Inflammatory Obstruction of the Olfactory Clefts and Olfactory Loss in Humans: A New Syndrome?

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Abstract

The first step in the olfactory perception is the activation by odorants of sensory neurones in the olfactory epithelium. In humans, this sensory epithelium is located at 2 narrow passages, the olfactory clefts, at the upper part of the nasal cavities. Little is known about the physiology of these clefts. We examined, in 34 patients, the impact of obstructed clefts upon detection and post-learning identification of 5 odorants. The location and extension of the obstructions were assessed using endoscopy, CT scans, and MRI. The inflammatory obstruction was usually bilateral, extending anteroposteriorly, and confined to the clefts, with no sign of obstruction or any inflammatory disease in the rest of the nasal cavities and sinuses. When tested with 5 odorants, these patients showed greatly impaired olfaction compared with a group of 73 normosmic subjects. The majority of these 34 patients had sensory deficits equivalent to that found in another group of 41 congenital anosmic patients, where inspection with MRI indicated the lack of olfactory bulbs. This study demonstrates that the olfactory clefts, in human, function as an entity that is different from other regions of the nasal cavity and is the target for local inflammatory events that are apparently not responding to corticoid and antibiotic treatments.

Key words: anosmia, human olfaction, olfactory bulb, olfactory clefts, olfactory test

Introduction

In humans, the free access of air to the olfactory clefts, 2 narrow vertical passages at the upper part of the nasal cavities, is a key element for olfaction. Biopsies at this level reveal the presence of the olfactory epithelium with olfactory receptor neurones to detect odorant molecules (Nakashima et al. 1984; Morrison and Costanzo 1992; Jafek et al. 2002). In some individuals, electrophysiological recordings (Knecht and Hummel 2004; Wang et al. 2004) indicate the presence of the olfactory epithelium in the anterior part of the olfactory cleft. The remaining part of the septum, the medium and the lower turbinates, are not covered by the olfactory epithelium but contribute to the detection of odorant molecules through the activation of the trigeminal nerve fibers (Laska et al. 1997). The access of odorant molecules to the olfactory clefts, and the olfactory epithelium, can be altered by obstructive pathologies at different levels of the nasal cavities (Doty and Mishra 2001). In many cases, medium and lower parts of the cavities are involved in the obstruction and the olfactory deficit is considered to reflect changes in the airflow directed toward the clefts. In some patients, however, the obstruction concerns only the olfactory clefts, with no sign of obstruction in the rest of the nasal passages nor inflammatory nasal and sinus diseases. Our interest in these patients evoked because the measurement of their olfactory abilities might give information about the actual impact of this obstruction upon olfaction. In addition, the contribution of the remaining parts of the nasal cavity to detect odorant molecules, through activation of intranasal trigeminal nerve fibers, could be estimated. To our knowledge, only one study (Biacabe et al. 2004) specifically studied this olfactory cleft
disease and demonstrated, on 13 patients, a decreased olfactory sensitivity; however, the comparison with normal patients was not assessed.

In the present study, we therefore examined a sample of patients with obstructed olfactory clefts and compared their olfactory sensitivity with that of normal subjects. Our hypothesis was that the obstruction of the clefts would be equivalent to a complete anosmia. However, the chosen odorant molecules might also activate the trigeminal system, innervating the rest of the cavities, freely accessible to the odorized air, and therefore could give rise to a sensation that would interfere with the detection and, eventually, the identification tasks. This activation may result from direct activation of the nerve fibers or participation of solitary chemoreceptor cells located in the nasal cavities (Finger et al. 2003). To evaluate the contribution of the trigeminal information, we also included anosmic patients without olfactory bulbs (congenital anosmia). These patients can rely only on their nasal trigeminal sensations to detect odorant molecules (Laska et al. 1997).

**Materials and methods**

**Clinical investigations**

Patients with olfactory complaints were examined in the ENT Department, Hôpital Lariboisière (Paris, France). All patients filled in a medical questionnaire to establish the nature of the olfactory complaint, the onset, timing, duration, and evolution of the symptoms, as well as past history like head trauma, upper respiratory infections, hypogonadic symptoms, sinus surgery, toxic exposure, or neurodegenerative pathologies. All subjects had a standard clinical ear, nose, and throat examination and, if needed, an allergologic screening as suggested by clinical history. Skin prick tests using allergen extracts (Allerbio: 5527, Varennes en Argonne, France; Stallerégens: Antony, France) were carried out. Nasal endoscopy using cold light and rigid 0° and 30° endoscopes (Karl Storz Endoscope GmbH & Co, Tuttingen, Germany) was performed for inspection of the septum, the turbinates, the meatus, the olfactory clefts, and the nasopharynx while patients were at rest. We assessed the presence or absence of rhinorrhea, mucosal erythema, edema or lesion, nasal obstruction, nasal crusts, or polyps.

**Groups of subjects**

On the basis of these observations, we selected 3 groups of subjects. One group (normal) consisted of 73 subjects without any declared or observed pathology related to olfactory troubles (31 males and 42 females; 41 ± 14 years [mean ± standard deviation (SD)]). These subjects had no special training for olfactory tests. A second group (obstructed olfactory clefts) gathered 34 subjects (16 males and 18 females; 48 ± 17 years) with inflammatory obstruction of the olfactory clefts without polyps or opacified sinuses. The obstruction, restricted to the clefts, was established using frontal and horizontal CT scans. The third group was 41 subjects (13 males and 28 females; 33 ± 15 years) who were totally anosmic since birth (congenital anosmia): MRI brain imaging was used to confirm the absence of both olfactory bulbs (Aiba et al. 2004).

**Imaging**

CT scans, for examining intranasal and intrasinus aspects, were performed using an helicoidal CT (16 row) “Siemens sensation 16,” and helicoidal transverse acquisition in low dose (120 mA, 120 kV, 16 cuts of 0.75 mm/5 mm, 6.3 mm by rotation; CT dose/volume: 25.32 milligrays). Multiplanar reconstructions used a filter bone “high resolution” and were applied to frontal (coronal), horizontal (axial), and profile (sagittal) plans.

MRI was performed, for assessment of intracranial structures, using a MAGNETOM Avanto Siemens 1.5 T (standard head matrix coil). Five sequences were performed: 2 on the whole of brain (sagittal SE T2, thickness 5 mm, repetition time [TR] 3800, echo time [TE] 94, FOV, 250 mm, matrix 384 × 384; FLAIR IRSE transverse, thickness 5 mm, TR 9000, TE 111, FOV 250 matrix 256 × 256); 2 sequences on the fronto-olfactory areas (T2 RST high resolution, coronal, thickness 2.5 mm; GE T1 VIBE coronal thickness 1.5 mm 3D, TR 7.87, TE 3.75, FOV 180, matrix 256 × 256), and 1 sequence on the temporal lobes, SE T2 thickness 5 mm, coronal oblique perpendicular with the axis of temporal lobes.

**Olfactory test**

The ability to detect, and identify odors after learning, was estimated using 5 odorants commonly used to test human olfaction (Kondo et al. 1998; Hashimoto et al. 2004); β phenyl-ethyl-alcohol (PEA; Janssen Chimica, ref. 13.017.19; +99%), cyclotene (CYC; Laserson Sabenay, France; 98%), isovaleric acid (IVA; Janssen Chimica, ref. 15.669.52; +99%), undecalactone (UND; Aeros, ref. 25949.0250; 98%), and skatole (SKA; Fluka, ref. 85460; 98%). These chemically stable substances evoke very different odor notes. According to our previous study (Eloit and Trotier 1994), 7 log10 step concentrations of each odorant were prepared by dilution with odorless 1,2 propanediol (Fluka, ref. 82280; 99.5%). The concentration of the more diluted solutions (C0) were (in μg·kg⁻¹) PEA: 63.1, CYC: 25.1, IVA: 10.0; UND: 79.4; SKA: 7.9. Twenty milliliters of each solution were adsorbed on a piece of odorless cotton in a 60-ml brown glass bottle closed with a cap. Bottles with a numeric identifier were placed in a wooden shelf in a random order for the patient who was installed in a ventilated room. Special care was taken to keep the subjects in a comfortable situation. A software was developed to assist in the procedure of the experiment. At the beginning, participants got accustomed with the 5 odorants and learned to name them: each odorant was presented at the highest concentration and subjects learned to associate the sensation with a semantic
descriptor so as flowers, rose and jasmine, for PEA; caramel and cake for CYC; goat cheese for IVA; fruits, apricot and peach, for UND; cowshed, slurry, and faecal odor for SKA. This learning was repeated 2 or 3 times when needed by the subject. During the test, the list of descriptors remained available to the subject. Then, the 7 concentrations of IVA were presented successively, starting from the highest concentration (descending series of concentrations). For each bottle, the subject was asked to decide whether it contained an odorant and, if so, which odorant was present. The subject had free access to the odorless reference. The interstimulus interval was about 1 min. The same procedure was repeated for PEA, UND, CYC, and then SKA. After a few minutes rest, the test was repeated starting with the lowest concentration up to the highest one (ascending series of concentrations). The order of presentation of the odorants was PEA, UND, IVA, SKA, and CYC. No information was given to the subject concerning the precise experimental procedure. We consider here only the results of the ascending series of concentrations (the descending series of concentrations gave very similar results, although the sensitivity of normal subjects was slightly diminished). For each odorant and each subject, the detection level was taken as the highest concentration not perceived plus one. The identification level was taken as the smallest concentration correctly identified in a series of correct identifications beginning with the highest concentration. For each group of subjects, the results for each odorant are presented (Figure 2) as the cumulative percentage of subjects able to detect (to identify) the odorant at a given level of stimulation. These levels, corresponding to the log of the ratio $C/C_0$, range from 0 to 6. For each odorant, statistical analysis was performed using Mann–Whitney test, with the number of subjects able to detect (to identify) at each level of concentration and an additional class with the number of subjects not able to detect (to identify) at the level 6.

Rhinomanometric measurements

Airway resistance of each nasal cavity ($R_{\text{left}}$ and $R_{\text{right}}$ in Pa · s · cm$^{-1}$) was measured, just before the olfactory test, during quiet and effortless nasal breathing using anterior rhinomanometry with nozzles (Instrumentation DIFRA, 4840 Welkenraedt; software SIB; 4140 Dolembreux, Belgium) at a pressure of 150 Pa for inspiration and expiration (average of at least 10 respiratory cycles). The nasal resistance ($R_n$) was calculated as $R_n = R_{\text{right}} \cdot R_{\text{left}} \cdot (R_{\text{right}} + R_{\text{left}})^{-1}$ (Davis and Eccles 2004).

Results

Anatomical observations

Normal subjects

An example of the anterior part of an olfactory cleft, observed on a normal subject using anterior endoscopy, is shown in Figure 1A. It appears as a narrow slit covered on both sides with a clear mucus layer. In the example of frontal CT scan shown in Figure 1B (anterior to the upper turbinate), the olfactory clefts (o.c.) is delimited superiorly by the cribiform plate, below the grooves containing the olfactory bulbs (o.b.), and laterally by the nasal septum and the upper part of the middle turbinate. In normal subjects, the clefts were free of any plugging material, and there was no visible pathology in the nasal cavity or sinuses although some subjects presented a deviated nasal septum. The
difference in swelling of the mucosa covering the middle and inferior turbinates (t.), obvious between the 2 nasal cavities (Figure 1B), resulted from the natural balance in congestion in one side from another. This differential congestion varies with the time of observation (Davis and Eccles 2004).

In CT scans, the olfactory bulbs could not be observed in the grooves (o.b.) above the cribriform plate (Figure 1B), but using MRI, they appeared as 2 oval or rounded entities (Figure 1C).

**Patients with inflammatory obstruction of the olfactory clefts**

In many patients, the obstruction of the clefts was detected by endoscopy. It appeared (Figure 1D) as a congestion, the opposite walls of the clefts being apparently in contact. In frontal CT scans (Figure 1E), the whole height of the clefts was opacified (arrows in Figure 1E). In the vast majority of patients, the occlusion was bilateral and symmetric on each side. In Figure 1E, it can be seen that the pathology of the clefts in some patients was accompanied by a bilateral concha bullosa (a significant expansion of the middle turbinates), but this association was not systematically observed in other patients. It is pertinent to note that the obstruction was confined to the clefts and did not extend basally to other regions of the nasal cavities that appeared free of any plugging material. Horizontal CT scans revealed that the obstruction concerned the entire length of the cleft including the upper turbinate (18% of patients), or the posterior two-third of the clefts (37% of patients; e.g., Figure 1F), or the middle part of the clefts (37% of patients). In about 8% of patients, only the anterior part of the clefts was obstructed. In the majority of cases, the length of the occlusions was identical on each cleft. In 10 patients observed with MRI imaging, the olfactory bulbs were visible.

**Patients with congenital anosmia**

The olfactory clefts and the rest of the nasal cavities were normal and free of plugging material. Abnormalities were only evidenced above the cribriform plate: the olfactory grooves were absent (or very small), and MRI observations could not reveal the presence of the olfactory bulbs (Figure 1G). Back to the expected position for the bulbs, the olfactory tracts were not observed either. At the cortical level, the olfactory sulci were absent or very reduced and the gyrus rectus were flattened (Figure 1H), as already observed (Aiba et al. 2004; Madan et al. 2004). The olfactory sulci are thought to be important for olfaction (Hummele et al. 2003).

**Olfactory test**

**Normal subjects**

For the detection task (Figure 2A), a rather large dispersion of sensitivity, over a range of about $10^4$ in concentration was observed between subjects, whatever be the odorant. About 50% of the subjects could detect 4 odorants between levels 2 and 3 and 1 (SKA) between levels 1 and 2. Only a minority of subjects could not detect the odorants at the level 4. The identification scores also span over 4 log units in concentration (Figure 2B). About half of the subjects could identify PEA, CYC, IVA between levels 3 and 4, and SKA between levels 2 and 3. More than 90% of subjects could correctly identify 4 odorants at level 6. It is noteworthy that a proportion of subjects was not able to correctly identify UND at level 6.

**Patients with inflammatory obstructed olfactory clefts**

All patients showed a severe deficit for both detection and identification (Figure 2C,D). The most sensitive patients began to detect the odorants only at level 3. Only a minority of patients (10–25% depending on the odorant) could detect the level 4 versus 90% or more for normal subjects. At level 6, about 50% of patients could not detect UND, CYC, SKA, and IVA and about 70% could not detect PEA. The olfactory deficit was particularly important for the identification task as only about 20% of patients could correctly identify the level 6 of the odorants versus 100% for normal subjects (Figure 2D).

**Patients with congenital anosmia**

The olfactory tests indicated that a minority of these anosmic patients (about 25%) was able to detect something at concentrations higher than the level 3 (Figure 2E). About 75% of patients could not detect UND, CYC, SKA, and IVA at level 6 and about 90% did not detect PEA at level 6. There was a constant failure to identify any of the 5 odorants (Figure 2F), even at the highest concentrations.

**Data analysis**

For each odorant and each task (detection, identification), Mann–Whitney tests were calculated. Highly significant differences ($P < 0.0001$) were observed between normal and obstructed clefts and between normal and congenital anosmia. The differences between obstructed clefts and congenital anosmia were not significant for the identification task ($P = 0.18$ or more); for the detection task, no significant difference was observed for PEA and SKA, but a significant difference was noted for CYC, IVA, and UND ($P$ in the range of 0.01–0.05).

**Rhinomanometric measurements**

In normal subjects, rhinomanometric measurements performed before the olfactory test indicated, eventually, the normal asymmetry between the left and right resistances to airflow (Figure 3A) due to the nasal cycle (Davis and Eccles 2004). The difference in patency is related to the difference in turgescence of the tissue covering the turbinates as observed with CT scans (Figure 1B). The mean total resistance ($R_t$) was $0.23 \pm 0.09$ Pa $\cdot$ s $\cdot$ cm$^{-3}$ (mean $\pm$ SD). The same range of asymmetry was observed for patients suffering from obstructed olfactory clefts, and the mean resistance was identical ($0.23 \pm 0.09$ Pa $\cdot$ s $\cdot$ cm$^{-3}$). Comparison
of the histograms (Figure 4B) did not reveal any significant statistical difference ($\chi^2$ test; $P = 0.63$). It should be realized that occlusion of the clefts seems to have no measurable effect on the total nasal airflow resistance.

**Discussion**

**Olfactory test**

**Normal subjects**

In a clinical context, precise olfactory threshold measurements for a number of odorant molecules are not practicable. The olfactory test used in the present study clearly displayed significant differences between normal subjects and patients with identified olfactory pathologies. Normal subjects presented rather large interindividual differences, over a range of about $10^4$ in concentration, both for the detection and the identification tasks. Almost all subjects were able to detect the odorants at the level 4 and nearly all of them correctly identified the odorants at the level 6, with an exception for UND. The reason for the lack of correct identification of UND is not clear. However, it should be noted that subjects had no special training with olfactory task and had to associate a semantic label for each odorant at the beginning of the test. This task of association could be easier for some odorants than for others, depending on the pertinence of the
labels. Many subjects did not agree with the labels proposed for UND.

**Patients with congenital anosmia**

The olfactory test with patients without olfactory bulbs confirmed the lack of sensitivity for the 5 odorants, as expected for complete anosmia: about 75% of patients were unable to detect the odorants at the highest concentrations. However, about 25% of this group of patients were able to detect the presence of the odorant molecules, and this sensitivity appeared around the levels 3 and 4. As these patients have no functional olfactory system, this sensitivity would correspond to the activation of the trigeminal nerve fibers innervating the nasal cavities. Interestingly, PEA, which is sometimes considered as lacking trigeminal activity (Silver and Moulton 1982), could indeed be detected by some anosmic patients. However, they apparently did not use this putative trigeminal information to detect the presence of odorants. It is possible that anosmic patients differ in the trigeminal sensitivity to odorants or are able to use this information at different degrees. There are few studies on the interaction between the olfactory and trigeminal systems. Subjects with congenital anosmia have higher peripheral responses to trigeminal stimulants than normal subjects (Frasnelli et al. 2007), but anosmia may also induce a decreased trigeminal sensitivity (Gudziol et al. 2001). The intranasal trigeminal information used, in the present study, by patients with congenital anosmia to detect the presence of odorants did not allow them to correctly identify the odorants (Figure 2F). Congenitally, anosmic patients are known to be able to distinguish, by immediate comparisons, odorants with strong trigeminal component (Laska et al. 1997). However, in our test, congenitally anosmic patients had to learn and memorize the possibly distinct trigeminal sensations at the beginning of the test and then use this information all along the test, demonstrating that identification of chemicals by use of the trigeminal system is a difficult task.

**Patients with inflammatory obstructed olfactory clefts**

Patients with obstructive inflammation of olfactory clefts have impaired olfaction, most of them being unable to detect the highest concentration of odorants. Among the sensitive patients, only half could correctly identify the odorants at the highest concentrations. It is clear that the obstructive inflammation of the olfactory clefts prevents odorant molecules to reach the olfactory epithelium. This obstruction appears different from that induced by polyps in the clefts (Masaki and Tanaka 1998): polyps appear as bulging, more or less translucent, entities. In addition, polyposis is an extended disease of the sinuso-nasal mucosa and CT scan imaging emphasizes edematous mucosa inside ethmoidal and/or maxillary sinuses. None of our patients with obstructed olfactory clefts presented these features.

For many patients with inflammatory obstructed clefts, the olfactory deficit was equivalent to the lack of olfactory bulbs. For these patients, the obstruction did not always concern the whole length of the clefts, suggesting that even a partial occlusion of the cleft (e.g., only the middle part) may have severe impact upon the airflow in the nonobstructed part. Present models of the air repartition in the nasal cavities are not clear on this point (e.g., Zhao et al. 2004). Interestingly, some patients with obstructed clefts were not completely anosmic and could detect (identify) some odorants, although only at much higher concentrations than normal subjects. For most of these patients, CT scans indicated that the obstruction concerned the posterior part of the clefts, leaving the anterior part free. Recently, it has been shown, using electrophysiological recordings, that odorant-induced surface potential signals (electroolfactograms, corresponding to the activation of olfactory sensory neurones) can be
Origin of the obstruction of the clefts

The obstruction of the olfactory clefts obviously corresponds to a local inflammation of the tissue, together with stagnation of secretion, which is important enough for opposite sides of the cleft to collapse, thus impairing air passage (conductive loss). The nasal tissue in the rest of the nasal cavities (as well as sinuses) is not concerned with this obstructive process: rhinomanometric measurements did not reveal any significant increase of the nasal resistances. The natural turgescence of the nasal mucosa covering the turbinates (Davis and Eccles 2004) did not seem to be altered. Our measurements also indicate that the nasal resistance measured by rhinomanometry corresponds mainly to the airflow in the lower part of the nasal cavity (close to the septum, middle, and inferior meatuses) and is of little use to determine the existence of obstructed clefts. According to Zhao et al. (2004) and other studies, only 5–10% of total external nares airflow actually passes through the clefts during breathing.

The exact origin of the obstruction of the clefts is not known. As previously described (Biacabe et al. 2004), this obstruction is sometimes associated with the hypertrophy of the middle turbinates (*concha bullosa*; e.g., Figure 2E). This anatomical malformation could favor the appearance of the pathology, by mechanical disturbance followed by local inflammation, but the association was not systematic in our observations. No other concomitant obvious anatomical malformation could be observed. Nevertheless, this aspect should be studied in more details in the future. Small anatomical volume differences in the olfactory region lead to differences in the airflow stream in the clefts (Zhao et al. 2004) and therefore the local ventilation during normal breathing.

Sometimes, the pathology appeared after a severe (but treated) nasopharyngeal infection. Other patients, not included in this study, presented obstructing polyps near the clefts (bulging out from the middle meatuses or from the upper part of the septal mucosa) and a decreased olfactory sensitivity (Masaki and Tanaka 1998). However, no evolution to polyposis could be observed after several years in patients included in this study in the obstructed olfactory cleft group.

Presently, the factors that trigger the pathology is not known and treatments remain to be found. The pathology persists in spite of inhaled corticosteroids or oral corticoid treatments (e.g., 1 week cortisone at a dose of 1 mg · kg⁻¹ · day⁻¹) associated with antibiotics. Some patients, after protocol agreement, received a delayed-release corticoid injection (triamcinolone 80 mg). CT scan imaging before and 3 weeks (maximum effectiveness) after treatment did not show any improvement in extension of obstructed area nor olfactory ability. In some patients, the obstructed olfactory clefts were easy to visualize (Figure 1D): a local application of vasoconstrictors associated with local anesthesia (Xylocain 5%-Naphazoline, Astra Zeneca, France) during half an hour failed to change the swelling, and there was no improvement of olfaction.

Recurrent infection in the cleft region damages the olfactory receptors with squamous metaplasia or fibrosis making the olfactory dysfunction permanent (Jafek et al. 2002). Surgery at this level (Leopold 2002) being potentially hazardous, an efficient treatment for obstructed olfactory clefts remains to be found.

In all patients with obstructed inflammatory clefts examined with MRI, we could observe the presence of the olfactory bulbs. However, it would be interesting to examine in more details the volume of these bulbs, as this long-lasting pathology, which prevents the normal functionality of all or a large portion of the olfactory epithelium, may modify the size of the bulbs, as previously observed for several other pathologies (Turetsky et al. 2003; Mueller et al. 2005; Rombaux et al. 2006).

The olfactory clefts, a specific domain of the nasal cavities

The physiology of the human olfactory clefts remains to be explored more extensively in order to determine the possible sources of local dysfunctions. Several lines of evidence indicate that the olfactory clefts function as an entity that is different from other regions of the nasal cavity. 1) In a previous study (Briand et al. 2002), we detected the presence of odorant-binding proteins in the mucus covering the olfactory clefts, not in the mucus covering the rest of the nasal cavity. These lipocalin-like proteins may play a role in the olfactory process. 2) It is a conspicuous observation that the nasal tissue in the rest of the nasal cavities is not concerned by any obstructive process in patients with occlusions of the olfactory clefts. 3) In the present study, the inflammation and the obstruction were not removed by vasoconstrictors, antibiotics, or corticoid treatments. This is in contrast to obstructive inflammation of the lower parts of the nasal cavity that is vulnerable to such treatments. Finally, little is known about the trigeminal innervation in the cleft region in humans. In other species, the trigeminal innervation of the olfactory mucosa is involved in the mucus secretion (Lucero and Squires 1998) and, possibly, could contribute to the development of local inflammation.
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