

Prognosis of postviral olfactory loss: Follow-up study for longer than one year

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ABSTRACT

Background: There have been very few studies on the prognosis of postviral olfactory dysfunction. The aim of the study was to evaluate its long-term prognosis and factors influencing the prognosis.

Methods: This study included patients who were diagnosed with postviral olfactory dysfunction at least one year ago in a Smell and Taste Clinic and whose telephone interviews were available. Their medical records were reviewed, and they were asked to score their subjective olfactory function on a 100-point scale by telephone interview.

Results: A total of 63 patients and 20 normal controls without nasal pathology were included. The mean age of the patients was 49.5 years, and 19 males and 44 females were included. The mean length of follow-up was 33.4 months. Olfactory dysfunction was subjectively improved in 85.7% of the patients. The recovery rate to subjective normosmia was 31.7%. The mean symptom scores for smell significantly increased in comparison with baseline from 25.6 to 69.0. Among the 25 patients (37.7%) who underwent follow-up butanol threshold test (BTT), the score improved from 4.6 to 7.3. Olfactory improvement was more frequently reported by females ($p = .003$) and in patients with follow-up duration for longer than 2 years ($p = .043$).

Conclusions: Follow-up of postviral olfactory loss revealed that over 80% of the patients reported subjective recovery after one year. The more favorable prognosis was associated with longer follow-up duration and female gender.

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Olfactory dysfunction is common in the general population¹ and caused mainly by head trauma, chronic sinonasal inflammation, and viral infection of the nose.² Despite its high prevalence and negative effect on quality of life,³ clinical investigations for olfactory dysfunction are still not so active as compared with other senses. Furthermore, the prognosis of olfactory dysfunction is not well understood. In particular, there have been a very few papers for prognosis of postviral anosmia or hyposmia.^{4–6} Postviral or postinfectious olfactory loss is a syndrome characterized by a sudden loss of olfactory function after upper respiratory infection (URI).⁷ Those who suffer from URI have nasal mucosal swelling and temporary conductive blockage in the olfactory cleft.^{8,9} Even though temporary olfactory loss resolves in most of them, it persists in patients with postviral olfactory loss and recovery is usually delayed for several months.¹⁰ Its presumed cause is viral damage of olfactory epithelium, olfactory receptor neurons, or central olfactory pathway.¹ The severity is various and patients' quality of life is compromised.¹¹ Although medical treatment, such as prednisolone, has been empirically administered in the early stage of disease,^{12,13} informing the patients about their prognosis is still challenging due to lack of evidence for the prognosis. Furthermore, otorhinolaryngologists do not follow-up with the patients for a long period, because further treatment modalities available are not present. However, in our actual clinical setting, it was not uncommon that we encounter patients whose sense of smell spontaneously improves to some extent after a couple of years. Therefore, we hypothesized that postviral olfactory loss may meliorate without a long-term treatment. Our study was aimed to identify the long-term

prognosis of postviral olfactory dysfunction and factors influencing the prognosis.

METHODS

Subjects

Medical records of patients who visited the Smell and Taste Clinic due to a reduced sense of smell after URI were retrospectively investigated. At the first visit, URI history was ascertained by questionnaires from a rhinologist, URI symptoms other than olfactory dysfunction were resolved, and all of the patients underwent an olfactory function test. The mean duration between URI history and clinic visit was 3.1 months. Inclusion criteria were as follows: history of URI immediately before olfactory loss, sudden onset of olfactory loss, visits to our clinic and diagnosed at least one year ago, no evidence of sinonasal inflammation on nasal endoscopy and paranasal sinus computed tomography scan, and telephone interviews available. Exclusion criteria were as follows: history of head trauma, history of long-term oral corticosteroid use, concurrent memory loss, the presence of nasal discharge, and allergic rhinitis and chronic rhinosinusitis.⁴ All of the patients with postviral olfactory loss were treated with prednisolone for 2 weeks and mometasone furonate nasal spray for 4 weeks. As a control group with normosmia, we included 20 subjects without any nasal pathology, who were admitted for tonsillectomy and reported having normal olfactory function. This study was approved by the institutional review board of Seoul National University Bundang Hospital.

Olfactory Tests

The odor threshold was determined by performing butanol threshold test (BTT), a forced-choice test using 13 concentrations of N-butanol (Sigma Co., St. Louis, MO) serially diluted threefold in mineral oil (Sigma Co.), from 100% N-butanol (concentration level 0, BTT score of 0) to concentration level 12 (BTT score of 12). At each examination, patients were given two sniff bottles (one bottle of mineral oil and the other bottle containing each concentration of butanol, starting with the most dilute concentration) and asked to identify the bottle containing butanol, with each nostril tested separately. The odor threshold was defined as the lowest concentration level at which the butanol bottle was correctly identified in 5 consec-

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Table 1. General characteristics of participants according to the severity of initial olfactory loss ($n = 63$)

	Anosmia ($n = 18$)	Severe Hyposmia ($n = 22$)	Mild to Moderate Hyposmia ($n = 23$)	Control ($n = 20$)	p Value
Age (years)	52.5 $\pm$ 13.1	50.9 $\pm$ 11.2	46.7 $\pm$ 13.5	47.5 $\pm$ 12.7	0.307
Number of females (%)	11 (61.1%)	18 (81.8%)	16 (69.6%)	14 (70.0%)	0.343
Mean follow-up duration (months)	37.4	30.9	32.7	NA	0.328
Initial BTT (scores)	2.7	4.7	6.8	10.7	<.001
Subjective olfactory function score	14.2 $\pm$ 15.3	27.5 $\pm$ 22.8	32.8 $\pm$ 20.0	80.5 $\pm$ 8.5	0.003

BTT = butanol threshold test; NA = not applicable.

utive trials. Anosmia was defined as BTT score of 0 to 3, severe hyposmia as BTT score of 4 to 6, and mild to moderate hyposmia as BTT score of 7 to 9. Follow-up BTT was performed only in the patients who agreed with it.

Telephone Interview

Telephone interviews were performed as follow-up assessments to ask following questions: (1) Do you think there is an improvement for your smell since you were diagnosed at first?; and (2) Score your subjective olfactory function on a 100-point scale at the first visit and at present.

Statistical Analyses

Statistical analyses were performed using a software package SPSS for Windows version 17.0 (SPSS, Inc., Chicago, IL). A paired t test was performed to compare initial smell scores with follow-up scores. One-way analysis of variance was used to assess differences between groups, and bivariate tabular analyses were performed by a χ^2 test.

A binary logistic regression analysis was used to identify the factors independently associated with presence of subjective olfactory improvement among risk factors such as gender, age (as a continuous variable), follow-up duration (shorter or longer follow-up by 2 years), and initial subjective olfactory score (as a continuous variable). Values are presented as mean $\pm$ SD; p values less than 0.05 were considered statistically significant. This study was approved by the institutional review board of Seoul National University Bundang Hospital.

RESULTS

Demographic Findings and Initial Olfactory Function Test Results

A total of 63 patients were included. The mean age of the participants was 49.5 years (ranges, 17 to 74 years) and 44 participants (70%) were females. The average follow-up duration was 33.4 months (ranges, 12 to 62 months). The mean BTT score was 5.3 $\pm$ 2.4 at the initial examination. Patients were categorized into 3 groups according to the BTT score at the first visit. Initially, 18 (28.6%) patients were classified into the anosmia group, 22 (34.9%) into the severe hyposmia group, and 23 (36.5%) into the mild to moderate hyposmia group. The age, proportion of females, and mean follow-up duration were not statistically different among 3 groups (Table 1). The mean age of the control group was 47.5 $\pm$ 12.7 years, and the proportion of females was 70.0%.

Subjective Improvement of Olfaction

A total of 54 patients (85.7%) reported an improvement in their sense of smell. The subjective improvement rate was 77.8%, 90.9%, and 87.0% in anosmia, severe hyposmia, and mild to moderate hyposmia groups, respectively ($p = .49$). The mean initial subjective olfactory function score of all participants was 25.6 $\pm$ 21.0, and it improved to 69.0 $\pm$ 26.0 ($p < .001$) at follow-up. The baseline subjective olfactory function score showed a significant correlation with

BTT score ($r = 0.316$, $p = .012$). In all of the 3 severity groups, the olfactory function scores at follow-up were significantly increased in comparison to the initial scores. The initial and final olfactory function scores were 14.2 $\pm$ 15.3 and 56.1 $\pm$ 31.3 in the anosmia group ($p < .001$), 27.5 $\pm$ 22.8 and 73.6 $\pm$ 18.5 in the severe hyposmia group ($p < .001$), and 32.8 $\pm$ 20.0 and 74.6 $\pm$ 25.6 in the mild to moderate hyposmia group ($p < .001$), respectively (Fig. 1). Overall, nine patients (14.3%) reported that there was no improvement from the initial olfactory loss. Of 19 males, eight (42.1%) reported no improvement, whereas only one of 44 (2.3%) females reported no improvement ($p < .001$) (Table 2).

The subjective improvement rate of olfactory function was 66.6% (2/3), 80.0% (4/5), 85.7% (36/42), and 92.3% (12/13) in each group of less than 20 years, 20–40 years, 40–60 years, and more than 60 years, respectively ($p = .68$). The length of follow-up duration was significantly associated with improvement rate when the patients were divided into 2 groups such as shorter follow-up group (less than 2 years) and longer follow-up group (more than or equal to 2 years). The improvement rate was 80.0% and 92.9% in the shorter follow-up group (less than 2 years) and longer follow-up group (more than or equal to 2 years), respectively ($p = .04$).

Recovery Rate to Subjective Normosmia

Mean olfactory function score of normal controls was 80.5. Based upon the normal score obtained from the normal controls, the overall recovery rate to subjective normosmia was 31.7%. The recovery rate was 27.8%, 22.7%, and 43.5% in the anosmia, severe hyposmia, and mild to moderate hyposmia groups, respectively ($p = .04$). The recovery rate to subjective normosmia was higher in females (55.6%) than in males (38.9%, $p = .02$).

BTT Score

The availability rate of follow-up BTT was 39.7% (25/63). Among the 25 patients who underwent follow-up BTT, the mean BTT score increased from 4.6 to 7.3 ($p = .01$). The follow-up BTT increased from 2.7 to 6.3 in anosmia group ($n = 6$, $p = .01$), 4.7 to 7.2 in severe hyposmia group ($n = 13$, $p = .001$), and 6.8 to 8.8 in mild to moderate hyposmia ($n = 6$, $p = .09$). We could not find a significant difference in the proportion of patients who reported their subjective olfactory improvement between the patients with follow-up BTT and those without follow-up BTT (88.0% and 82.5%, respectively; $p = .301$).

Factors Associated with Prognosis

Logistic regression analyses showed that factors associated with improvement of subjective olfactory function were female sex (odds ratio = 13.026, 95% significance interval = 2.258–81.871; $p = .003$) and follow-up duration longer than 2 years (odds ratio = 6.609, 95% significance interval = 1.046–41.867; $p = .043$) (Table 3). On the other hand, age ($p = .75$) and severity of initial olfactory loss ($p = .65$) were not correlated with prognosis.

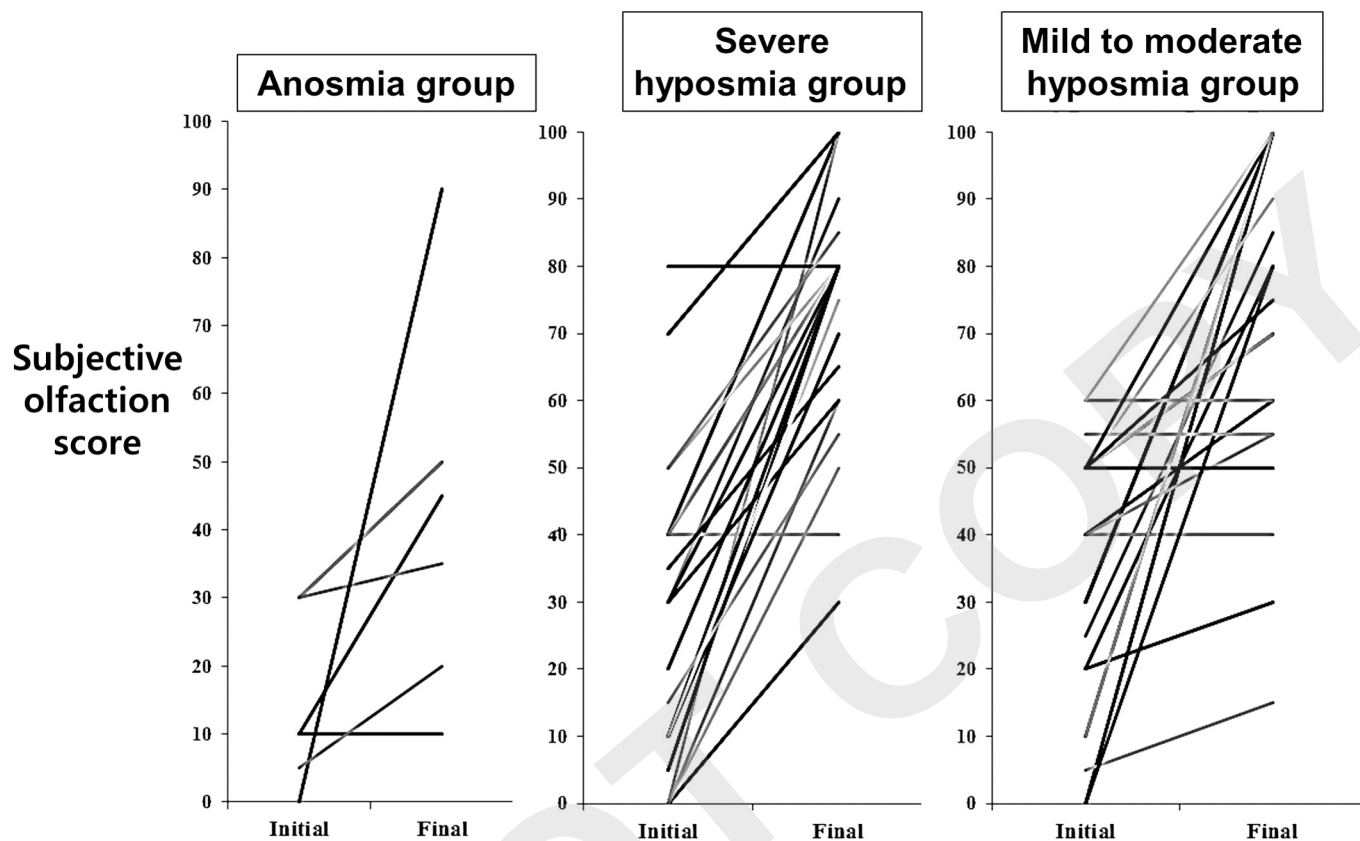


Figure 1. Changes of subjective olfaction score according to initial butanol threshold test (BTT) score.

Table 2. Patient characteristics according to presence of subjective improvement and gender

	Improvement (+) (n = 54)		Improvement (–) (n = 9)	
	Male (n = 11)	Female (n = 43)	Male (n = 8)	Female (n = 1)
Age (years)	51.6 ± 12.4	45.8 ± 13.8	51.0 ± 10.5	49
Follow-up duration (months)	35.0 ± 8.9	33.6 ± 9.1	33.4 ± 2.2	25
Initial BTT (scores)	4.3 ± 2.8	5.5 ± 2.1	5.1 ± 1.4	4
Olfactory function score				
Initial	21.1 ± 12.1	29.4 ± 23.4	45.7 ± 22.8	30
Final	60.3 ± 27.1	72.9 ± 26.1	42.9 ± 25.5	30

BTT = butanol threshold test.

DISCUSSION

Our study may be unique, because there have been very few studies on the prognosis of postviral olfactory dysfunction despite its relatively high prevalence. The University of Cincinnati Taste and Smell Center reported a viral etiology in 78 of 354 patients (22%) presenting with a smell loss.¹⁴ The Connecticut Chemosensory Clinical Research Center reported that 82 of 441 patients with olfactory dysfunction (18.6%) experienced an olfactory loss after viral URI.¹⁵ Unexpectedly, based upon our long-term follow-up results, approximately 86% of the patients with postviral olfactory loss reported subjective improvement. In a small cohort study with a follow-up over one year, improvement of olfactory function was also frequently observed. The scores on the University of Pennsylvania Smell Identification Test increased in 19 of 21 patients (90%) and 13 of 21 (62%) reported subjective improvement in their sense of smell.¹⁶ However, in another study comparing head trauma and URI, 32% of patients with postviral olfactory loss showed improvement in an olfactory

function test, whereas there was only 10% of improvement in post-traumatic patients.¹⁷ Recently, olfactory training is suggested to be effective in postviral anosmia, which showing two thirds of the patients with postviral anosmia had an improvement with training.¹⁸ This study with olfactory training showed that a 16-week short-term exposure to specific odors may increase olfactory sensitivity in patients with postinfectious and posttraumatic olfactory dysfunction.

Our study also demonstrated that a longer period after onset of olfactory loss positively affected spontaneous recovery. This suggests that regeneration of the olfactory epithelium and olfactory bulb might continue for a long time after damage,¹⁹ or the patients might just be accustomed to their loss of olfactory function.²⁰ However, because the etiology of postviral olfactory dysfunction is not well understood, the mechanism of long-term recovery cannot be explained until now. As for the etiology, there were studies that implicate viruses. Rhinovirus was reported to cause olfactory dysfunction through mechanisms other than nasal obstruction and to induce various severities and time

Table 3. Binary logistic regression of various factors to presence of subjective olfactory improvement

Variable	Odds Ratio	95% SI	β	p Value
Gender (female)	13.026	2.258–71.871	2.567	.003
Age (continuous variable)	0.990	0.932–1.053	0.015	.753
Initial BTT (continuous variable)	1.078	0.786–1.477	0.075	.646
Longer follow-up (≥ 2 years)	6.609	1.046–41.867	1.888	.043

SI = significance interval; BTT = butanol threshold test.

courses of olfactory dysfunction.²¹ Parainfluenza virus type 3 may also be the causative virus of postviral olfactory dysfunction.¹¹ Whether the primary damage occurs in the olfactory neuroepithelium or olfactory bulb is also unclear. When it comes to another etiology of olfactory dysfunction, such as rhinosinusitis, many studies have proven that with medication or surgery, the olfaction can improve over one year follow-up.^{22–24}

Another interesting finding was that the recovery rate to normosmia was most frequent in patients with mild to moderate hyposmia. There was a study showing that the severity of histopathological changes within the olfactory epithelium was significantly correlated with recovery.⁸ London et al²⁵ suggested that prognosis primarily depends on the presence of residual function. They also showed that sex, smoking, age, and parosmia were prognosticators.²⁵ We also found that sex may be a significant prognosticator. Most female participants in our study were housewives, and continuous olfactory stimulation during cooking might have accelerated regeneration of olfactory neurons.²⁶

Although our study revealed interesting findings, there are still some limitations. Our study mainly relied upon telephone interviews, hence there may be a recall bias. The recall could be more inaccurate when the duration between the onset of olfactory loss and telephone interview was longer. There may also be a selection bias, because our study was performed retrospectively.

CONCLUSION

Our long-term follow-up study for postviral olfactory dysfunction showed that more than 80% of the patients experienced subjective improvement from their loss and recovery to normosmia was reported in approximately 30% of the patients. Longer follow-up duration and female gender were good prognosticators. This suggests that postviral olfactory loss could be recovered or normalized a couple of years after its development with long-term follow-up. However, because the present study was retrospectively performed having a selection bias, prospective studies are required to verify the favorable natural course of postviral olfactory dysfunction observed in our study.

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