who previously underwent surgery for SNp on several occasions (Group 4; 0.93 ± 0.77 pg/mL). Mann-Whitney-U test showed significant difference in PGE2 levels between the Groups 1 and 2 (P= .002; see Table 2), as well as between the Groups 2 and 3 (P= .048), but there was no significant difference between the groups with SNp (Group 1, Group 2, Group 4) and normal mucosa (Group 3).

Table 1 also shows that the concentration of PGI_2 in Group 1 (2.06±2.46 pg/mL) was lower then in Group 2 (2.51±1.76 pg/mL), but higher then in Group 3 (1.46±1.035 pg/mL) or in Group 4 (1.63±1.29 pg/mL). No significant difference was observed in synthesis in PGI2 in investigated groups.

The mean TxA2 concentration in Group 2 (2.03±0.95 pg/mL) was higher than in Group 2 (2.02±0.81 pg/mL) or in Group 3 (1.54±0.42 pg/mL), and lower than in Group 4(2.42±0.29 pg/mL) (Table1). Significant difference was found between Group 1 and Group 3 (P= .046) as well as between GR3 and GR4 (P= .002) (Table 2).

The concentration of LTC4 was the lowest in Group 1 (8.99±4.04 pg/mL), followed by Group 3 (12.30±6.10 pg/mL), Group 2 (21.44±12.42 pg/mL) and Group 4 (21.01±9.99 pg/mL) (Table 1). Significant difference was found between Groups 1 and 2 (P= .001), Groups 1 and 4 (P= .004), Groups 2 and 3 (P= .041), and Groups 3 and 4 (P= .050) thus highest LTC4 concentrations were observed in the patients who were not free of the disease, i.e. in the patients with SNp recurrences during the postoperative period or in the patients who suffered from SNp and previously underwent surgery for the mentioned pathology on several occasions.

Table 3 shows the incidence of SNp recurrences in surgically treated patients according the level of LTC4 production at the time of surgery. The patients were divided into 2 groups; those who had an increased LTC4 production, i.e. value which was 2 SD higher then the mean value in healthy mucosa (Group 3) (ł24.51 pg/mL) and those with the production of LTC4 within the normal range (Ł24.51 pg/mL).

Recurrences were recorded in 4 out of 4 patients (100%) with increased LTC4 concentration, and in only 6 of 18 patients (33.3%) with decreased LTC4 concentration. The difference was significant (Fisher exact test; P= .28). Concentration of other metabolites did not show any similar correlation.

Using Kruskal- Wallis one-way Anova analysis of variance for LTC4, we observed significant differences (P= .0019) with 3 degrees of freedom (chi-square = 14.9). The highest Mean Rank is in the Group 4 (30.0), then in Group 2, Group 3, and Group 1. PGE2 data tests also had significant differences (P= .03) with 3 degrees of freedom (chi-square = 8.46). The highest Mean rank is in the Group 2 (28.65), then in Group 4, Group 3, and Group 1. While testing PGI2, we observed no significant differences (P= .39). TxA2 data tested with this test showed significant differences (P= .04), chi-square 0 8.0 with highest mean rank in group 4 (27.1) (Table 4).

Post hoc multiple comparisons were done with Tukey-HSD for unequal sample sizes (Test modified according to Spjotvoll and Stoline). This test showed significant differences between Groups 1 and 2 (PŁ .05) and groups 1 and 4 (PŁ .05) for LTC4. Significant difference was observed only between Groups 1 and 2 (PŁ .05) for PGE2. No two groups are significantly different at the 0.05 level for PGI2 and TxA2.

Discussion

Several recent investigations have shown AAm characteristics have change, i.e. it's more active in SNp allergic patients then in non-allergic patients.[26] In our study, we also found a higher mean AAm concentration in allergic patients than in non-allergic patients (59.1% and 40.9% of all patients, respectively), but the difference was not significant (data not shown). This may be caused by the small number of patients included in study.

Furthermore, an increased synthesis of lipooxygenase products of AA, predominantly LTs, has been reported, which may account for the increased glandular secretion in the upper airways.[27] In addition, conversion of LTA4 to lipoxins and 15-HETE acid has been reported to be 3 to 5 times higher in SNp,[28,29] suggesting the possible pathogenetic role of this products. Finally, high level of LTs and low level of PGs in SNp were found to be associated with aspirin-sensitive asthma (ASA).[30] Although we found a somewhat higher LTC4 level and lower levels of PGE2, PGI2 and TxA2 in our ASA patients, these differences were not significant, probably because of the small number of patients included in study (data not shown). However our results appeared to indicate that LTC4 production is higher in patients in whom SNp recurred after surgery (Group 2) or in those who had had several surgeries and recurrences (Group 4), then in patients free of disease recurrence after the surgery (Group1). The level of LTC4 production appeared to have a predictive value, i.e. the higher the production the more frequent the disease recurrence after the surgery. The possible pathogenic role of LTC4 might be the induction of vascular dilatations and mucous secretion, or formation of stromal edema, or cellular infiltration, and so on.[8] LTC4 itself may be responsible for creating "adequate" local conditions for SNp recurrences.[31]

Furthermore, we found significantly different production of both LTC4 and TxA2 in Group 3 then in Group 4 (P= .05, Table2.). Single values are lower in Group 3 then in Group 4. Such a relation is interesting because these 2 groups represented healthy control and positive control subjects (i.e., patients with persistent SNp). However, no such difference found between other groups (Group 1 v others, Group 2 v others, Group 3 v Group 1/Group2), and could not be expected between Group 2 and Group 4, as they both included patients with SNp recurrences (21.44±12.42 pg/mL v 21.01±9.99 pg/mL; P= .71). Bearing in mind the opposite biological functions of LTC4 and TxA2 (i.e., vascular dilatation vs. vasoconsctrictive effects), one could not expect a simultaneous increase of booth eicosanoids in the same group. We have no rational explanation for this finding. Similarly to LTC4, Group 1 had a significantly lower PGI2 production then Group 2, but it was not significantly lower then in Group 4. Data from a grater number of patients appear to be required to determine whether the change in the production of this eicosanoid has the same meaning as LTC4. In conclusion, our results clearly showed that LTC4 synthesis was increased in the patients in whom polyposis tended to recur (Group 2 and Group4). Of course, the cellular source of LTC4 is undefined because it is known that nasal mucosa is consists of many cell types able to produce the above mentioned metabolites.

If these differences in the production of AAm are important for the pathogenesis of SNp, as suggested by our results, they open away for the application of a appropriate therapy in the treatment of this disease, i.e., administration of the components that inhibit AA release from membrane phospholipides. The beneficial effect of the use of corticosteroids (CS) in therapy of SNp has been described elsewhere.[32-34] This method has been found better then the treatment of SNp with surgery alone, resulting in a varying and uncontrollable proportion of recurrences.[35-37] Future studies comparing the effects of CS with postoperative findings[38] and different concentrations of AAm expressed in SNp are expected to shed more light on the ethiology of SNp[39]. Therefore, such investigations have just begun at our laboratory.

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TABLE 1. Median and Mean Aam Concentrations According to Groups of Subjects

GROUP	GR1	GR2	GR3	GR4
PGE2median	0.50	1.00	0.57	0.68
Mean = SD	0.52±0.27	1.24±0.72	0.79±0.72	0.93±0.77
PGI2 median	1.19	2.21	1.01	1.70
Mean = SD	2.06±2.46	2.51±1.76	1.46±1.03	1.63±1.29
TxA2 median	2.33	2.30	1.50	2.30
Mean = SD	2.03±0.95	2.02±0.81	1.54±0.42	2.42±0.29
LTC4 median	8.13	17.15	12.60	17.22
Mean = SD	8.99±4.04	21.44±12.42	12.30±6.10	21.01±9.99

Abbreviations: PGE2, prostaglandin E2; PGI_2, prostaglandin I2; TxA2, Tromboxane A2; LTC4, leukotriene C4; GR1, patients without sinonasal polyposis recurrence in post operative period; GR2, patients with sinonasal polyposis recurrence in post operative period; GR3, healthy volunteers; GR4, patients operated several times for sinonasal polyposis

TABLE 2. Mann-Whitney-U Test Significance (p-values) Between Aam Concentrations in the Observed Groups of Patients with SNp and in Control Mucosa

Groups	PGE2	PGI2	TxA2	LTC4
GR 1 v GR 2	P= .0023	P= .1139	P= .8368	P= .0013
GR 1 v GR 3	P= 1.0000	P= .8147	P= .0459	P= .1775
GR 1 v GR 4	P= .4857	P= .8531	P= .7096	P= .0091
GR 2 v GR 3	P= .0480	P= .1120	P= .0680	P= .0410
GR 2 v GR 4	P= .3900	P= .3900	P= .4120	P= .7130
GR 3 v GR 4	P= .5381	P= .8060	P= .0020	P= .0500

Abbreviations: Aam, arachidonic acid metabolites; SNp, sinonasal polyposis; PGE2, prostaglandin E2; PGI2, prostaglandin I2; TxA2, thromboxane A2; LTC4, leukotriene C4

TABLE 3. *SNp Recurrences According to Preoperative LTC4 Concentrations*

LTC Concentration (pg/mL)	No of Patients		
	Total	Without recurrence	With recurrence
Ł24.508*	18	12	6
ł24.508	4	0	4

*The level by 2 SD higher than the mean value in healthy mucosa (GR3) (12.3 ± 6.104) 18 months after operation. Fischer exact probability for the upper tail is P= .0287

TABLE 4. *Kruskal-Wallis One-Way Anova Statistics and Observed Significance for Groups Tested*

	GR1 (Mean Rank)	GR2 Chi Square	GR3 P Value	GR4	
PGE2	12.3	27.6	18.1	30.0	14.9 .0019
PGI2	15.7	28.6	16.9	20.8	8.5 .0300
TxA2	18.3	25.2	17.4	19.4	2.9 .0390
LTC4	22.3	21.5	11.7	27.1	8.0 .0400

TREATMENT OF SINUSITIS RECURRENCE IN PATIENTS WITH CHRONIC POLYPOUS SINUSITIS

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Etiology of nasal polyposis is still unclear at present. Modern surgical technologies allow removing polyps from all paranasal sinuses with more or less minimal trauma. In principle, there is no fundamental importance what kind of optical systems are used. Some surgeons prefer endoscope and the others prefer microscope. Every surgeon considers that his technique (endoscopic or microscopic) has advantages. Nevertheless the problem of sinusitis recurrence is still actual.

We think that long term results depend on several factors. Firstly, only a qualified surgeon must perform surgery as much less traumatically, as radically. Secondly, only a doctor, who really understands modern sinus surgery, should perform postoperative care. Thirdly, intensive local treatment must be started immediately after appearance of recurrence.

The goal of this study was to evaluate the effectiveness of YAMIK sinus-catheter in treatment of polypose sinusitis recurrence in patients, who previously underwent endonasal sinus surgery for chronic polypose sinusitis.

Material

There are 130-150 patients, who undergo endonasal sinus surgery for chronic polypose sinusitis in our department annually. All surgical procedures are performed under microscopic or endoscopic control. Doctors of our department observe all the patients for 1.5 months after the surgery. Postoperative care is standard and consists of nasal cavity cleaning, nasal shower, and local steroids. Patients are assigned to perform nasal showers themselves. Also patients are informed that in case of acute episode of sinusitis they must immediately apply to the clinic for consultation. Usually 20 - 30 patients apply for consultation with recurrent sinusitis in one year after the surgery. Twenty-four patients operated in 1997 were included in this study. There were 16 males and 8 females ranging from 24 to 56 years old, with the average age of 42,6 years. All of them had undergone endonasal sinus surgery for chronic polypose sinusitis in our department. All patients were under our observation for 4 years. All of them received standard postoperative treatment - nasal showers with 0,9% saline solution and local steroids on a daily basis. Appearance or increase of nasal congestion, mucous or purulent discharge, and headache were the main reasons to address for consultation. A thorough clinical examination, including anterior rhinoscopy and nasal endoscopy, was performed to evaluate the pathological condition of the nose and PNS. Patients with polyps in middle meatus with or without mucous or purulent discharge were included in this study. Patients with severe polyposis were excluded

from this study. Clinical symptoms and findings of rhinoscopy and endoscopy were evaluated during each observation.

Method

The procedure with the use of YAMIK-3 sinus-catheter was described earlier, and therefore we give just a short explanation of it in this paper. YAMIK- 3 sinus-catheter allows to evacuate pathological secretion from all paranasal sinuses at one side simultaneously via sinuses ostia and to introduce medicinal solution to the sinuses via ostia as well. The principle of this method is similar to that of Proetz (1926) method. The only difference is that YAMIK sinus-catheter allows to block nasal cavity from the nostril and choana. It means that controlled (negative and positive) pressure could be created in nasal and PNS cavities. The change of the pressure from negative to positive allows evacuating the secretion from PNS when a patient is in sitting position. The change of the pressure from negative to positive allows introducing the medicinal solution to PNS when a patient is in reclining position and his head is bent to the side of infected sinuses. The use of YAMIK sinus-catheter in patients after endonasal sinus surgery is optimal because sinuses ostia are enlarged during surgery.

We consider YAMIK sinus-catheter to be not only a device for the evacuation of secretion, but also a drug-delivery system. The most important thing is that the evacuation of secretion and the introduction of medicine are performed during one procedure.

All 24 patients were treated with YAMIK-3 sinus catheter in the form of monotherapy. During 4 years 3 patients were treated twice in a year annually, 17 patients were treated once in a year, and 4 patients - once in two years. The course of treatment consisted of 3-5 YAMIK procedures during two weeks. The time of two weeks was sufficient for intensive local treatment. Fungi were found in the nasal secretion of 4 patients, who had been undergoing YAMIK therapy twice in a year. In those patients Amphotericin B was used as a medicine for introduction to the sinuses with YAMIK sinus-catheter. The purulent process developed in 14 patients out of 17, who underwent YAMIK therapy once in a year. In those 14 patients different microbiological cultures were found in the nasal secretion and fungi were found in 3 patients. Antibiotic solution in combination with cortisone was introduced to sinuses with YAMIK sinus-catheter in patients with purulent process. In other 3 patients Amphotericin B was used.

Acute episode of purulent process developed in four patients, who were treated once in two years. In those patients an antibiotic solution in combination with cortisone was used.

Results

No one from this group of patients underwent revision surgery.

EFFECT OF ANTIFUNGAL LOCAL TREATMENT ON NASAL POLYPOSIS

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Introduction

Nasal polyposis (NP) is considered the ultimate stage of chronic rhinosinusitis (CRS), but the etiology of polyp formation is still unknown. It has been recently reported that 96% of patients suffering from CRS, with or without NP, are fungi carriers (1). The same study showed that all asymptomatic volunteers have fungi in their upper respiratory airways. Therefore, one mechanism involved in the development of NP could be an allergic reaction to these organisms. Allergic fungal rhinosinusitis (AFRS) is a disease known for many years (2, 3). The physiopathological mechanisms, diagnostic procedures regarding the identity of involved fungi and effective forms of treatment remain open to controversy. As immunological and histological data accumulated, AFRS represents most likely an immunologically mediated disorder (4).

The aim of this study was to evaluate the effects of the intranasal topical application of an anti-fungal agent on NP.

Material and method

This prospective study included 115 consecutive patients with a male/female ratio of 77/38. The mean age was 45 years, with a range of 19 to 73 years. All patients had over 6 months persistent NP in spite of nasal lavage with isotonic saline and conventional topical corticosteroid spray, twice a day (400 *g/day).

Eighty patients (70 %) had undergone previously endoscopic sinus surgery (ESS). According to the staging described by Malm (4) 33 of the 115 patients (29 %) were stage I (polyps confined to the middle meatus), 62 patients (54 %) were stage II (polyps extended beyond the middle turbinate) and 20 patients (17 %) were stage III (polyps occluding the entire nasal cavity). The anti-fungal treatment used was a suspension of 1 ml of Amphotericin B (Ampho-Moronal, Bristol-Myers Squibb AG, Switzerland) diluted in 1000 milliliter of distilled water. With this dilution, we obtained a concentration of Amphotericin B with the minimal inhibition concentration being effective. In the first group of patients (n = 75) each patient did nasal lavages with 20 ml of this suspension in each nostril, twice a day, during 4 weeks. In the second group (n = 40), patients applied intranasaly twice a day the same suspension with a hand push nasal spray (800 ml/day). Nasal lavage with saline and conventional topical corticosteroid spray were continued, twice a day in the following order; saline, Amphotericin B, corticosteroid spray. Patients have been considered as

cured when endoscopic examination of nasal cavity and middle meatus on both sides revealed total disappearance of polypoid mucosa.

Statistical Analysis

All data were computerized for analysis using the GraphPad InsStat3 package for scientific statistical analysis. The data for the stage dependent analysis has been done by the Chi-Squared test for trend. Further analysis of the influence of previous ESS has been done by a one-sided Fisher's Exact Test. The level of significance was chosen at $p<0.05$.

Results

Intranasal application of Amphotericin B suspension was well tolerated by all patients and no side effects were observed.

After 4 weeks of treatment, total disappearance of NP was observed in 29 patients (39 %) in group I. Eight patients (62 %) with stage I of NP were cured. In stage II, 44 % (21) of patients were cured while none of patients with a stage III has been cured. In the second group, after anti fungal nasal spray, total disappearance of NP was obtained in 17 patients (43 %). Ten patients were stage I and seven were stage II. None were stage III. The higher stage of NP was associated with lower rate of patients cured. The efficiency of the two modes of application of the anti fugal suspension was similar. The percentage of patients with stages I and II of NP cured was statistically significant ($p < 0.0012$, Chi-Squared test for trend) in both groups.

When patients had previously undergone ESS before the anti-fungal treatment, 25 (48 %) were cured in group I and 18 (64 %) in group II. On the other hand, in the group of patients who did not have surgery before this treatment, the rate of patients cured was only 22 % ($p< 0.033$, one-sided Fisher's Exact Test).

Discussion:

Intranasal application of the fungicide agent Amphotericin B seems to induce the disappearance of NP in about 40 % of patients. When patients had previous ESS, a therapeutic effect of Amphotericin B was observed in 54 %. The potency of anti fungal nasal lavage versus nasal spray is similar. The beneficial effect of such treatment could be due to various factors.

Amphotericin B has a direct action on fungal cell membrane (6-8). This molecule has an ability to bind to a lipophilic component of the fungal cell membrane, ergosterol, increasing the cell membrane permeability, with leakage of intracellular components and finally fungi cell death. This could be one of the mechanisms of action of Amphotericin B if hyperreactivity to local fungi is involved in NP. Indeed, Amphotericin B has also the ability to bind, to a lesser degree, to cholesterol in mammalian cell membrane (9) with the same effects on the polyp epithelial cells. We have observed, in vitro, that a short term treatment with Amphotericin B markedly modi-

fies the transepithelial ion transport without cytotoxicity. In contrast, a long-term treatment with Amphotericin B had a significant cytotoxic effect on epithelial cells (data on file). Therefore, the disappearance of polyps could be either due to the elimination of fungi or to a direct effect of Amphotericin B on polyps mucosa cells, or both of these.

In this study, anti-fungal nasal lavage or spray was given in addition to the classical corticosteroid topical spray. We cannot exclude that an increasing in cell membrane permeability induced by the fungicide agent could also have an influence on the efficiency of the corticosteroid treatment (9). An average of 48 % of patients with stages I and II of NP was cured. This treatment was not effective in patients with a stage III of NP.

Fifty four percent of patients were cured after this treatment, if they had previously undergone ESS, as opposed to the 22 % of patients who had not undergone surgical treatment. The higher efficiency of the treatment after surgery could be due to a better penetration of the drug, by an improved application via the surgical cavities.

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HISTOLOGICAL COMPARISON OF NASAL POLYPOSIS IN BLACK AFRICAN, CHINESE AND CAUCASIAN PATIENTS

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We have compared the histological aspects of nasal mucosa biopsies (n= 130) obtained during the bilateral polypectomy and ethmoidectomy performed in black African (N=50), Chinese (N=30) and Caucasian patients (N=50) suffering from bilateral nasal polyposis (NP). The three groups of patients were matched for age and sex. The African and Chinese patients did not receive any medical treatment befor the endoscopic nasal surgery (ENS). All Caucasian patients were treated with corticosteroid nasal spray (400 mg/day) for 6 months. In the absence of subjective and objective clinical improvement, ENS was performed after antibiotic treatment for 10 days and prednisolone 1 mg /kg/ day for 5 days.

Clinical staging of the NP was graded from I to III (I= polyps limited to the OMC, II= polyps extending beyond the middle meatus, and III= polyps occupaying the entire nasal cavity). Stage I NP was present in 22% of the Caucasians and 30% of the Chinese. Stage II was found in 58% of the Caucasians, 56% of the Chinese and 8% of the Africans. Stage III was found in 92% of the Africans, whereas only 20% of the Caucasians and 14% of the Chinese patients had stage III.

The extent of submucosal edema and number of mast cells were similar for the three groups of patients. A significantly greater number of eosinophils was observed in African polyps. Lymphocytes as well as plasmocytes were rare in African but abundant in polyps from both Chinese and Caucasian. Ulceration of the ovelying epithelium of the epithelium of the polyps was observed in 20% of the African and 10% of both Chinese and Caucasians patients. We did not find any significant thickening of the basal membrane.

We cannot exclude the possibility that the histological difference observed between African and Chinese polyps is related to the very common use among the Chinese population of topical intranasal treatment according to their traditional medicine practices.

Since no major histological difference was found in the nasal mucosa and polyps obtained from the three groups of patients, NP in African, Chinese and Caucasian patients, is very probably a similar inflammatory disease in all of three ethnic groups.

STEROIDS: WHEN, WHY AND HOW

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When

Steroids are inevitable tool to put most of the cases of nasal polyposis under control. The term "under control" means to reduce the polypous mass occupying nasal cavities and making the turbinates invisible. So, the answer to the question "when steroids" seems to be "at once after you find polyps in someone's nose". There are at least two good reasons for this.

First, about 5-7% of all cases of nasal polyposis show an absolute resistance towards steroids, be to their topical or systemic use. The reason for that still remains unclear, but what is not unclear is the fact that in these cases the rhinosurgeon has to operate immediately. No conservative therapy will gain any remarkable improvement. Furthermore, these cases show, fortunately, very low recurrence incidence and the intraoperative bleeding as a rule is very scarce enabling surgeon to smoothly remove most of the pathology and to cleanse the nasal cavities almost entirely. These polyps, in addition, usually go no further than ground lamella, i.e. their extension is normally limited with the posterior ethmoid. The sphenoidal sinus is affected very rarely as it is also the frontal sinus.

So, the steroid therapy can make a distinction between two main groups of nasal polyps, looking from the clinical point of view: steroid-refractory but surgically most favourable, and steroid-reactive but surgically problematic.

The second reason to apply steroids at once after polyps are discovered is the fact that in most of the cases the polyps are simply dissolved by means of topical use of sprays, drops etc. and the systemic use of peroral or even intramuscular steroids.

The ability to dissolve the polypous masses, to reduce them at the limits of the ostiomeatal complex (OMC) is a great advantage for the surgeon since this makes possible a good orientation, easier intraoperative search for the roots of the polyps themselves etc.

Steroids have to be applied until the responsible doctor (but must be always the same person!) realizes that the reduction does not go any further. Once the steroid treatment reaches the "bottom" of the conservative treatment possibilities, the local pathological situation must be kept under control by means of the adequate doses to maintain the achieved clinical picture. At that very moment a CT-scanning must be performed for the first time to have a realistic view inside the nose and paranasal sinuses and the situation with the polyps. What can be seen at the CT scans is in fact the same what the surgeon can expect during the surgery. Therefore, the surgeon can do precise plans for the operative removal of the polypous tissues.

Usually the dose that has lead to the remarkable reduction of the polypous tissue is double or triple diminished to serve as a therapy for the maintenance.

The steroid drugs are not applied during the early postoperative period (first week after the surgery), but are continued, usually as a topical application, at least for three months postoperatively. The dose has to be modified individually meaning that the controlling of the clinical status must be frequent, i.e. once a week or two weeks.

Topical treatment with nasal sprays can be continued for years, but with a great caution and in a very low dose.

Why

The steroids inhibit the release of arachidonic acid from the cellular membrane. In this way they directly act against the onset of edema. How? First, once derived from the cellular membrane, the arachidonic acid can be dissociated under the influence of the enzyme cyclooxygenase into prostaglandins (PGs) and thromboxanes (Txs). Both of these metabolites can influence the onset of tissue edema. Second, another enzyme, lypooxygenase, converts arachidonic acid into hydroxyeicosatetraenoic acids (HETEs) and leukotrienes (LTs).

Again, both of these metabolites are promotors of tissue edema.

But on the other hand, arachidonic acid metabolites play an important role in modulation of immune (1) and allergic response (2) inflammation (3) and cancer (4,5). The steroids therefore can strongly block the onset of edema, but at the same time they block the complete cascade of physiological events. This particularly concerns to the role of cyclooxygenase 2 (COX-2) which is considered as a "housekeeper" for the whole organism (protects the normal function of the kidneys, brain, gastrointestinal system etc.). This enzyme is completely blocked by means of steroids and non-steroid anthirheumatics as well. Hence the question arises of whether or not the administration of steroids is always welcome.

This fact must be kept in mind whenever steroids are given in the treatment of nasal polyposis. They are the reason why modern conservative treatment of tissue edema, be it in bronchial tree in asthmatic patients, or in nasal polyposis which is considered as "asthma of the nose", tends to avoid the extreme use of steroids and replace them by other drugs which should be more selective in blocking the physiological events in the organism. One of them could be the montelucast sodium, although the first two-three years of experience do not offer much in the field of nasal polyposis.

This is the answer why we still use steroids in nasal polyposis. They act very effectively in the vast majority of the cases and they can be administered topically. The topical use makes steroids more acceptable since the systemic absorption is not remarkable. This particularly concerns to the mometasone fluorate which absorption is practically zero.

This is not the only answer to the question "why" we use steroids. The other part of the question refers to the fact that before even thinking of surgical treatment, we must try to at least diminish the volume of the polyps. This will enable the surgeon to approach polyps by means of an endoscope in an attempt to precisely see their roots inside the nose and sinuses and than to remove them.

The use of steroids is also strongly recommended after the surgery since in a certain number of cases the operated polyps behave like a wounded beast: they show a strong tendency of revival.

How

In our experience the best results are obtained by the steroids protocol that consists of two parts: preop and postop. The preop one means the so called *breeze dose*, meaning a long lasting (one, up to two months duration) peroral administration of 5 mg dexamthasone. At the very beginning of treatment it is given 2-3 times daily, depending on the clinical picture, i.e. how voluminous are the polyps. The dose is subsequently diminished according to the reduction of the polyps volume. The patient must see the doctor every week, if possible. Once the doctor realises that no more reduction can be achieved, the dose has to be fixed until the patient gets ready for the surgery. At that time the CT scans are performed.

It is our attitude to give the patient also steroid spray in parallel, at the beginning twice a day, one puff in each nostril. This dose is usually diminished to once a day, depending on the clinical picture and the polyps reduction velocity. We insist on mometasone.

In cases of a voluminous polyposis that makes impossible the use of nasal sprays, we start with peroral steroids first, and add nasal spray once the nasal vestibule is clear of polyps.

In the postoperative period we do recommend mometasone spray alone, usually twice a day, beginning from the seventh day after the surgery, i.e. after the removal of Mikulitz package from the OMC and cleansing of the whole nasal cavity.

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LOWER AIRWAY FUNCTION AND THE RELATION BETWEEN MICROBIOLOGY AND CELL POPULATIONS IN SECRETIONS OF THE UPPER AND LOWER AIRWAYS IN PATIENTS WITH CHRONIC RHINOSINUSITIS

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In this prospective study (Ragab A. 2002) of 25 patients that failed conservative treatment and were scheduled for functional endoscopic sinus surgery the authors studied pre-operatively the lung function and compared the microbiology (bacteria and fungi) and cell populations of the MML (middle meatal lavage) and BAL (broncho alveolar lavage).

First the symptoms, endoscopic findings and CT scans scores of these patients were obtained. According to the subjective symptoms 6 patients were diagnosed as asthmatic and 19 patients as non asthmatic. Using objective evaluation of the lower airways baseline function test (FVC, FEV1, FEV1/FVC% and FEF 75 %) was performed in all patients and a histamine bronchial provocation test in those patients without manifest asthma. In patients with manifest asthma a bronchodilatator inhalation test (200 µg salbutamol) was used instead. According to these objective tests 3 subgroups could be differentiated. A first subgroup consisted of asthmatic patients (3 mild, 2 moderate, and 1 patient needed continuous medication), a second subgroup consisted of 9 patients with small airway disease (SAD) and a third subgroup included 10 patients with normale lower airways.

The subjective symptoms were obtained according to the Lund McKay staging system (1993), using a VAS on 6 symptoms (nasal congestion, nasal discharge, facial pain, headache, anosmie, overall discomfort). The endoscopic findings in both nasal cavities were rated according to the Lund-Kennedy scale and the CT scan evaluation was performed using the Lund-McKay scoring system.

No significant correlation ($p>0.05$) was seen between histamine bronchial provocation on one hand and the chronic rhinosinusitis total symptom score, single symptoms score and total CT scans scores.

Using the Wilcoxon signed rank test no significant difference existed for the total symptom scores between the 3 subgroups ($p >0.05$) and for the CT scan scores between the 3 subgroups ($p>0.05$). The polyposis score, however, showed only a significantly higher presence of polyps (100 %) in the asthma group ($p=0.038$).

Using Spearman's test inside each subgroup there existed a positive correlation between nasal blockage ($p=0.02$) and nasal discharge ($p=0.02$) on one hand and the CT scan scores on the other hand.

In conclusion the authors found objective lower airways disease in 60 % of the adults with chronic rhinosinusitis not responding to conservative treatment. Of these 60 %, 24 % met the diagnostic criteria of asthma and were aware of there disease. A higher percentage (36 %), however, was diagnosed as small airways disease and was not aware of their condition (no subjective complaints).

This is the first time that lower airways involvement using objective criteria has been studied in a prospective way in chronic rhinosinusitis patients and that such a high percentage (60 %) of disease was demonstrated.

Secondly the authors compared the cellular content of the middle meatal lavage and BAL in the same group of patients with chronic sinusitis scheduled for surgery, and not responding to medical treatment. So just after intubation and before the start of the surgery 50 middle meatal lavages (MML) were performed and 25 BAL's. At 1000 x light microscope magnification 48 MML's and 24 BAL's cytospin slides were examined for total and differential cell counts (DDC). This showed that eosinophils were the dominant inflammatory cell type in MML's of the asthma subgroup and that they were significantly correlated to FEV1 ($p=0.042$) and the Tiffeneau index ($p=0.037$). On the other hand, neutrophils were the dominant inflammatory cells in the MML's of the SAD subgroup and significantly correlated to FEV 75 % ($p=0.013$) and the Tiffeneau index ($p=0.012$).

Finally there existed no significant correlation in the differential cell counts between MML's and BAL's ($p>0.05$). There existed, however, a significant higher eosinophilia in the BAL of the asthma patients 2.3 ± 3.3) compared to the eosinophilia of the SAD (0.66 ± 0.7) and the NLA patients (0.22 ± 0.5).

The conclusion of this part of the study is that the lower airways involvement in chronic rhinosinusitis patients can be related to the dominant cell type in the middle meatus.

In a third part the authors studied the bacterial cultures of the MML's and BAL's. Positive bacterial cultures were found in 71 % of the MML cultures and only in 2 cases (8 %) of the BAL's. Concerning aerobic bacteria the most common cultures strains in the 50 MML's were Gram-positive bacteria (70 %) with no significant difference for the different subgroups. Among these Gram-positive strains the predominant bacteria were coagulase- negative staphylococci (40 %), again with no significant difference between the different subgroups. The second most common cultured bacteria were Staphyloccus aureus (in 18 % of all the cases) with a significantly higher culture rate (35 % ($p=0.046$) in NLA subgroup.

In the entire CRS group only 6 % showed Gram-negative bacteria mainly Enterobacter (6 %), followed by Proteus mirabilis, E. coli and Klebsiella each 4 % and no significant difference between the subgroups. Anaerobes were present in 20 % of the CRS patients mainly in the SAD subgroup (39 %) significantly ($p=0.025$) higher than in the other subgroups. The most common bacteria were Peptostreptococcus (14 %) and Propionobacteria (8 %).

In 92 % of the BAL's no bacteria were cultured. In one case of the SAD subgroup Staphylococcus aureus was cultured and in another case Acinobacter.

Only in the SAD subgroup there existed a significant correlation between the cultured bacteria of the left (p=0.04) and right (p=0.04) and the neurophilic inflammation. From all subjective symptoms only in the asthma subgroup nasal blockade (p=0.04) correlated with positive cultures and in the same subgroup the CT scan scores (p=0.04) correlated with positive culture rates as well.

In the fourth part of this investigation fungal samples were taken from the middle meatal lavages (MML's), nasal cavity lavage (NCL) and nasal vestibule swab for culture.

For the MML's there didn't exist an important difference between positive cultures of the right (20 %) and the left side (24 %) and there existed no significant difference between the positive culture rates of the different subgroups (asthma 50 %, SAD 22 % and NLA 60 %). The identified genera were Aspergillus in 63 % and Penicillium in 27 %. Fungal balls were found only in 2 cases (8 %) of the 25 CRS patients.

The NCL's gave positive culture rates in 36 % of the cases, and again no difference in the different subgroups (asthma 33 %, SAD 22 % and NLA 50 %). Different genera were found i.e. Aspergillus 66 %, Penicillium 44 %, Cladosporin 33 % and other fungi 55 %).

Only 44 % of the MML cultures were identical to the NCL cultures results. The nasal vestibule gave only in 2 cases (8 % positive cultures) positive results i.e. Aspergillus Niger and yeast.

Finally the BAL culture rates were positive in 28 % of the cases and again no significant difference between the subgroups i.e. asthma (16 %, SAD 22 % and NLA 40 %).

The histopathological examination showed only presence of hyphae in the 2 cases with a fungal ball, one showed a combination of Aspergillus together with Dematiacious (melanine pigment) and the other case showed only Aspergillus. In both cases with a fungal ball the MML cultures turned out to be negative.

MML eosinophilia was only seen in 33 % of the cases with a positive fungal culture.

In conclusion one can state that the recovery rate of positive fungal cultures is highly dependent of the recovery site. The highest percentage of positive cultures was seen in the middle meatus (MML). Aspergillus and Penicillium are the most frequent fungus present over the whole respiratory tract. Cladosporium was only cultured in the nasal cavity. Because of the lack of correlation between eosinophilia and presence of fungi in the MML's and the fact that the highest fungal culture rates were found in the BAL of patients with no lower airways disease (40 % for NLA versus 22 % in SAD and 16 % for asthma) compared to those with asthma and small airway disease, the authors have their doubts about the importance of fungi in the pathophysiology of chronic inflammation. Especially the genus of Penicillium seems to commence colonisation of the mucosa rather then a pathogen.

As a general conclusion one can state that in chronic sinusitis resistant to medical therapy 60 % of the patients showed lower airways disease. Concerning the cell

population in the secretions of the middle meatus neutrophils seem to be the dominant inflammatory cell in the patients with small airway disease and eosinophils the predominant cell in the asthmatic patients. Only in the small airway disease group there existed a significant correlation between the cultured bacteria and the neutrophilic inflammation of the middle meatal lavage. Nasal blockage and high CT scan scores seemed to be significantly related to positive cultures of the MML Fungi seemed to be present in all sites of the airway but mostly not related to inflammatory cells. Therefore the authors suppose that the presence of fungi in the respiratory tract is not the major cause of chronic inflammation.

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NEW TREATMENTS FOR ASPIRIN SENSITIVE NASAL POLYPOSIS

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Adverse reactions to aspirin have been reported almost as long as it has been used as an analgesic and anti-inflammatory. Symptoms of aspirin intolerance include rhinitis, bronchial asthma, urticaria, angioeodema, pupae and anaphylaxis (Widal et al 1922).

Widal first decreased the association of asthma, nasal polyposis and aspirin hypersensitivity in 1922, although this triad is often ascribed to Santer. Aspirin sensitivity occurs in 6% of perennial rhinitis and in 15% of nasal polyposis (Schapowal et al 1995). Aspirin intolerance occurs in some 10% to 20% of adult asthmatics (Dor 1985). Although considerable progress in understanding aspirin sensitivity has occurred with respect to diagnosis, biochemistry, cross-reactivity with non-steroidal anti-inflammatory drugs (NSAIDs), and desensitisation (Sczeklik 1997),(Ferrerri et al 1988), and (Pleskow 1982), the underlying mechanism remains unclear. Aspirin and NSAIDs act by inhibiting cycloxygenase. When this pathway is blocked the products of arachidonic acid metabolism are metabolised via the lipoxygenase pathway releasing large amounts of leukotrienes (LTs) (Vane 1971) and (Sczeklik 1975). AS patients demonstrate an increased sensitivity to leukotrienes as well as increased production. The shunting theory has been questioned because of a lack of an inverse correlation between lipoxygenase and cycloxygenase (prostaglandin) products (Ferrerri et al 1988). There is also the question of where or why arachidonic acid breakdown is occurring in the first place.

Other abnormalities have been noted in AS patients. Aspirin sensitivity is not usually associated with IgE mediated disease and mast cell or other inflammatory cell degranulation is thought to occur as a direct result of contact between aspirin/NSAIDs and the mast cell membrane. This however does not occur experimentally in all AS patients (Assem 1970). The DQ association suggests immunological involvement of T-lymphocytes. The role of IgE in aspirin sensitivity remains controversial. The time course of challenge is different from that of allergen challenge with symptoms after aspirin beginning at around 45 minutes (Scezklik 1997). Skin prick tests are usually, but not always negative to aspirin itself however specific IgE antibodies to the metabolised products of acetylsalicylic acid have been detected in the serum of patients with aspirin sensitivity by some (Daxun 1993), (Zhu 1997), but not all investigators (Schlumberger 1980) and (Scezklik 1997). Whatever the underlying mechanisms the response to conventional treatment in this disease is poorer than for aspirin tolerant patients with higher rates of recurrence following surgery.

Other treatment approaches: the usual therapies for nasal polyposis, viz topical and oral corticosteroids with judicious surgical intervention do not control AS polyps well in most sufferers. Other possibilities exist.

*1. **Diet:*** in addition to reacting to aspirin and NSAIDs some AS patients also find that similar molecules such as coal tar dyes, preservatives and other additives and high salicylate foods also worsen their symptoms. There has been no placebo-controlled, double blind study, but a report suggests that on a diet avoiding these factors improvement occurred within 5 days and was maintained for up to a year. In a recent questionnaire survey of 336 asthmatic adults in Western Australia 33% reported that alcohol had triggered asthma attacks. Wine predominated and was strongly associated with reactions to sulphites in food ($p<.001$). Such reactions are not confined to AS individuals, but there was also an association with intolerance to aspirin and NSAIDs ($p<.01$) (Valley et al). In our patients at the Royal National Throat, Nose and Ear Hospital approximately 50% of AS patients are sensitive to dietary factors, this can be reduced when they respond to anti-leukotrienes.

*2. **Desensitisation:***

a. **Oral:** Zeiss & Lockey first noticed that following aspirin challenge patients could tolerate the drug without ill effects for a period of between 2 days to a week. This phenomenon is thought to be a form of biochemical desensitisation and is associated with a reduction in the amount of leukotriene generated on aspirin challenge. Open studies using this phenomenon by giving patients regular oral aspirin were reported by Stevenson and Mathison. Unfortunately double blind, placebo-controlled studies have not been possible, but Stevenson in a subsequent article reports the results of 65 AS patients treated for between 1 and 6 years, mean 3.5 years who showed significant improvements. Schapowal has produced a comparison of treatment modalities including intranasal ethmoidectomy, topical nasal corticosteroids and oral aspirin. Unfortunately the doses of aspirin needed are high and gastrointestinal side effects occur in 20% of patients taking 500mgs a day and in 46% at 1300mgs per day (Schapowal 1985). This has led some workers to try the effects of lower doses of a completely soluble form of aspirin, lysine aspirin, used topically.

b. **Topical:** Lysine aspirin is soluble, but unstable in solution so that it needs to be freshly prepared before each use. 16mgs given intranasally as a challenge dose in order to determine whether aspirin sensitivity is present, has a sensitivity of 0.93 and a specificity of 0.97 with minimal bronchial side effects in .05% of patients (Schapowal 1985). Patriarca attempted to use intranasal lysine aspirin 2mgs per week in nasal polyposis patients both AS and AT. (Patriarca et al, 1991). He noted that 65% of the AT patients were free of recurrence versus 23% of the AS at one year. Our studies using intranasal lysine aspirin as an alternative to topical steroid in AT patients with recurrent nasal polyposis show that it is at least as efficacious as topical steroid in preventing recurrence and was significantly better at 2 time points when patients histories were compared with their performance on lysine

aspirin. Parikh et al has recently completely a double-blind, placebo-controlled cross-over study of topical lysine aspirin given as 8mgs on alternate days over 6 months compared to placebo in AS patients. There was a significant reduction in the rate of polyp regrowth as assessed by acoustic rhinometry. Immunohistology of inferior turbinate biopsies in these patients suggests that leukotriene receptors (LTRs) are upregulated in AS compared to AT subjects with a decrease in LTR after topical aspirin treatment (Sousa 2002). Other results including pulmonary effects and the effects of aspirin challenge are still being assessed.

c. **Anti-leukotrienes:** there are 2 groups of these drugs: the first inhibits the leukotriene formation by inhibition of the FLAP protein. Zileuton which acts at this level, is not available in the UK, but is used in the USA and results in nasal polyposis have been reported by Sczklik. One important finding was that this drug could in some individuals restore olfaction, suggesting a profound influence on nasal polyposis.

The other class of anti-leukotrienes are the receptor antagonists of which montelukast, zafirlukast and pranlukast are examples. There are a few reports in the literature on their effect on nasal polyps, but Parnes & Chuma suggested that 9/15 patients showed significant improvement. Our own audit found that approximately 50% of AS patients derived benefit from montelukast compared to 60% of AT patients (p=ns). However the numbers experiencing highly significant improvement were higher in the AS group. There was a good correlation between the effect of anti-leukotrienes upon polyps and upon the concomitant asthma, however in most cases a greater response was seen in the lower than the upper respiratory tract (Ragab and Scadding 2001).

Some antihistamines (eg) azelastine, mizolastine have anti-leukotriene properties in the laboratory. A trial of azelastine in nasal polyposis

produced inconclusive results. As yet there has been no placebo-controlled trial of mizolastine.

Other therapies have been suggested such as misoprostol, because of the beneficial of prostaglandin E2. Clinically this has proved disappointing.

One recent benefit to AS patients it that the majority of them appear able to tolerate specific Cox II antagonists for analgesia without ill effects, suggesting that Cox I inhibition is very relevant to the pathogenesis of their disease.

Despite these advances in therapy aspirin sensitive nasal polyposis and asthma remains a difficult condition for patients and their physicians.

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