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Risk factors for olfactory dysfunction in chronic rhinosinusitis☆

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ABSTRACT

Objective: Although risk factors for olfactory dysfunction in patients with chronic rhinosinusitis (CRS) have been examined, most studies did not distinguish between classified eosinophilic chronic rhinosinusitis (ECRS) and noneosinophilic chronic rhinosinusitis (NECRS). The incidence of eosinophilic disease in Japan differs from that in the West. Thus, when olfaction in CRS is investigated, ECRS and NECRS should be examined separately. In the present study, we examined the clinical characteristics associated with olfactory dysfunction in Japanese patients with ECRS and NECRS enrolled in a large multicenter, prospective cohort study.

Methods: Olfactory examination results, demographic data, clinical factors, and comorbidity data were analyzed for 418 patients with CRS at 3 tertiary care centers. We used T&T olfactometry, intravenous olfactory test (the Alinamin test) and Likert scale to assess subjects' olfactory function. Data were analyzed with univariate and multivariate analyses.

Results: Olfactory dysfunction was more severe and more prevalent in ECRS than in NECRS. We found that olfactory cleft polyps (odds ratio [OR], 3.24), ethmoid opacification (OR, 2.64), asthma (OR, 2.29), current smoking (OR, 1.74) and age ≥50 years (OR, 1.66) were associated with olfactory dysfunction in CRS. Ethmoid opacification (OR, 3.09) and olfactory cleft polyps (OR, 3.05) were associated with olfactory dysfunction in NECRS. Olfactory cleft polyps (OR, 3.98), current smoking (OR, 2.67), IgE ≥400 IU/ml (OR, 2.65), ethmoid opacification (OR, 2.51), and asthma (OR, 2.34) were associated with olfactory dysfunction in ECRS.

Conclusions: Olfactory dysfunction was more severe and prevalent in ECRS than in NECRS. Physician should pay attention to these clinical findings to diagnose olfactory dysfunction, especially in ECRS, and should provide appropriate explanation, guidance, and care. In addition, smokers should be advised to stop smoking to help prevent olfactory dysfunction.

1. Introduction

Olfactory function is an essential sensory function in animals and is deeply involved in appetite, motivation, and libido. Patients with anosmia often feel isolated and emotionally impaired [1], and their quality of life is decreased [2]. However, many people are unaware of olfactory dysfunction [3], because information can be obtained via the other senses. There is also a general lack of awareness regarding the problem of olfactory dysfunction, even on the part of clinicians. Olfactory dysfunction may not directly cause systemic problems, but if left untreated, harmful effects may manifest in regard to nutrition, reproductive activity, and even survival.

Little data are available regarding olfactory dysfunction in Japan, but 40–50% of cases of olfactory dysfunction are caused by chronic rhinosinusitis (CRS) [4,5]. In the West, approximately 90% of patients with nasal polyps show a mixed cellular infiltrate with prominent eosinophilia [6]. Tissue eosinophilia [7,8] and local increases in IgE levels [9] are hallmarks of nasal polyps and are thought to be risk factors for disease recurrence. In Japan, eosinophilic chronic rhinosinusitis (ECRS) has recently been classified and induces severe olfactory dysfunction even at an early stage [10,11]. However, the incidence of eosinophilic disease in Japan is lower than in the West, but the incidence of noneosinophilic chronic rhinosinusitis (NECRS) is much higher

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in Japan [11]. Thus, when olfaction in CRS, ECRS, and NECRS are investigated, they should be considered distinct entities. Age, nasal polyposis, smoking, and asthma are considered risk factors for olfactory dysfunction in patients with CRS [12]. However, the risk factors and severity remain unclear for ECRS and NECRS. In the present study, we examined the clinical characteristics associated with olfactory dysfunction in Japanese patients with ECRS and NECRS enrolled in a large multicenter, prospective cohort study.

2. Materials and methods

2.1. Study population

We performed a multicenter prospective cohort study of 621 patients who underwent endoscopic sinus surgery (ESS) from April 2007 through March 2008 at the Department of Otorhinolaryngology, The Jikei University School of Medicine, Ota General Hospital, or Tokyo Dental College Ichikawa General Hospital. Of these patients, 418 (67.3%) for whom preoperative olfactory data were available were included in the analyses. The Ethics Committee of The Jikei University School of Medicine approved the study protocol. Cases of CRS were diagnosed in accordance with the criteria of the Task Force of the American Academy of Otolaryngology-Head and Neck Surgery [13]. Patients were excluded from this study if they had undergone ESS with an external approach, had a follow-up period of less than 1 month, or had a tumor, allergic fungal rhinosinusitis, odontogenic sinusitis, fungal disease, or mucocele.

2.2. Olfactory examination and symptoms of patients

T&T olfactometry (Takasago Industry, Tokyo, Japan) [14] and an intravenous olfactory test (Alinamin® test, Takeda Pharmaceutical Co. Ltd., Osaka, Japan) are the most commonly used olfactory examinations in Japan. For T&T olfactometry, a Jet Stream Olfactometer (Nagashima Medical Instruments Co., Ltd., Tokyo, Japan), with modified injection procedures, was used [15]. To reduce the laboratory technicians' workload and to analyze more patients with olfactory dysfunction, we simplified the test to include 3 types of odorants: β-phenyl ethyl alcohol (odorant A), cyclotene (odorant B), and isovaleric acid (odorant C), as previously described [16]. The detection and recognition thresholds were determined for each odorant, and the recognition thresholds of the 3 odorants were averaged to evaluate olfactory acuity [16]. A recognition threshold of −2 to 1 is defined as "normosmia," 1.1–2.5 as "mild hyposmia," 2.6–4.0 as "moderate hyposmia," 4.1–5.5 as "severe hyposmia" and 5.6–5.8 as "anosmia," in accordance with the Japanese Olfactory Test Committee criteria [17].

Alinamin® is a thiol derivative of vitamin B_1 and smells like garlic. The latent time is measured as the interval from the start of injection until recognition of the garlic smell, and the duration is recorded as the interval from recognition until the disappearance of the garlic smell [18]. In healthy subjects, the latent time is 7–9 s, and the duration is 1–2 min. Patients who do not respond to the Alinamin® test have a poor prognosis for the recovery of olfactory acuity [18].

For each patient, the severity of olfactory dysfunction, nasal obstruction, nasal discharge, and postnasal drip was assessed with a 7-point Likert scale [19] in which 0 is none, 2 is mild, 4 is moderate, and 6 is very severe.

2.3. Asthma, allergic rhinitis, smoking and operative history

Patients were asked specific questions regarding their history of wheezing and asthma, use of asthma medications, history of chronic lung disease, smoking habits, and nasal surgery [20]. Allergic rhinitis was diagnosed on the basis of a blood examination finding of allergen-specific IgE. Patients were considered to have asthma if they reported a history of wheezing or a diagnosis of asthma or both without a significant smoking history or a history of chronic lung disease other than asthma.

2.4. Computed tomography findings and endoscopic findings

The extent of sinus disease identified with computed tomography (CT) was quantified with the Lund-Mackay scoring system [21]. We used the total score for bilateral anterior and posterior ethmoid sinus opacification. The bilateral olfactory clefts were endoscopically evaluated for nasal polyps using a scale of 0–3 (0 is no polyps, 1 is edema, 2 is polyps, and 3 is polyposis).

2.5. Sinus mucosal or polyp eosinophils

At the time of ESS, sinus mucosal or polyp tissue was removed and subjected to pathologic examination using hematoxylin–eosin staining. All specimens were examined microscopically in a blinded fashion, and the number of eosinophils was counted per high-power field (HPF, 400×, 0.238 mm^2). For each specimen, eosinophils were counted in the 3 HPFs containing the largest numbers of eosinophils, and the mean number of mucosal or polyp eosinophils per HPF was calculated.

2.6. Diagnosis of ECRS and NECRS

Diagnoses of CRS were made in accordance with the criteria of Meltzer et al. [22]. The diagnostic criteria for ECRS were: (1) CRS with nasal polyps and (2) mucosal eosinophilia of 120/HPF or more or eosinophilic mucin or both [7]. The diagnostic criteria for NECRS were: (1) CRS with nasal polyps or CRS without nasal polyps and (2) mucosal eosinophilia less than 120/HPF and no eosinophilic mucin.

2.7. Statistical analyses

Analyses were performed with SPSS v 11.0 statistical software (SPSS, Chicago, IL). Individual correlations between ECRS and NECRS were analyzed with the *t*-test (for normal distributed data), the Mann–Whitney *U*-test (for not normal distributed data), or the chi-square test. Multivariate logistic regression models were constructed to compare the characteristics of patients with CRS and patients with CRS plus olfactory dysfunction. The first model examined variables associated with CRS, the second model examined variables associated with NECRS, and the third model examined variables associated with ECRS. As dependent variables, the results of T&T olfactometry ($\geq$4.1 for 1, and $<$4.1 for 0) were used. Independent variables were sex, age, peripheral eosinophil count, total IgE level, ethmoid opacification, olfactory cleft polyps, percent of predicted vital capacity (%VC), the percent predicted forced expiratory volume in 1 s (%$FEV_{1.0}$), history of previous surgery, allergic rhinitis, asthma, past smoking, current smoking, and Brinkman index. Patients were divided by age into 2 groups – $\geq$50 and $<$50 years – on the basis of the cut-off point from 40 to 75 years old that would provide the highest accuracy on multivariate analysis. Patients were also divided into 2 groups on the basis of IgE level – $\geq$400 and $<$400 IU/ml – on the basis of the cut-off point from 100 to 700 IU/ml that would provide the highest accuracy on multivariate analysis.