PROGNOSIS OF OLFACTORY DYSFUNCTION ACCORDING TO ETIOLOGY AND TIMING OF TREATMENT

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Prognosis of Olfactory Dysfunction according to Etiology and Timing of Treatment

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INTRODUCTION

- olfactory function has been shown to affect mood and quality of life, to modify dietary behavior, and to play important roles in safety and danger avoidance.

- The prevalence of self-reported olfactory dysfunction in recent epidemiologic studies showed age-related increases in adults, ranging from 3.8% to 24.5%.
## Causes of Olfactory Dysfunction

### Table 1. Common causes of olfactory dysfunction

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive/conductive</td>
<td>Septal deviation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nasal polyposis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sinonasal and skull-base neoplasm</td>
<td>Inverted papilloma, meningioma, esthesioneuroblastoma, sinonasal undifferentiated carcinoma, squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Head and neck surgery</td>
<td>Tracheotomy, total laryngectomy</td>
</tr>
<tr>
<td>Sensorineural</td>
<td>Aging</td>
<td>Multifactorial</td>
</tr>
<tr>
<td></td>
<td>Postinfectious</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neurodegenerative disease</td>
<td>Parkinson’s disease, Alzheimer’s disease, amyotrophic lateral sclerosis, Huntington’s disease</td>
</tr>
<tr>
<td></td>
<td>Head and facial trauma</td>
<td>Isolated anosmia, Kallmann syndrome</td>
</tr>
<tr>
<td></td>
<td>Congenital</td>
<td>Cigarette smoke, cocaine, formaldehyde, cyanocrylates, herbicides, pesticides, alcohol, benzene, sulfuric acid, cadmium, ammonia</td>
</tr>
<tr>
<td></td>
<td>Toxins</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>Chronic rhinosinusitis</td>
<td>Likely complex combination of conductive and sensorineural mechanisms especially in chronic rhinosinusitis with nasal polyposis</td>
</tr>
<tr>
<td></td>
<td>Sinonasal surgery</td>
<td>Septoplasty, endoscopic sinus surgery</td>
</tr>
<tr>
<td></td>
<td>Nutritional deficiencies</td>
<td>Major depressive disorder, schizophrenia, schizoaffective disorder, autism spectrum, bipolar disorder, anorexia nervosa, seizure disorders, headache syndromes</td>
</tr>
<tr>
<td></td>
<td>Neuropsychiatric</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medications</td>
<td>Multiple agents have been implicated. Common examples include inorganic zinc gluconate, chemotherapy agents, antihypertensive medications (diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers), antimicrobials (macrolides, terbinafine, fluoroquinolones, protease inhibitors, penicillins, tetracyclines, and nitroimidazoles), antiarrhythmics, antipsychotics, antidepressants, and anticonvulsants</td>
</tr>
<tr>
<td></td>
<td>Chronic medical illness</td>
<td>Renal and hepatic failure (may be related to encephalopathy), type 2 diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Idiopathic</td>
<td></td>
</tr>
</tbody>
</table>
TREATMENT OPTION

- **Correction** of the cause.
- **Surgical** management if indicated.
- **Olfactory training**
- **Medical** management?
WHAT MEDICAL MANAGEMENT AVAILABLE

- The administration of corticosteroids is still the evidence-based treatment in most cases of olfactory dysfunction, including in idiopathic, upper respiratory tract infection, and trauma situations by its anti-inflammatory effect.

- Other options have been proposed. Administration of Ginkgo biloba, zinc, retinoic acid, α-lipoic acid, caroverine, minocycline, and theophylline have been reported as alternative treatments; however, there is a lack of evidence regarding the effectiveness of these alternatives.
RESEARCH QUESTION?

- **Primary outcome**
  - Among patients with smell loss, Is the duration of smell loss important in predicting the prognosis?

- **Secondary outcome**
  - Benefit of systemic and local corticosteroid.
  - measured the severity of olfactory impairment according to risk factors.
  - compared responses with risk factors and treatment timing, and investigated prognosis according to treatment.
  - analyze results between subjective smell recovery and objective smell tests.
This study was approved by the institutional review board of hospital korea (KC16RISI0603).

**Study design**

retrospective study reviewing the medical records of patients who complained of smell loss.

**Study population**

725 patients were selected who had received systemic or topical administration of corticosteroids for smell disorders Between January 2006 and May 2016 in Department of Otolaryngology–Head and Neck Surgery, Seoul St Mary’s Hospital.
Inclusion criteria

- Patient with smell disorder who received oral or systemic steroid.

Exclusion criteria

- Patients with neurodegenerative diseases, neuropsychiatric diseases, chronic medical illnesses, and toxin/medical problem.
- Patient who didn’t go for olfactory test in the same institute.
- Patient who didn’t go smell test after treatment.
- Patient who went for nasal surgery in study period.
- If suspected malingering.
Included patients received systemic or topical administration of corticosteroids for smell disorders (n = 725)

- Excluded patients who did not undergo olfactory tests in our hospital (n = 182)
- Excluded patients who did not undergo smell tests after treatment (n = 24)
- Excluded patients undergoing nasal or sinus surgery during the study period (n = 18)
- Excluded patients suspected of malingering (n = 10)

Total study population (n = 491)

**Figure 1.** Flowchart of the study population.
GROUPING THE PATIENTS

- Causes of olfactory dysfunction was divided to:
  - Post URTI
  - Nasal sinus disease and anatomical variation group (after resolution of other sinonasal symptom)
  - Head trauma
  - Previous sinonasal surgery
  - Congenital disease affecting olfaction
  - Xerostomia
  - Idiopathic
butanol dissolved in mineral oil. Beginning with a 1-butanol concentration of 4% (v/v; dilution step 0), 9 successive 3-fold dilutions were prepared. The threshold was defined as the dilution at which the alcohol was identified in 4 consecutive trials. Olfactory function was graded. Scores of 9 to 11 were considered normosmia, 5 to 8 as hyposmia, and 0 to 4 as anosmia. Right and left nostril scores were averaged to yield a mean olfactory function score. We used the CCCRC test to check the odor threshold.

Malingering was determined by a negative response to ammonia during the CCCRC test or repeated 0-1 scoring during the CCSIT tests, pre- and posttreatment.
- **Treatment** was performed on the same day that the patients underwent their first smell tests.
- Systemic steroids was not administered when contraindicated.
- Systemic or intranasal steroid was not given if the patient was unwilling to take such methods.
TREATMENT GROUP

**Systemic steroid**

- oral prednisolone, 40 mg for 14 days, followed by a daily reduction of 5 mg

**Topical steroid**

- mometasone furoate monohydrate (Nasonex), 2 sprays in each nostril (total, 200 mg/d).

**Systemic and topical steroid**
Follow-up olfactory tests were performed 1 month after treatment.

Recovery of olfaction was reported from the patients as ‘‘no recovery’’ or ‘‘recovery’’ after treatment.

The CCCRC and CCSIT tests were also performed at the end of treatment.
All measured parameters are expressed as mean ± standard deviation.

Smell test value differences pre- and posttreatment were analyzed with paired t tests or the Wilcoxon signed-rank test.

Differences among groups were analyzed with analysis of variance or Kruskal-Wallis tests.

In cases of statistical significance, the ranked parameters were compared by 1-way analysis of variance and Bonferroni’s multiple comparison test.

A P value \( \leq 0.05 \) was considered to indicate statistical significance.

All statistical analyses were conducted with SAS 9.3 (SAS Institute, Cary, North Carolina).
RESULT

- The mean age of the patients was (range 9-91)
- 168 (34.2%) were males
- 323 (65.8%) were females
# RESULTS

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Patients, n (%)</th>
<th>Duration of Smell Loss, wk</th>
<th>Follow-up, d</th>
<th>CCCRC Results, n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>Median</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Post-URI</td>
<td>178 (36.3)</td>
<td>44.0 ± 171.8</td>
<td>4</td>
<td>40.5 ± 12.6</td>
</tr>
<tr>
<td>Head trauma</td>
<td>96 (19.6)</td>
<td>105.8 ± 286.0</td>
<td>32</td>
<td>39.1 ± 12.3</td>
</tr>
<tr>
<td>Nasal/sinus diseases</td>
<td>94 (19.1)</td>
<td>100.3 ± 216.1</td>
<td>24</td>
<td>36.4 ± 9.2</td>
</tr>
<tr>
<td>Previous sinonasal surgery</td>
<td>23 (4.7)</td>
<td>63.7 ± 69.1</td>
<td>36</td>
<td>41.7 ± 16.4</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>9 (1.8)</td>
<td>225.3 ± 166.0</td>
<td>192</td>
<td>47.4 ± 22.9</td>
</tr>
<tr>
<td>Congenital</td>
<td>2 (0.4)</td>
<td>N/A</td>
<td>N/A</td>
<td>31.5 ± 5.0</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>89 (18.1)</td>
<td>84.1 ± 248.1</td>
<td>12</td>
<td>38.5 ± 15.4</td>
</tr>
<tr>
<td>Total</td>
<td>491 (100)</td>
<td>78.4 ± 220.2</td>
<td>12</td>
<td>39.2 ± 13.1</td>
</tr>
</tbody>
</table>

Abbreviations: CCCRC, Connecticut Chemosensory Clinical Research Center; N/A, not applicable; post-URI, post-upper respiratory infection

73.5% 37.4% 1%
<table>
<thead>
<tr>
<th>Smell Recovery</th>
<th>Patients, n (%)</th>
<th>Mean ± SD</th>
<th>P Value</th>
<th>Threshold</th>
<th>P Value</th>
<th>Identification</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-URI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>106 (59.6)</td>
<td>7.32 ± 10.7</td>
<td>.001</td>
<td>1.6 ± 1.3</td>
<td>&lt;.001</td>
<td>1.0 ± 0.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No</td>
<td>72 (40.4)</td>
<td>96.1 ± 262.0</td>
<td>.001</td>
<td>0 ± 0.2</td>
<td>.776</td>
<td>0.2 ± 0.8</td>
<td>.19</td>
</tr>
<tr>
<td>Head trauma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12 (12.5)</td>
<td>34.3 ± 56.9</td>
<td>.022</td>
<td>1.5 ± 1.4</td>
<td>.017</td>
<td>1.6 ± 1.6</td>
<td>.028</td>
</tr>
<tr>
<td>No</td>
<td>84 (87.5)</td>
<td>116.0 ± 303.9</td>
<td>.022</td>
<td>0 ± 0.1</td>
<td>.208</td>
<td>0.4 ± 0.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nasal/sinus diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>52 (55.3)</td>
<td>48.5 ± 86.0</td>
<td>.009</td>
<td>1.5 ± 1.1</td>
<td>&lt;.001</td>
<td>1.1 ± 0.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No</td>
<td>42 (44.7)</td>
<td>164.6 ± 298.4</td>
<td>.009</td>
<td>0 ± 0.1</td>
<td>.792</td>
<td>0.1 ± 0.8</td>
<td>.352</td>
</tr>
<tr>
<td>Previous sinonasal surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (34.8)</td>
<td>56.0 ± 79.7</td>
<td>.294</td>
<td>2.4 ± 1.0</td>
<td>.011</td>
<td>1.3 ± 1.3</td>
<td>.068</td>
</tr>
<tr>
<td>No</td>
<td>15 (65.2)</td>
<td>67.7 ± 65.3</td>
<td>.294</td>
<td>0 ± 0.1</td>
<td>.655</td>
<td>0.5 ± 0.6</td>
<td>.02</td>
</tr>
<tr>
<td>Xerostomia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (44.4)</td>
<td>243.0 ± 195.1</td>
<td>.73</td>
<td>1.5 ± 0.5</td>
<td>.063</td>
<td>1.5 ± 1.0</td>
<td>.109</td>
</tr>
<tr>
<td>No</td>
<td>5 (55.6)</td>
<td>211.2 ± 161.4</td>
<td>.73</td>
<td>0 ± 0</td>
<td>1</td>
<td>0.4 ± 0.5</td>
<td>.157</td>
</tr>
<tr>
<td>Congenital</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>No</td>
<td>2 (100)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>39 (43.8)</td>
<td>57.0 ± 167.9</td>
<td>.365</td>
<td>1.9 ± 1.2</td>
<td>&lt;.001</td>
<td>1.6 ± 1.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No</td>
<td>50 (56.2)</td>
<td>105.3 ± 260.0</td>
<td>.365</td>
<td>0 ± 0.1</td>
<td>.234</td>
<td>0 ± 0.3</td>
<td>.782</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>221 (45.0)</td>
<td>33.4 ± 94.1</td>
<td>&lt;.001</td>
<td>1.7 ± 1.2</td>
<td>&lt;.001</td>
<td>1.2 ± 1.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No</td>
<td>270 (55.0)</td>
<td>115.3 ± 279.5</td>
<td>&lt;.001</td>
<td>0 ± 0.1</td>
<td>.797</td>
<td>0.2 ± 0.7</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: N/A, not applicable; post-URI, post–upper respiratory infection.

*Posttreatment – pretreatment. Values presented as mean ± SD.
Nearly half (48.0%) of the patients with recovered olfaction had been medically treated 1 month after olfactory loss.

**Figure 2.** Number of recovered olfaction patients according to duration of olfactory loss. Post-URI, post-upper respiratory infection.
<table>
<thead>
<tr>
<th>Treatment Method</th>
<th>Smell Recovery, n (%)</th>
<th>Smell Test Differences&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Threshold</td>
<td>P Value</td>
<td>Identification</td>
<td>P Value</td>
</tr>
<tr>
<td>Systemic + topical</td>
<td>250 (51.0)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.8 ± 1.3</td>
<td>&lt;.001</td>
<td>1.2 ± 1.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Yes</td>
<td>137 (54.8)</td>
<td>0.1 ± 0.2</td>
<td>.103</td>
<td>0.1 ± 0.7</td>
<td>.092</td>
</tr>
<tr>
<td>No</td>
<td>113 (45.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>60 (12.2)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.6 ± 1.3</td>
<td>&lt;.001</td>
<td>1.3 ± 0.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Yes</td>
<td>33 (55.0)</td>
<td>0.1 ± 0.2</td>
<td>.317</td>
<td>0.3 ± 0.7</td>
<td>.047</td>
</tr>
<tr>
<td>No</td>
<td>27 (45.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical</td>
<td>181 (36.9)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.4 ± 1.1</td>
<td>&lt;.001</td>
<td>1.1 ± 0.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Yes</td>
<td>51 (28.2)</td>
<td>0 ± 0.1</td>
<td>.421</td>
<td>0.3 ± 0.7</td>
<td>.001</td>
</tr>
<tr>
<td>No</td>
<td>130 (71.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Posttreatment – pretreatment. Values presented as mean ± SD.

<sup>b</sup>Percentage based on total of the 3 treatment methods.
DISCUSSION

- **Percentage of olfactory dysfunction**
- post-URI (17%-45%) is the most common etiology of olfactory loss.
- nasal/sinus disease (7%-56%)
- idiopathic causes (0%-34%)
- head trauma (8%-20%)
- congenital issues (0%-4%)
- Neuroimaging studies, psychiatric evaluation, medical status (eg, chronic renal diseases, toxin/medical problems) were important factors that affect olfactory functions. Therefore, the effort of evaluating these causes is important to find the etiology of olfactory dysfunction
Compare to previous study:

1) in terms of **etiology** → were comparable with other reports.

2) in term of **treatment** → corticosteroids have been the main treatment option for olfactory dysfunction except for patients with neurodegenerative diseases, neuropsychiatric diseases, metabolic diseases, and toxin/medical issues, where there is a need to correct the underlying condition.
In terms of steroid treatment results, our study confirmed that systemic corticosteroids showed better efficacy on olfactory outcomes than topically applied steroids, as in previous studies.

Among the patients who recovered olfaction after treatment, the systemic and systemic 1 topical groups showed better olfactory threshold results than the topical-only group. Moreover, when we compared subjective improvements in smell with significant differences between pre and post treatment smell test results, the threshold test showed a better relationship than the identification test.
An algorithmic approach to the evaluation and treatment of olfactory disorders

Opeyemi O. Daramola\textsuperscript{a, b} and Samuel S. Becker\textsuperscript{a, c}

Purpose of review
To review the current evidence in diagnosing olfactory disorders and suggest an algorithmic approach to patients with relevant complaints.

Recent findings
New literature suggests that the incidence of olfactory loss increases with age. Age-associated olfactory loss is often multifactorial and requires careful history and physical exam. Psychophysical tests have a role in screening patients at risk for Parkinson's and Alzheimer's disease, but there is lack of evidence regarding timing and patient selection. Prediction of olfactory improvement in patients with chronic rhinosinusitis (CRS) is difficult with variable results from different studies. Olfactory training is suggested to be an emerging modality in patients with postinfectious olfactory loss.

Summary
There is no standard treatment for olfactory loss. Each patient must be approached individually based on the suspected cause. Patients with CRS may require medical management and surgical treatment for alleviation of their olfactory dysfunction.

Keywords
anosmia, chronic rhinosinusitis, dysosmia, hyposmia, olfaction, olfactory
Medical Treatment of Traumatic Anosmia

Rong-San Jiang, MD, PhD\textsuperscript{1,2,3}, Chih-Wen Twu, MD\textsuperscript{1,3}, and Kai-Li Liang, MD\textsuperscript{1,2,3}

Abstract

Objectives. To study the effects of zinc and steroid in the treatment of traumatic anosmia.


Setting. Academic medical center.

Subjects and Methods. Patients with a clear history of loss of smell after head injury and whose thresholds were \textsuperscript{1} measured by the phenyl ethyl alcohol threshold test were included in this study from January 2010 to May 2013. They were randomly divided into 4 groups. Patients in group 1 were treated with zinc gluconate for a month and high-dose prednisolone with tapering for 2 weeks. Those in group 2 took only zinc gluconate, and those in group 3 took only prednisolone. Patients in group 4 did not take any medicine. All patients were followed up by phenyl ethyl alcohol threshold testing, and magnetic resonance imaging was performed to measure the volume of olfactory bulbs.

Results. Thirty-nine patients in group 1, 35 in group 2, 34 in group 3, and 37 in group 4 completed the study. The recovery of olfactory function was observed in 11 patients (28.2\%) in group 1, in 9 (25.7\%) in group 2, in 4 (11.8\%) in group 3, and in 1 (2.7\%) in group 4. The recovery rates of olfactory function of groups 1 and 2 were significantly higher than the recovery rate of group 4. The volume of olfactory bulbs was not significantly different between those with and without improved olfactory function.

Conclusion. Our results show that zinc gluconate has a promising effect in treating traumatic anosmia.

reported to be between 4\% and 7\%.\textsuperscript{2} Several pathophysiological mechanisms have been assumed to result in posttraumatic olfactory loss. These include shearing of olfactory fibers at the cribriform plate, mechanical nasal obstruction, and central brain trauma.\textsuperscript{3} Although spontaneous recovery of olfactory function has been observed in approximately one-third of patients with posttraumatic olfactory dysfunction, the prognosis is generally poor.\textsuperscript{4,5}

There is no standard treatment for patients with posttraumatic olfactory loss.\textsuperscript{2} A few drugs such as steroid, zinc, and minocycline have been used to treat posttraumatic olfactory dysfunction, but the effectiveness of these regimens is inconclusive.\textsuperscript{1,4,5} In our previous study, a course of high-dose oral prednisolone (1 mg/kg) was used to treat patients with traumatic anosmia. A 16.4\% improvement rate of olfactory threshold by phenyl ethyl alcohol test was observed.\textsuperscript{4} However, in another study of ours, the improvement rate of olfactory threshold was not significantly different between patients who took oral steroids (20 mg/d for 2 weeks) and those who did not take oral steroids.\textsuperscript{6} Other investigators have used zinc salts to treat sensorineural olfactory loss. It was expected that zinc would help in the regeneration of olfactory receptor cells.\textsuperscript{6} Therefore, in this study we investigated the effect of combined oral zinc and steroid treatment in patients with traumatic anosmia.

Materials and Methods

Subjects

The flow chart and design of this study are shown in Figure 1. Patients with a clear history of loss of smell after head injury were included in this study from January 2010 to May 2013. The history of head injury was recorded,
The treatment of hyposmia with intranasal steroids.

Golding-Wood DG\(^1\), Holmstrom M, Darby Y, Scadding GK, Lund VJ.

**Abstract**

Hyposmia is a neglected symptom in patients with rhinitis. We studied 25 patients presenting with perennial rhinitis. Fifteen patients expressed hyposmia as a significant symptom. University of Pennsylvania smell identification test (UPSIT) and visual analogue scales (VAS) were used to score the symptoms of hyposmia, nasal obstruction and nasal discharge before and after six weeks treatment with betamethasone sodium phosphate drops. Those patients with initial symptoms of hyposmia significantly improved their UPSIT scores \((p = 0.00009)\) and their VAS scores for hyposmia \((p = 0.00133)\). Despite a significant decrease in the sensation of nasal obstruction, the non-hyposmics showed no increase in UPSIT scores after betamethasone therapy. There was no clear correlation between UPSIT results and other symptom scores. The judicious use of betamethasone drops in the treatment of rhinogenic hyposmia can be recommended.
Treatment of Postviral Olfactory Loss With Glucocorticoids, Ginkgo biloba, and Mometasone Nasal Spray

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Objective: To analyze the efficacy of treating postviral olfactory loss with glucocorticoids, Ginkgo biloba, and mometasone furoate nasal spray.

Design: Randomized trial.

Setting: Academic research.

Patients: Seventy-one patients who were diagnosed as having postviral olfactory loss.

Main Outcome Measures: All patients underwent olfactory function tests, including the butanol threshold test (BTT) and the cross-cultural smell identification test (CCSIT), and follow-up tests were performed 4 weeks later. In the interim, 28 patients were treated with prednisolone for 2 weeks (monotherapy), and the other 43 patients were treated with prednisolone for 2 weeks plus G biloba for 4 weeks (combination therapy). All patients used mometasone nasal spray twice daily for 4 weeks.

Results: Scores on the BTT and CCSIT significantly increased after treatment in both groups (P < .001 for both).

The mean (SD) BTT score changes were 1.4 (2.2) in the monotherapy group and 2.2 (2.9) in the combination therapy group (P = .22). The mean (SD) CCSIT score changes were 0.9 (1.7) in the monotherapy group and 1.9 (2.7) in the combination therapy group (P = .11). On the BTT, the treatment response (defined as a score increase of ≥3) rates were 32% (9 of 28) in the monotherapy group and 37% (16 of 43) in the combination therapy group (P = .66), and the odds ratio was 1.25 (93% confidence interval, 0.46-3.42). On the CCSIT, the treatment response rates were 14% (4 of 28) in the monotherapy group and 33% (14 of 43) in the combination therapy group (P = .08), and the odds ratio was 2.89 (93% confidence interval, 0.84-9.97).

Conclusions: Olfactory function in patients with postviral olfactory loss was significantly improved by both treatment modalities. Although the treatment response was not statistically different between the monotherapy group and the combination therapy group, the addition of G biloba showed a tendency of greater efficacy in the treatment of postviral olfactory loss.

Topical Therapy in Anosmia: Relevance of Steroid-Responsiveness

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Objectives/Hypothesis: The use of steroids either systemically or topically is known as a common therapy in patients with anosmia. Nevertheless, investigations giving proof for the benefit of a topical therapy are very rare, and no prognostic factors are known. In our study, we for the first time evaluated the additional effect of a topical therapy not only with steroids but also with antibiotics after conventional pretreatment with oral steroids and propose the steroid-responsiveness of an anosmia as a prognostic factor.

Study Design: Retrospective design.

Methods: We analyzed the data of 299 patients with olfactory dysfunction. Eighty-nine underwent initial pretreatment with systemic steroids and presented data over a sufficient follow-up time. In a second step all these patients were given a topical treatment in a head down forward position, namely either budesonid alone or in combination with neomycin. Primary outcome parameter was the threshold, discrimination and identification (TDI) score.

Results: Initial therapy with oral steroids changed the TDI from 15.5 to 18.7 in the means (P < .001). In general, leaving away systemic steroids while applying local therapy did not lead to a reduction of the TDI (P < .001). Dividing up the patients into those suffering from a steroid-responsive anosmia (SRA) and those without benefit from initial systemic steroids (non-SRA), the topical treatment led to a significant difference between the two groups (P < .001).

Conclusions: The steroid-responsiveness of anosmia seems to be a relevant prognostic indicator for a significant benefit of a topical therapy in general. Within all patients, the effect of an initial systemic therapy could be maintained by the adjacent topical treatment whereas in non-SRA patients a topical therapy has a significant greater impact. Furthermore, antibiotics even seem to have an additional effect in this group. Different reasons, first of all an overwhelmed steroid resistance by additional antiinflammatory effects of antibiotics, e.g., the inhibition of apoptosis might play a role and are discussed.

Key Words: Olfactory dysfunction, topical therapy, corticosteroids, antibiotics, steroid-responsiveness.

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INTRODUCTION
With about 5.8% of people suffering from anosmia and even 19.1% suffering from olfactory dysfunction in general,1 the disease is relatively wide spread. Smell loss can result in problems including safety concerns, hygiene matters, appetite disorders, and changes in emotional and sexual behavior. The relative indifference on the part of most otolaryngologists and neurologists who treat these problems, coupled with the paucity of any significant translational research on the topic, is responsible for the current stagnant state of affairs.
Local and systemic administration of corticosteroids in the treatment of olfactory loss.

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Abstract
BACKGROUND: The aim of this study was to evaluate the benefit of patients with olfactory dysfunction from local (group A) or systemic (group B) administration of corticosteroids.

METHODS: This unblinded study was conducted at a smell and taste outpatient clinic of an institutional referral center. Patients with olfactory loss after infections of the upper respiratory tract, patients with apparent sinonasal disease, and patients suffering from "idiopathic" smell loss were included. Effects of mometasone nasal spray, administered for 1-3 months, were studied in 37 patients. In addition, effects of oral prednisolone were analyzed in 55 patients who received decreasing doses over 21 days, starting with a dose of 40 mg. Olfactory function before and after treatment was measured.

RESULTS: Although odor identification scores tended to increase \( (p = 0.05) \), mometasone nasal spray did not significantly improve olfactory function, when looking at the entire group of patients or when analyzing the three diagnostic categories separately. In contrast, after systemic administration of corticosteroids, improvement of olfactory function was seen over all diagnostic categories \( (p < 0.001) \). Interestingly, olfactory function also improved in patients diagnosed with olfactory loss after upper respiratory tract infection \( (p = 0.05) \) and in patients initially diagnosed with "idiopathic," olfactory dysfunction \( (p = 0.008) \).

CONCLUSION: In many patients, local application of corticosteroids appears to have little or no positive effect on olfactory dysfunction, especially when considering long-term changes. Duration of disease, the patient's age/sex, or the presence of parosmia does not appear to predict the response to therapy with corticosteroids.

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Retinoic acid regulates olfactory progenitor cell fate and differentiation

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Abstract

Background: In order to fulfill their chemosensory function, olfactory neurons are in direct contact with the external environment and are therefore exposed to environmental aggressive factors. Olfaction is maintained through life because, unlike for other sensory neuroepithelia, olfactory neurons have a unique capacity to regenerate after trauma. The mechanisms that control the ontogenesis and regenerative ability of these neurons are not fully understood. Here, we used various experimental approaches in two model systems (chick and mouse) to assess the contribution of retinoic acid signaling in the induction of the olfactory epithelium, the generation and maintenance of progenitor populations, and the ontogenesis and differentiation of olfactory neurons.

Results: We show that retinoic acid signaling, although dispensable for initial induction of the olfactory placode, plays a key role in neurogenesis within this neuroepithelium. Retinoic acid depletion in the olfactory epithelium, both in chick and mouse models, results in a failure of progenitor cell maintenance and, consequently, differentiation of olfactory neurons is not sustained. Using an explant system, we further show that renewal of olfactory neurons is hindered if the olfactory epithelium is unable to synthesize retinoic acid.

Conclusions: Our data show that retinoic acid is not a simple placodal inductive signal, but rather controls olfactory neuronal production by regulating the fate of olfactory progenitor cells. Retinaldehyde dehydrogenase 3 (RALDH3) is the key enzyme required to generate retinoic acid within the olfactory epithelium.

Keywords: Olfactory neurons, Neuronal differentiation, RALDH, Retinoid signaling, Sensory systems, Stem cells
in term of **prognosis** 2th duration → it was reported that spontaneous recovery of olfactory nerve function may occur within the first **6 to 12 months** and that after 12 months the recovery prognosis is very poor. In our study, none of the post-URI patients beyond 1 year experienced any improvement following treatment.

- Although the prognosis is poor for patients with head injury, steroids may have efficacy in recovery after olfactory nerve injury.
Olfactory dysfunction in patients with head trauma

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Abstract

Objective: There are few reports about following up olfactory acuity of the patients who have post-traumatic olfactory dysfunction. In this study, we studied about patients with post-traumatic olfactory dysfunction for a short period under a treatment. Methods: The olfactory function of 27 patients with head trauma was studied. The olfactory acuities of all the patients were examined using olfactory tests before the treatment, and 18 patients were examined again after the treatment. Olfactory functions were evaluated in 26 patients by T&T olfactometry and in 27 patients by Alinamin test. All of the patients were treated with a local injection of suspended steroid solution into the nasal mucosa [J Otolaryngol Jpn 102 (1999) 1175]. Results: Before the treatment, 16 patients (61.5%) presented anosmia, five patients (19.2%) presented severe hyposmia, three patients (11.5%) presented moderate hyposmia, and two patients (7.7%) presented mild hyposmia. Eighteen cases (69.2%) were negative for the Alinamin test and eight cases (30.8%) were positive. The improvement rates of recognition and detection thresholds by T&T olfactometry were 35.3 and 23.5%, respectively. Conclusion: Olfactory dysfunction caused by head trauma can be recovered to a limited degree in some cases by the local injection of steroid within the relatively short period from the start of the therapy.
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\section*{Abstract}

To investigate factors that influence the degree of neural regeneration and recovery, we studied 2 olfactory nerve injury models. Transection of the olfactory nerves along the surface of the olfactory bulb was performed in OMP-tau-lacZ mice using either a flexible Teflon blade (mild injury) or a stainless steel blade (severe injury). Histological assessment of recovery within the olfactory bulb was made at 5, 14, and 42 days after injury. We used X-gal staining to label the degenerating and regenerating olfactory nerve fibers and immunohistochemical staining to detect the presence of reactive astrocytes and macrophages. Areas of injury-associated tissue were significantly smaller in the mild injury model, and at 42 days, the regenerated nerves had reestablished connections to the glomerular layer of the bulb. With severe injury, there were larger areas of injury-associated tissue, more astrocytes and macrophages, and a decrease in regenerated nerve fibers. When dexamethasone (DXM) was injected after severe injury, there was a significant reduction in injury-associated tissue, better nerve recovery, and fewer astrocytes and macrophages. These results demonstrate that recovery in the olfactory system varies with the severity of injury and that DXM treatment may have therapeutic value by reducing injury-associated tissue and improving recovery outcome.

\textbf{Key words}: dexamethasone, injury, olfactory bulb, olfactory nerve, recovery, regeneration
Regarding **time of treatment**

- In this study, more favorable olfactory recovery outcomes were seen in the earlier-treated patients with post-URI, head trauma, and nasal/sinus diseases.
- Earlier treatment could decrease the inflammatory process, reduce injury-associated tissues, and facilitate nerve recovery, which, together, could limit irreversible nerve degeneration and permanent olfactory loss.
- There is a report that duration of disease did not influence the response to systemic corticosteroid therapy; however, our results showed significant differences according to treatment timing with a larger sample size.
STUDY LIMITATION

1) patients who present to a tertiary center with olfactory disturbances may have, on average, more long-standing and intractable dysfunction than patients who present elsewhere with such problems.

2) due to sample size considerations, the number of etiologic factors was limited.

3) the retrospective nature of the work makes the findings weaker than those from randomized controlled studies also inherent selection bias might exist.

4) it is possible that the repeated test results were influenced by prior testing, due to a learning effect.

5) olfactory training has been introduced, and it recently showed good clinical results. However, we have yet to perform olfactory training in our institute.
CONCLUSION

- Study suggest that time until initial treatment is important for better olfactory outcomes with most etiologies.

- The effect of systemic steroids was better than that of topical steroids, regardless of combined treatment, and we confirmed the results through analyzing subjective recovery and smell tests.
CRITICAL APPRAISAL

1) Relevance of study
   - Study is addressing common problem in my practice
   - Study is introducing important outcome to me and to the patient (patient oriented outcome)
   - Study will lead to change in my practice
2) Validity

- It's not randomize control trial trial.
- Despite they have good exclusion criteria, still base line of the patient is not the same so this increase bias.
- The group of the patients are not equal because it's retrospective.
- The sample size is good.
3) Result, clinical significant?
4) Applicability?