






# Postinfectious Olfactory Complaints: A Follow-up Study

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## Abstract

**Introduction** Acute upper respiratory infection (AURI) is the most common cause of postinfectious olfactory dysfunction (PIOD).

**Objective** We investigated the prevalence of PIOD in a large group of patients reporting persistent smell impairment perception after the AURI resolution.

**Methods** Olfactometry was performed within 1 month after the common cold resolution and after 1 year in 467 (299 males, mean age 41.7 years) outpatients. The Sniffin' Sticks olfactory test (Burghart instruments, Wedel, Germany) was used.

**Results** Anosmia was documented in 28 (6%) patients, hyposmia in 33 (7%), and cacosmia in 55 (11.7%). After 1 year, PIOD improved in 82 (79.6%) patients re-tested.

**Conclusion** The current study demonstrated that persistent olfactory dysfunction is a relevant symptom in patients with AURI, even though many patients had normal olfactometry. Thus, smell impairment deserves careful attention and requires objective documentation.

## Keywords

- ▶ olfactory dysfunction
- ▶ acute upper respiratory infection
- ▶ olfactometry

## Introduction

A smell dysfunction may be quantitative (anosmia, hyposmia, and hyperosmia) or qualitative (parosmia and phantosmia), temporary or permanent, and acquired or congenital. Acute upper respiratory infections (AURI), mainly the common cold, are the most frequent cause of anosmia/hyposmia. This topic has received renewed attention to indicate biologics in chronic rhinosinusitis with nasal polyps, and, more recently, for COVID-19.

The worldwide annual number of viral rhinitis episodes could be ~ 20 billion cases; presently, more than 200 types of viruses can cause the common cold, including mainly rhinovirus, adenovirus, and coronavirus.<sup>1</sup> Patients whose olfactory problems are triggered after an upper airway infection frequently report distorted taste.<sup>2</sup> Most patients with com-

mon cold recover their normal olfactory state more or less quickly. Still, in a small segment (not negligible in absolute numbers), the partial or total loss of their sense of smell persists as a sequel for months or permanently.<sup>3</sup> It has also been indicated that, given how suddenly it is established, this loss of smell is accompanied by significant affective discomfort and loss of quality of life.<sup>4</sup> In particular, people who suffer from olfactory dysfunction for more than 6 months from a cold usually present severe smell impairment.<sup>5</sup> The olfactory mucosa's damaging mechanism consists of the invasion of the nasal mucosa's epithelial cells (both olfactory and non-olfactory) by the different viruses, and the successive destruction of these cells. This mechanism is what leads to the loss of both olfactory epithelial cells and non-olfactory mucosa cells (stratified epithelium), with the peculiarity that

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sensory terminals of the trigeminal nerve are found in both types of the mucosa.

Moreover, it has been demonstrated that there is a significant contemporary alteration of the olfactory, trigeminal, and gustatory neuronal pathways during a cold.<sup>6</sup> On the other hand, nasal inflammation associated with viral rhinitis causes mucosal swelling that, in turn, reduces nasal airflow. Notably, nasal blockage impairs access of the odors to the olfactory region.<sup>7</sup> However, smell impairment is a subjective perception that needs an objective evaluation performing olfactometry.

Another important aspect associated with postinfectious olfaction dysfunction concerns its recovery. In this regard, some studies have previously investigated this topic. A retrospective study included 262 patients with an olfactory loss after AURI.<sup>8</sup> The olfactory function has been re-evaluated on average after 14 months. Thirty-two percent of patients improved, but only 10% of 99 patients with post-traumatic olfactory loss recovered. This study demonstrated a negative correlation between age and recovered function in patients with postinfectious smell impairment. A further study, including 542 patients, objectively assessed the olfactory function on two occasions separated from one another by 3 months to 24 years.<sup>9</sup> Olfaction recovery was observed in a relevant number of patients; recovery predictors were patient age, the severity of initial olfactory loss, and duration of smell impairment at first testing. Notably, both patients' cohorts performed no rehabilitation method, but the recovery, if any, spontaneously occurred. In addition, a large study evaluated 894 subjects twice reported to an interdisciplinary center for smell and taste.<sup>10</sup> The prevalence of functional anosmia decreased from 48.2 to 31.1%, the prevalence of hyposmia increased from 49.7 to 55.5%, consistently, and normosmia increased from 2.1 to 13.4%. This study identified a few prognostic factors associated with smell recovery, including residual function, female sex, parosmia, smoking habit, and young age.

Based on this background, the present study aimed at investigating the postinfectious olfactory dysfunction (PIOD) prevalence in a group of patients with a recent AURI, and the potential olfaction recovery after 1 year.

## Materials and Methods

The study included 467 patients (299 males, mean age 41.7 years) who consecutively accessed a third-level ENT clinic during the 2000 to 2019 period. These patients were visited

because they reported the perception of smell impairment persisting from at least 1 month after the common cold resolution.

The inclusion criteria were persistent smell dysfunction and previous AURI. The exclusion criteria were chronic infectious and/or inflammatory disease of the upper airways, including allergic rhinitis, non-allergic rhinitis, and chronic rhinosinusitis. In addition, the workup excluded the most common causes of smell impairment, mainly concerning trauma, cancer, neurological and endocrine-metabolic disorders, drugs, and inflammatory diseases. Patients paused local and systemic treatments at least 2 weeks before testing.

During the follow-up, no rehabilitation was performed.

The olfactometry was performed as a usual complement of the visit to the specialist. The study procedure was approved by the local ethics committee (ID 0022546/20). All patients signed an informed consent about privacy and approved of the procedure.

The investigators used the Sniffin' Sticks olfactory test (Burghart instruments, Wedel, Germany) to measure the threshold, discrimination, and identification test, as already described.<sup>11</sup> First, subjects had to discriminate which of the three pens smelled differently. Triplets were subsequently presented with a 20 to 30 seconds interval between them; the interval between individual pens' presentations was ~3 seconds. Next, subjects were blindfolded to prevent visual identification. Next, patients assessed odor identification for 16 common odors. Finally, we calculated the threshold discrimination identification score (TDI), ranging from 0 to 48.

Patients were classified as normosmic (TDI > 30.5), hyposmic (TDI < 30.5 and > 16.5), or anosmic (TDI ≤ 16.5), while values < 5 must not be considered as reliable. Parosmia was a referred symptom; the smell function was normal in most of them.

The patients with olfactory dysfunction were recalled to evaluate the persistence of symptoms after 1 year.

The statistical analysis was descriptive.

## Results

► **Table 1** reports the olfactometry outcomes in 467 patients with referred smell impairment after the common cold resolution. Anosmia was detected in 28 (6%) patients, hyposmia in 33 (7%), and parosmia in 55 (11.7%). Normosmia was documented in 351 (75.3%) patients.

**Table 1** Distribution of olfactory dysfunction in 467 patients with the common cold

Symptoms	Number of patients	Frequency	Mean TDI value
Anosmia	28	6%	12.5 (2.6)
Hyposmia	33	7%	20.5 (3.1)
Parosmia	55	11.7%	30.5 (2.2)
Normosmia	351	75.3%	40.2 (5.3)

Abbreviations: TDI, threshold discrimination identification.

Data are reported as absolute numbers, frequencies, and mean ± standard deviation.

After 1 year, 116 patients with olfactory alteration were re-evaluated, but only 103 underwent new olfactometric testing (13 did not come to a further evaluation for various causes).

Fifty-one (93%) patients with initial parosmia recovered after 1 year. Ten anosmic patients became hyposmic or normosmic. Twenty-one hyposmic patients recovered a normal sense of smell. Globally, 82 (79.6%) patients improved olfactory function after 1 year.

## Discussion

Postinfectious olfactory dysfunction is a frequent cause of short- and long-term smell impairment, as evidenced by a recent systematic review.<sup>12</sup> Postinfectious smell defects recognize multiple olfactory pathways' disruptions, including cell damage, inflammatory events, and cytokine hyperactivity. Therefore, olfactory dysfunction depends on direct inflammatory phenomena, including impaired nasal airflow and neurological damage. As smell impairment represents a relevant symptom, it requires adequate management.<sup>13</sup>

The most interesting aspect of this dataset was that among patients with self-reported olfactory dysfunction, 75% were normosmic on testing. This outcome underlined the discrepancy between self-reported and objective olfactory dysfunction and the limitations of current data on this topic among patients with postviral symptoms. The present study also reported a slight prevalence of persistent olfactory dysfunction in patients with previous AURI. Olfactometry documented an olfactory dysfunction in almost ¼ of the patients. This finding also underlined the clinical importance of smell impairment during the common cold. Unfortunately, these olfactory symptoms are neglected and not adequately considered by doctors, mainly concerning general practitioners (GPs). Namely, olfactory dysfunction is a symptom that may have profound relevance for the patient with a remarkable impact on the quality of life and may range from dangerous up to life-threatening.

On the other hand, the current study provided two relevant pieces of information. First, objective assessment. Using olfactometry, we documented and confirmed an objective smell impairment in ~ 25% of patients. In other words, this study demonstrated that 75% of patients perceiving olfactory disorders had normal olfaction if objectively measured. This fact underlines the importance of using adequate methods in patients with persistent postviral smell disorders. Moreover, this outcome highlights that smell perception is a subjective variable that is frequently not associated with objective smell impairment. As a result, a thorough workup should include an objective measurement of smell function.<sup>14,15</sup>

Moreover, this study showed that the vast majority (~ 80%) of patients improved within 1 year. Also, this outcome highlights the relevance of adequate follow-up in these patients.

In particular, parosmia was the most common symptom, and patients recovered from it more frequently than from quantitative symptoms. This could be due to the fact that this

symptom is connected more to alterations of the nasal environment, such as secretion thickness, epithelium integrity, nasal secretions, and pH. Therefore, patients could recover quickly from parosmia after an acute and postacute viral infective period. Moreover, the current outcomes partially conflicted with those of a previous study that explored the duration of parosmia.<sup>16</sup> This study included 56 patients with parosmia, 24 of whom had had an upper respiratory infection; the mean duration of parosmia was 63 months. However, the number of patients was somewhat limited, and precise details on infections were missing. However, another study enrolled 392 patients with olfaction dysfunction.<sup>17</sup> Parosmia was most frequently (56%) associated with post-infectious olfactory loss. Moreover, the dysfunction had resolved in 29% of patients with parosmia after an average of 12 months.

The current study has some strengths, including the large sample size, the objective measurement of olfactory dysfunction, and the real-world setting. On the other hand, the main limitations include the lack of a control group, quality-of-life measurement, descriptive statistics alone, and biomarkers assay.

## Conclusion

In conclusion, the current study demonstrated that persistent olfactory dysfunction is a relevant symptom in patients with the common cold, even though many patients with referred smell dysfunction had normal olfactometry. Thus, smell impairment deserves careful attention and requires objective documentation as reported by Hummel et al. in their study.<sup>18</sup>

### Conflict of Interests

The authors have no conflict of interests to declare.

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