ORIGINAL CONTRIBUTION

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Otitis media with effusion as a marker of the inflammatory process associated to nasal polyposis*

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SUMMARY

Despite the close location of polyps with the Eustachian tube, association between nasal polyposis (NP) and otitis media with effusion (OME) has not been described in the literature. Our retrospective case-control study aimed at assessing the relative risk to develop OME when NP is associated to factors such as asthma, aspirin intolerance (AI), atopy, eosinophil infiltration of polyp tissue, and history of surgical treatment (HST).

We compared the charts of 25 NP patients presenting symptomatic OME with 50 NP patients without OME. All the charts contained validated data about OME, asthma, AI, atopy, eosinophil count in polyp tissue, and HST.

Our study showed that the risk to develop OME in NP patients is five times higher in patients presenting aspirin triad (NP + asthma + AI) (OR = 5.6, p = 0.009) and three times higher in HST patients (OR = 3.5, p = 0.03), than in isolated NP patients. A linear trend exists between the different degrees of respiratory disease and the risk of OME (p = 0.01).

Our data suggest that the development of OME could be considered as another marker of severity of the inflammatory disease leading to NP, asthma and AI. Better characterisation of NP patients with OME could allow is to define more accurately the nature, type and severity of the underlying inflammatory process.

Key words: nasal polyposis, otitis media with effusion, asthma, aspirin sensitivity, eosinophil

INTRODUCTION

Otitis media with effusion (OME) is defined as a chronic inflammation of the middle ear mucosa characterized by retention of fluid within the middle ear space and leading to deafness and tinnitus, which impair quality of life [1,2]. Although the cause of OME is multifactorial, one of the most important factors is Eustachian tube (ET) dysfunction [3]. Indeed, the ET exerts a major function in middle ear homeostasis via its role in ventilation and mucociliary clearance. The function of ET can be impaired in several rhinopharyngeal mucosa diseases, by different mechanisms [3]. For example, adenoid hypertrophy or naso-pharyngeal tumour can be associated to OME because of mechanical obstruction of the pharyngeal ET orifice, but also because they are reservoirs of bacteria and result in inflammation of rhinopharyngeal mucosa.

Nasal polyposis (NP) [4] is a chronic inflammatory disease of the nasal and sinusal mucosa, characterized by the presence in both nasal fossae of oedematous polyps coming from the ethmoidal meati, causing symptoms such as nasal obstruction, rhinorrhea, hyposmia and facial pressure which can have a major impact on quality of life [5]. The inflammatory disease leading to NP has different target organs and clinical presentations: it can be limited to the nose and sinus cavities, but can also be associated with a lower respiratory tract inflammation leading to asthma. Aspirin intolerance occurs more frequently in patients with NP and asthma than in patients with NP alone [6,7]. The association of NP, asthma and aspirin sensitivity is called the aspirin triad (AT), the Samter's triad [8], or the Widal's triad [9].

The association between NP and OME has not been described in the literature. The aim of our retrospective case-control study was to assess the relative risk to develop OME, when NP is associated to classical factors, such as asthma, aspirin intolerance (AI), atopy, eosinophil infiltration of polyp tissue, and history of surgical treatment (HST).

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MATERIALS AND METHODS

Selection of cases and controls

The charts of all patients operated on idiopathic NP between January 1, 2006 and December 31, 2007 in the ENT department of a French University Hospital were reviewed to look for patients with symptomatic OME. All these patients were operated on NP according to the nasalization procedure [10], because of failure of medical treatment (i.e. these patients were reporting ineffectiveness of topical steroids, or needed more than 2 or 3 courses of systemic steroids per year or had side effects or contra-indication for systemic corticosteroid therapy) or prior other surgical treatments. These patients were operated for the first time in our department, but most of them underwent previous surgical treatment, such as polypectomy or ethmoidectomy, performed by other medical team(s). In our practice, NP patients do not receive a preoperative systemic corticosteroids treatment, except for asthmatic patients with uncontrolled asthma who are at risk for the general anaesthesia.

Patients with sinusitis or nasal polyps related to specific diseases like fungal sinusitis, Churg Strauss syndrome, cystic fibrosis, ciliary dyskynesia or immunodeficiency were excluded.

The diagnosis of symptomatic OME was considered positive in charts in which we could find either a known history of OME with or without ear drums, or the following data: spontaneous complaint of hearing loss and/or fullness sensation in the ear, unpolished aspect of tympanic membrane in the otoscopic examination by the physician and conductive hearing loss identified with audiometric assessment.

Controls were selected among the charts in which there was no clinical suspicion of OME, i.e. no known history of OME or ear drums, no data about spontaneous ear complaints, otoscopic examination or audiometric assessment.

In both groups, the following parameters were assessed: age, gender, history of surgical treatment for NP, history of asthma, of asthma with aspirin sensitivity (Aspirin triad) (AT), of atopy, and pathology of nasal polyps removed during surgery.

Asthma, aspirin intolerance and atopy had been carefully and systematically investigated in every patient with NP for more than 20 years in our clinical practice, looking for the expertise of a pneumologist or an allergologist in difficult cases. Aspirin intolerant patients were those having experienced typical clinical asthmatic manifestation after inadvertently intake of aspirin or after a controlled oral provocation test. Atopic status was considered positive in patients with positive skin prick tests or blood multirast tests. Eosinophils had also been systematically semi-quantitatively counted on surgical specimens by the pathologist for 20 years [11]. Only the charts in which we got clear data on all these criteria were considered for selection in the study. Controls for the study were randomly selected according to a 1:2 paired-matched case-control study, with controls matched to the cases by age and gender.

Statistical analysis

Categorical variables were compared using the Chi-square test. Crude Odds Ratios (ORs) and adjusted ORs from logistic regression and 95% confidence intervals (95%CI) were calculated to measure the association between each parameter and "NP+OME". Variables with a p-value of 0.10 or less in bivariate analysis were included in the logistic regression model. The modeled probability was the probability of being Case (PNS with OME). We also performed a Cochran-Armitage test for trend especially for the lower respiratory tract attempt. All analyses were performed using SAS version 9.1.

Sample size

To detect an OR of AT in cases relative to controls equal to 4, with a probability estimated of AT in controls equal to 25%, with a 80% power and Type I error probability equal to 5%, the sample size needed, in this 1:2 paired-matched Case-Control study, is 25 cases and 50 controls.

RESULTS

A total of 25 cases and 50 controls were included in the study. Mean ages were respectively 52 years (SD = 13) and 49 years (SD = 12); 60% were women.

In bivariate analysis (Table 1), no differences were observed in proportion of asthmatic or atopic patients, between cases and controls. Aspirin sensitivity significantly increased the risk of OME (OR = 5.4, p = 0.005), but not asthma (OR = 1.3, p = 0.28). We showed a linear trend between the different degrees of lower respiratory tract status (AT, asthma, nothing) and the risk of OME (p = 0.01) (Figure 1). Presence of a history of surgical treatment was associated with a higher risk of OME (OR = 3.8, p = 0.008), and the existence of more than 15% of eosinophils in polyps tissue was associated with a decrease of risk of OME (OR = 0.4, p = 0.048).

Table 1. Factors associated with OME, in bivariate analysis.

	Cases n	Controls n	Crude OR* [95%CI]	p**	p***
Lower respiratory tract status					
Aspirin sensitivity	12	8	5.4 [1.6-18.2]	0.005	0.01
Asthma	6	17	1.3 [0.4-4.4]	0.280	
Nothing	7	25	1		
History of surgery					
Yes	17	18	3.8 [1.3-10.5]	0.008	
No	8	32	1		
Atopy status					
Yes	9	17	1.1 [0.4-2.3]	0.863	
No	16	33	1		
Eosinophils in polyps tissue > 15%					
Yes	14	39	0.4 [0.1-1.0]	0.048	
No	11	11	1		

*The modelled probability is the probability of being Case

**Chi-square test ***Cochran-Armitage test for trend

The multivariate analysis (Table 2) confirmed these findings: on one hand, AT and history of surgical treatment were independently and respectively associated with an increase of risk

factor of OME (OR = 5.6, p = 0.009 and OR = 3.5, p = 0.03) and on the other hand eosinophilia superior to 15% was independently associated with a decrease of risk (OR = 0.24, p = 0.02).

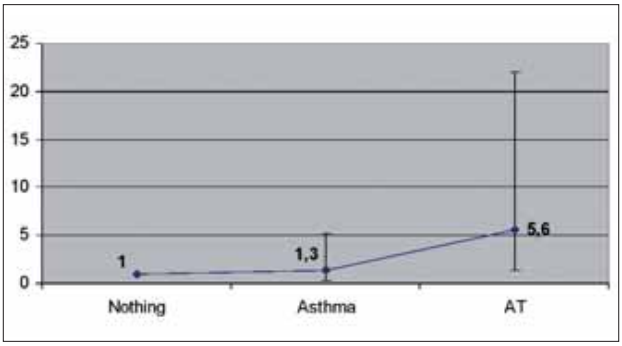

Figure 1. Relation between lower respiratory tract status and risk of OME (p = 0.01).

Table 2. Relation between asthma and OME, in multivariate analysis.

	Cases n	Controls n	Adjusted OR* [95%CI]	p*
Lower respiratory tract status				
Aspirin sensitivity	12	8	5.6 [1.4-22.1]	0.009
Asthma	6	17	1.3 [0.3-5.1]	0.326
Nothing	7	25	1	
History of surgery				
Yes	17	18	3.5 [1.1-10.9]	0.031
No	8	32	1	
Eosinophils in polyps tissue > 15%				
Yes	14	39	0.2 [0.1-0.8]	0.019
No	11	11	1	

*The modelled probability is the probability of being Case

DISCUSSION

Our study shows that the risk to develop OME in patients with NP is five times higher when NP patients are already affected by the aspirin sensitivity. In addition, a linear trend does exist between the risk to develop OME and the degrees of the associated lower respiratory tract inflammatory disease. Actually, NP patients without clinical asthma have a crude OR to develop OME that equals 1, whereas NP patients with asthma but without aspirin sensitivity have an adjusted OR of 1.3 [0.3 – 5.1] and NP patients with AT an OR of 5.6 [1.4 – 22.1] (p = 0.009). These results suggest that OME could represent a higher degree of severity in the inflammatory process associated to NP, independently of history of surgical treatment and eosinophil infiltration. Aspirin triad is one of the best-defined asthma phenotypes [12,13]. Although many patients with AT present stable postoperative nasosinusal cavities and stable controlled asthma with an adequate medication and an optimal patient's compliance, AT is often encountered in the severe asthma population with poor response to steroids treatment [14] and nasal polyps, which are often difficult to treat with high recurrence rates after surgery [15]. Nasal polyp tissue of the AT classically also shows higher eosinophil infiltration (70%) than polyps associated with asthma (60%) or not (50%) [11]. All together, these data suggest a gradation in the severity of the respiratory mucosal inflammatory disease, which leads to the formation of nasal polyps, development of concurrent asthma, revelation of aspirin sensitivity and finally involvement of the middle ear. As suggested by Nguyen et al. [16] for atopic patients, middle ear disease should be included in the concept of united airways inflammatory disease.

In others respects, our study shows that the risk to develop OME in patients with NP is three times higher when NP patients already present a history of surgical treatment for their NP. Thus, a relationship exists between the history of surgical treatment and the presence of OME in NP patients. The time of OME occurrence, with regards to the history of surgery, cannot be précised because of the retrospective feature of our study. Then, the hypothesis that one or more previous surgical treatments could promote the development of OME cannot be excluded here. However in view of the other results of this study, we could also assume that the existence of a history of prior surgery reflects a higher degree of the inflammatory process leading to the recurrence of NP. That is a further argument to consider the presence of OME as another marker of the inflammatory process associated to NP.

The relationship between allergy and OME in adult remains controversial. Several studies have highlighted the contribution of allergic inflammation in the genesis of OME, with the presence of allergic cells and mediators in middle ear mucosa and fluids of atopic patients [16-18], but many others confounding factors exist, such as sinusitis or gastroesophageal reflux diseases (GERD). Our results suggest that atopic NP patients do not present more risk to develop OME than non-atopic NP patients. Thus, according to our clinical experience, when NP exists, the role of allergy as co-factor in the pathogenesis of OME seems to be questionable. Actually, Nagamine et al. [19] have described a non-allergic OME with eosinophil infiltration of the middle ear mucosa on biopsies. Here, none of our patients had a middle ear biopsy, but this would be a new field to study, as the main pathological feature of NP tissue is eosinophil infiltration too.

Surprisingly, our results showed that eosinophil infiltration of polyps tissue was associated with a decrease of risk of OME. This is only apparently surprising as our NP patients were selected from a surgical population, meaning in our practice that asthmatic patients and especially those with AT had more chance to receive systemic steroids before surgery in order to control their asthma [12] before the general anaesthesia with intubation, than non-asthmatic patients who we never prepared for the NP surgery with a burst of systemic steroids. In another study [11], we have actually shown that NP patients receiving steroids before surgery have much less eosinophils in

their surgically removed specimen that the untreated. So to study the eosinophil infiltration of middle ear mucosa in patients with the tetrad syndrome (NP, asthma, aspirin intolerance and OME), we should keep in mind the steroid treatment confounding factor.

Finally, our study does actually not tell us if this tetrad syndrome is in reality as rare as it seems, as we have probably selected in this retrospective case-control study only the more severe cases of OME with clinical expression; actually, we can have missed the mild cases of OME or those temporarily improved at the time of the visit or the surgery by an intake of systemic steroids. Moreover, if our study suggests that OME could represent a higher degree of severity in the inflammatory process associated to NP, the mechanisms remain unknown. So such a condition should incline clinicians to systematically look for other contributing factors such as GERD, presence of staphylococcus aureus endotoxins or concomitant allergic fungal sinusitis. To better characterise those NP patients presenting OME could allow best defining not only the severity, but also the type and the nature of the inflammatory underlining process.

CONCLUSION

In conclusion, otologists and rhinologists should work together to better define this tetrad syndrome, but also in order to improve the quality of life of these patients, whose OME has most of the time revealed very difficult to treat in our clinical experience. The development of OME could be considered as one more step of severity of the underlining inflammatory respiratory disease leading to NP, asthma and aspirin intolerance. OME should be systematically inquired by otoscopic and audiometric evaluation in NP patients. A sharper characterization of those patients could allow best defining not only the severity, but also the type and the nature of the inflammatory underlining process.

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