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Epidemiological aspects of olfactory disfunction*

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SUMMARY

Purpose: *This study aimed at assessing the most common aetiological factors causing total or partial olfactory deficit and the statistical analysis of some clinical aspects.*

Materials and Methods: *243 patients reporting alfactory dysfunction were enrolled in this* ***Study:*** *A case history was drawn up for each patient, and all of them underwent otolaryngology objective examination, including nasal endoscopy, paranasal sinuses CT-scan, and Utrecht method (GITU) based smell indentification test.*

Results: *Upper respiratory viral infections (40.2%), ceanial-facial traumas (39.3%), and rhinosinusal pathologies (6.3%) were the main aetiopathological factors indentified. A relevant number of case were recorded with unknown aetiology (14.2%). In 2 cases, olfactory dysfunction was due to neurological diseases, in 1 case it was due to intoxication and, in another case, it was congenital. The correlation between aetiology, gender, age, symptoms duration and deficit severity was studied.*

Conclusions: *many different aetiological factors caused the loss or weakening of the sense of smell. They mainly affected olfactory neurosensorial structures and odorant conduction. However, there were many cases of unknown aetiology. Women, over 40 in particular, were the most affected. Anosmia and severe hyposmia were mainly correlated with traumas and viral pathologies.*

Key words: olfaction, anosmia, hyposmia, identification, smell test

INTRODUCTION

Olfaction is considered as a "chemical sense" as external stimuli are composed of molecules or particles, which direct contact with sensory cell receptors, cause a biochemical reaction. By directly stimulating nerve tracts, such biochemical reaction allows individuals to closely interact with the surrounding environment. Just like other senses, this constant relation gives rise to man's instinctive behaviours, such as those relating to nutrition, danger or defence, as well as a series of more complex cortical processing activities, including the ones involving the sexual, emotional and social spheres. This explains why anosmia and hyposmia have negative consequences on patients' lives, as they become insecure due to their incapability to detect potentially dangerous situations, including the presence of gas and fire, or to avoid the ingestion of spoiled food; moreover, the fact that they cannot enjoy pleasant or familiar smells, as well as the aromatic components of food, has negative psychological repercussions on such patients [1,2]. There exist various olfactory dysfunction aetiological factors; they interact at odorant conduction level, as well as at sensory and neural levels; however, in some cases, it is clinically impossible to certainly identify the relevant causes. The authors of this present study examined a group of patients who suffered from dysosmia, with a view to ascertaining the main aetiopathogenetic factors and epidemiological features for their dysfunctions.

MATERIALS AND METHODS

Patients and their analyses

In this prospective study, conducted in our department from February 2002 and October 2004, we have enrolled 234 patient (113 male and 130 female), aged between 8 and 84, that had been examined for olfactory dysfunction. Simultaneously, a face to face short questionnaire was completed with information about their subjective weakening of the sense of smell or anosmia. A medical history was drawn up for each patient, especially we asked them to remember the most important circumstances about the onset of dysosmia like respiratory and otorhinolaryngology diseases or correlates symptoms, neurological pathologies, toxic exposure, or traumas. No patient refused the interview. All of them underwent otolaryngology objective examination, including nasal endoscopy. The medical records of the patients showing olfactory deficit initial symptoms following cranio-facial traumas or due to neurological pathologies, including CT and MRI scan, were examined. Patients who had had previous rhino-sinusal inflammatory or obstructive pathologies, and those whose aetiological factors were uncertain, underwent skull and face high-definition CT,

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focussing in particular on the osteo-meatal complex. We excluded in the study patients with evidence of nasal polyposis. All patients underwent the Utrecht method (GITU)-based smell identification test, consisting in the identification of 36 substances. They had to select the right answers in a multiple choice test. Each patient's olfactory deficit severity was assessed based on the number of substances correctly identified by the patient under consideration. Up to a maximum of 6 correct answers, the result is considered as a simulation; hence, the test is carried out again, once or more, on different dates. If patients provide 7 to 12 correct answers, they are considered to be affected by anosmia, while results ranging from 13 to 19 correct answers indicate severe hyposmia; results between 20 and 26 indicate moderate hyposmia; 27 to 30 indicate mild hyposmia; while 31 to 36 indicate normal sense of smell [3].

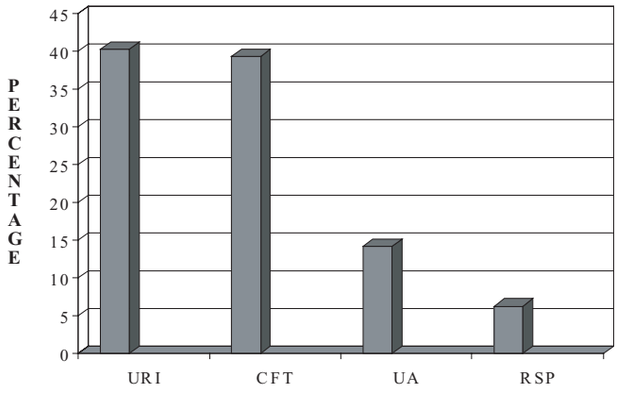

Figure 1. Distribution of 4 major aetiologies of dysosmia.

Statistical analysis

Continuous data is expressed as mean ± SD. Baseline data was compared by means of the χ^2 test for categorical variables and unpaired-t-test for continuous variables. ANOVA, with the Tukey post hoc test, was used to analyse differences between age groups and the Kruskal-Wallis test was used to evaluate differences between categorical variables. We used the multivariate analysis, logistic regression, in an exploratory manner to identify subset of variables associated with the olfactory function score. The covariates were: age, sex, aetiology, duration of the olfactory loss; stepwise procedure were used. Odds ratios including 95% confidence interval were presented for the dichotomous explanatory variable. A value of $p<0.05$ was considered statistically significant. Statistical analysis was performed with SPSS 10.0 for Windows.

RESULTS

By observing our 243 patients, we identified four people who showed rare pathogenesis. In particular, there were two 41- and 55-year-old women, both suffering from anosmia, who showed neurological causes (namely cerebral haemorrhage and olfactory groove meningioma); 1 male aged 55 who had suffered from severe hyposmia for about 10 years due to exposure to para-dichlorobenzene for working reasons; one 8-year-old female showing anosmia: her mother said that she had been suffering from it since her birth. The 239 remaining patients were divided into three groups, and classified based on the main aetiopathological factors: upper respiratory infection (URI) (96 pts, 40.2%); cranio-facial traumas (CFT) (94 pts, 39.3%); rhinosinusal pathologies (RSP) (15 pts, 6.3%). The fourth group consisted of 34 people (14.2%), with unknown aetiopathogenesis (UA) or who could not be included in the three previous groups (Figure 1).The CTs of craniofacial trauma sufferers included in their old medical records did not show any obvious brain injury. UA and URI patient facial bone CTs did not show any significant pathology that could be related to their olfactory dysfunctions. All RSP patients suffered from chronic rhinitis (6 had allergic rhinitis, while 9 of them suffered from non-allergic rhinitis). No nasal polyps had been identified; in fact, in 11 cases, CT showed diffused opacity in the antero-posterior ethmoid only, in 4 cases in the ethmoid and, partially, in both maxillary sinuses, due to obvious edematous obstruction of the osteo-meatal complex.

Relations between sex, age and aetiopathological factors

The URI group mean age was 58.2 ± 11.1 yrs; it consisted of 28 male (29.16%) and 68 female (70.84%) patients. The CFT group's mean age was 45.6 ± 16.0 yrs, and it included 60 male (63.8%), and 34 (36.2%) female patients. The RPS group's mean age was 49.6 ± 13.2 yrs, and consisted of 10 male (66.7%), and 5 female (33.3%) patients. Finally, the UA group's mean age was 60.8 ± 15.1 yrs, and consisted of 14 male (41.2%) and 20 female (58.8%) patients. The mean age ANOVA showed a statistically significant difference ($p< 0.0001$); such difference is due to the URI vs. CFT and CFT vs. UA groups (Tukey post hoc). With respect to gender, the mean age difference between the various aetiological sub-groups is also statistically significant (ANOVA $p< 0.0001$, URI vs. CFT and CFT vs. UA). All patients were divided into three age classes, namely: A = up to 40; B= between 41 and 60; C= over 60. In the URI group, there were 3.6% male and 7.4% female patients in the A age class; 71.4% and 44.1% respectively in the B age class; and 25.0% and 48.5% respectively in the C one. The URI group situation was the following: 43.3% and 32.4% respectively in age class A; 41.7% and 44.1% in age class B; 15.0% and 23.5% in age class C. As to the RSP group, 40.0% male and 0% female patients belonged to the A age class; 50.0% and 60.0% respectively were included in the B age class; while 10% and 40% respectively were included in the C one. Finally, the UA group patients were aged as follows: 14.3% and 10.0% belonged to age class A; 35.7% and 35.0% to age class B; while 50.0% and 55.0% respectively were included in the C age class (Figure 2).

Relations between aetiopathology, age classes and olfactory dysfunction severity

As to the olfactory dysfunction severity, overall, 159 patients

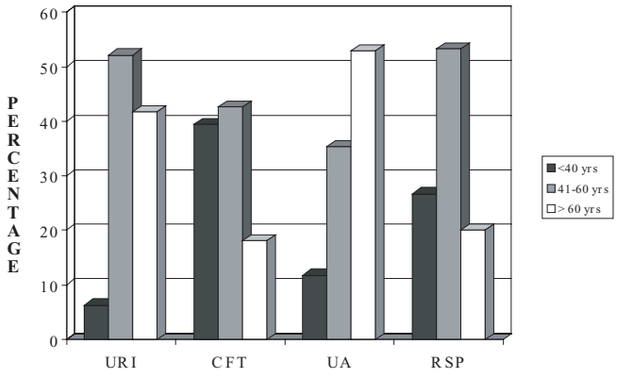

Figure 2. Classes of age and major aetiologies of dysosmia.

suffered from anosmia (66.5%); 43 suffered from severe hyposmia (18.0%); 32 of them suffered from moderate hyposmia (13.4%); and 5 suffered from slight hyposmia (2.1%). No statistically significant difference was observed with respect to gender. By analysing the association between deficit severity and aetiopathology, it was observed that 48.4% (n=77) of patients suffering from anosmia belonged to the CFT group; 32.1% (n=51) belonged to the URI group; 14.5% (n=23) to the UA group; and 5% (n=8) to the RSP group. Moreover, 55.8% (n=24) of patients suffering from severe hyposmia belonged to the URI group; 20.9% (n=9) belonged to the CFT group; 18.6% (n=8) belonged to the UA group; and 4.7% (n=5) belonged to the RSP group. 55.3% (n=18) of patients suffering from moderate hyposmia belonged to the URI group; 21.9% (n=7) of them belonged to the CFT group; 15.6% (n=5) belonged to the RSP group, while 6.3% (n=2) belonged to the UA group. Very few patients (n=3) suffered from slight hyposmia, with them being divided as follows: 1 belonged to the URI group, 1 to the CFT group; and one to the UA group (Chi-square test p=0.003) (Figure 3).The age-pathogenesis relation was statistically significant for anosmia and severe hyposmia ($p < 0.0001$ and p=0.007 respectively). In this respect, we observed that, for anosmia, traumatic aetiology prevailed in patients belonging to the A and B age classes, while the pathogenesis of severe hyposmia

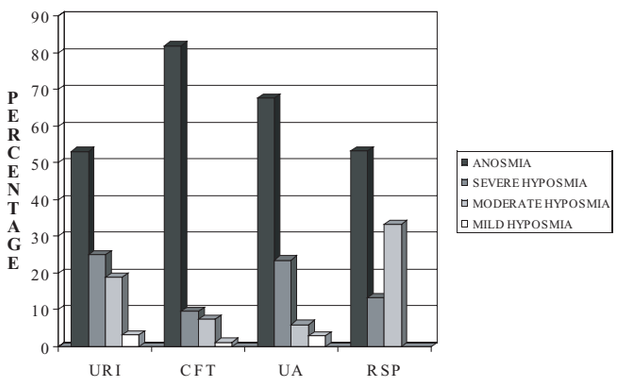

Figure 3. Distribution of olfactory loss and major aetiologies of dysosmia.

was mainly of viral origin and prevailed in B and C age class patients.

Relations between aetiopathological factors and symptomatology

As we observed remarkable spread with respect to the duration of symptoms reported by patients (average: 29.3 months ± 52.6; median: 12; range 1-360), we divided it into four time intervals: up to 3 months, between 6 and 12 months, between 12 and 24 months, and over 24 months. With reference to the different pathologies, the following percentages were observed. Fist interval: URI group = 40.6%, CFT group = 37.2%, RSP group = 20.0%, UA group = 11.8%. Second interval: URI = 29.2%, CFT group = 28.7%, RSP group = 26.7%, UA group = 23.5%. Third interval: URI = 16.7%, CFT = 14.9%, RSP = 20.0%, and UA 8.8%. Fourth time interval: URI = 13.5%, CFT = 19.1%, RSP = 33.3%, UA = 55.9%. Data analysis shows that patients suffering from viral and traumatic pathologies turned earlier to a specialist compared to patients with unknown pathology (Chi-square test $p < 0.0001$) (Figure 4).

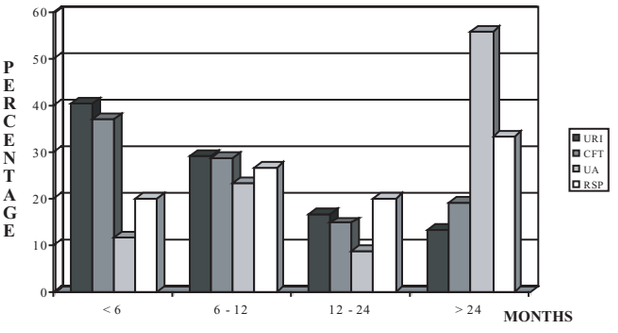

Figure 4. Symptoms duration and major aetiologies of dysosmia.

Multivariate Analysis

In order to evaluate the independent contribution of covariates, we performed logistic regression with the dependent variable was olfactory function: anosmia vs. non-anosmia. The only variables that entry in the model was traumatic aetiology: the odds ratio (OR) was 3.9 (95% CI, 2.1- 7.7 OR), that means patients with traumatic aetiology risk to develop olfactory dysfunction about 4 times more than patients with viral aetiology.

DISCUSSION

From the results obtained it can be inferred that infectious diseases of the upper airways, cranio-facial traumas and rhinosinusal pathologies were the aetiopathogenetic factors that were mainly responsible for olfactory dysfunctions. In essence, viruses could be the viral agents involved. A research study carried out by Sugiura [4] shows the likely role played by parainfluenza virus, adenovirus, herpex simplex and zoster. In this study all patients with olfactory disorders after URI had increased antibody titres in particular for parainfluenzae virus type 3. Viruses attack the olfactory neuroepithelium, destroy-

ing it and favouring its metaplastic transformation into respiratory epithelium [4]. Head traumas mainly cause nerve tract interruption, thus directly damaging the "*filia olfactoria*" by avulsion of the cribriform plate, as a result of the brusque movement of the brain in the skull. There is evidence that the severity of the olfactory dysfunction increases proportionally to the severity of the head trauma, based on the Glasgow Coma Scale score, when post-traumatic amnesia and radiological lesions are present [5]. Among the various forms of central lesions, some authors proved the breaking of the first cranial nerve in patients who had suffered from occipital traumas [6,7], the encephalomalacia of the olfactory bulb and tract or of sub frontal and temporal lobes[8], brain contusion or intraparenchymal hemorrage [9]. A lower number of olfactory dysfunctions were identified having unknown causes and relating to rhinosinusal pathologies. Presumably, among idiopathic causes, there are those degenerative conditions due to silent viral infections or with few other nasal and general symptoms; to lack of physiological regeneration of the neuroepithelium, as it happens due to ageing or sexual hormone dysfunction [10,11] or to exposure of toxic inhalants, including cigarette smoke [12]. Nasal pathologies entail airflow conduction deficits in the olfactory mucosa. This mechanism may be triggered especially by rhinitis and rhinosinusitis, which lead to the formation of oedema or middle meatus polyposis, with stagnation and alteration of the mucus film over the neuroepithelium [13]. Some retrospective studies showed olfactory sensitivity improvement after nasosinusal endoscopic surgery, including cases with no polyposis [14-16]. Friedman described the non-relevance of medialization in comparison or middle turbinate bone partial resection [17,18], while according to Stevens and Doty, olfaction improvement has not been adequately proven, yet, after postoperative local or systemic steroidal treatment [19,20]. Moreover, in olfactory mucosa biopsies, some authors observed the occurrence of olfactory nerve cell apoptosis in patients suffering from chronic rhinosinusitis [21], as well as an increase in respiratory tissue islets, which was proportional to the olfactory loss, thus showing that long-standing and untreated inflammation may cause metaplasia [20-22]. In this study we had a percentage of dysosmia due to head trauma greater than rhino-sinusitis and upper respiratory infections in comparison to studies of other authors. We could explain this either because we noted in the medical history that a lot of people affected by head trauma were send to our olfactory assessment by neurologists and medico-legal specialists or because probably we had only patients with dysosmia due to rhinosinusal patologies not complicated by nasal polyps and not improved by therapy. Our case study involved very few patients suffering from olfactory dysfunctions due to neurological diseases, toxic factors and accidental reasons. In Table 1 we show the percentage of major etiological categories reported in literature [1,13,23-26] during the last seventeen years, where we can observe several differences between them. As to gender, overall, women were the most affected. In particular, for all aetiology categories, women prevailed in the over age 60 bracket. This was possibly due to the weakening of the protective action of estrogens on the olfactory epithelium in the post-menopause period. A group of women in menopause had olfactometric tests, and Deems [23] obtained better results with women who underwent estrogenic replacement therapy. However we have not forgotten that generally women undergo a medical check more often than men. Patient age data showed that most infectious, traumatic and rhino-sinusal pathogenesis sufferers were aged between 40 and 60. More than 50% of the unknown aetiology group patients were over 60, as idiopathic causes may include the gradual physiological decrease in olfactory sensitivity, caused by the neuroepithelium reduction, due to weaker spontaneous regeneration caused by ageing. As a consequence, there is a consequent high vulnerability to viral infections, whose outbreak cannot be perceived by patients [24]. It was important to observe that the youngest age bracket was mainly represented by patients with cranio-facial trauma-related olfactory pathologies, mostly due to road accidents. Olfactory deficit severity-related results showed that, in all groups, most patients suffered from anosmia. In particular, it was the case for trauma sufferers who, in general, showed serious olfactory pathway damage. Severe, moderate and slight hyposmia cases concerned patients included in the URI, CFT and UA groups, as olfactory dysfunction was caused by the more or less severe reduction in sensory cell turnover. On the other hand, in RSP patients, local inflammatory pathologies mainly caused severe or moderate deficit. The olfactory deficit duration reported by each patient when our assessment was carried out was shorter in the URI and CFT groups (considering the relatively high

Table 1. Percentage of major aetiological categories in six clinical studies [1, 13, 23-26].

ETIOLOGICAL CATEGORY	Goodspeed 1987 n = 441 %	Deems 1991 n = 750 %	Mori 1998 n = 889 %	Seiden 2001 n = 428 %	Miwa 2001 n = 345 %	Temmel 2002 n = 278 %
Cranial-facial Trauma	8.6	18	10.5	18	17.1	17
Upper respiratory Infection	18.6	26	23.6	18	17.1	36
Rhinosinusal Pathologies	30.2	15	48	14	21.4	21
Unknown	25.8	22	14.6	27	28.4	18
Tossic		2		6		
Congenital		4	0.3	3		3
Miscellaneous	16.8	13	3	14	16	5

number of patients suffering from the aforesaid pathogenesis), compared to the UA and RSP groups. In fact, in the latter group, dysfunction appeared more gradually. However, a remarkable percentage of trauma sufferers had an olfactometric assessment more that 12 and 24 months after their accidents, as they had to undergo top-priority rehabilitation treatments first.

CONCLUSIONS

Olfactory dysfunction may be caused by various aetiopathogenetic factors, damaging the olfactory pathway's neurosensory or conduction structure. Based on our experience, upper respiratory infections were the main cause for olfactory sensory deficit; cranio-facial traumas, idiopathic causes and rhinosinusal pathologies came next. We observed very few cases of neurological, toxic and congenital pathologies. Female patients and women over 60 in particular, were the most affected. Most serious olfactory dysfunction was observed in trauma and respiratory infection sufferers.

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