Disorders of Olfaction

Mike Puricelli, MD
Dana King, MD
2004 Nobel Prize – Physiology/Medicine

• Richard Axel & Linda B. Buck
  – Prize motivation: "for their discoveries of odorant receptors and the organization of the olfactory system”
  – Richard Axel and Linda Buck published the fundamental paper jointly in 1991, in which they described the very large family of about one thousand genes for odorant receptors.

• The basic principles for recognizing and remembering about 10,000 different odors were not understood. This year's Nobel Laureates in Physiology or Medicine have solved this problem and in a series of pioneering studies clarified how our olfactory system works.
• They discovered a large gene family, comprised of some 1,000 different genes (three per cent of our genes) that give rise to an equivalent number of olfactory receptor types. These receptors are located on the olfactory receptor cells, which occupy a small area in the upper part of the nasal epithelium and detect the inhaled odorant molecules.
  – The large family of odorant receptors belongs to the G protein-coupled receptors (GPCR) family.
  – 1,000 different genes within the olfactory receptor gene family in rodents; many however are pseudogenes. The human olfactory gene family with 339 intact receptor genes and 297 pseudogenes has fewer receptor genes than mice.
• Each olfactory receptor cell possesses only one type of odorant receptor, and each receptor can detect a limited number of odorant substances. Our olfactory receptor cells are therefore highly specialized for a few odors.
  – It was possible to show, by registering the electrical signals coming from single olfactory receptor cells, that each cell does not react only to one odorous substance, but to several related molecules – albeit with varying intensity.

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Summary of the Nobel Prize

- The cells send thin nerve processes directly to distinct micro domains called glomeruli (in the olfactory bulb). Receptor cells carrying the same type of receptor send their nerve processes to the same glomerulus – even though odorant receptor cells are located in different areas of the olfactory epithelium.
  - There are some 2,000 well-defined glomeruli. There are thus about twice as many glomeruli as the types of olfactory receptor cells.
  - Most odors are composed of multiple odorant molecules, and each odorant molecule activates several odorant receptors. This leads to a combinatorial code forming an "odorant pattern" – somewhat like the colors in a patchwork quilt or in a mosaic. This is the basis for our ability to recognize approximately 10,000 different odors.
  - Axel's research group demonstrated in mice the role of the receptor in the linkage of odorant receptor cells and glomeruli.
- From these micro domains in the olfactory bulb the information is relayed further to other parts of the brain, where the information from several olfactory receptors is combined and decoded.
  - In the glomeruli we find not only the nerve processes from the olfactory receptor cells but also their contacts with the next level of nerve cells, the mitral cells. Each mitral cell is activated only by one glomerulus, and the specificity in the information flow is thereby maintained.
  - Buck showed that these nerve signals in turn reach defined micro regions in the brain cortex. Here the information from several types of odorant receptors is combined into a pattern characteristic for each odor. This is interpreted and leads to the conscious experience of a recognizable odor.
  - Therefore, we can consciously experience the smell of an odorant and recall this olfactory memory at other times.

Summary of the Nobel Prize

• The general principles that Axel and Buck discovered for the olfactory system appears to apply also to other sensory systems. Pheromones are molecules that can influence different social behaviors, especially in animals.

• Axel and Buck, independent of each other, discovered that pheromones are detected by two other families of GPCR, localized to a different part of the nasal epithelium. The taste buds of the tongue have yet another family of GPCR, which is associated with the sense of taste.

Other Awarded Nobel Prizes Related to Otolaryngology?
Other Awarded Nobel Prizes Related to Otolaryngology

• 1909 Physiology or Medicine
  – Theodor Kocher
    • “for his work on the physiology, pathology and surgery of the thyroid gland“

• 1914 Physiology or Medicine
  – Robert Bárány
    • "for his work on the physiology and pathology of the vestibular apparatus“

• 1961 Physiology or Medicine
  – Georg von Békésy
    • "for his discoveries of the physical mechanism of stimulation within the cochlea"
Overview

• Background
• Nasal Anatomy & Physiology
• Diagnostic Assessment
• Pathophysiology
• Selected Disorders & Management
Common Chemical Sense

• Sensory experience is a combination of olfactory, taste and other sensory inputs

• Free nerve endings of three cranial nerves trigeminal (the most important), glossopharyngeal, and vagus provide added chemoreceptivity in the mucosa of the respiratory tract

# Definitions

<table>
<thead>
<tr>
<th>Classification of olfactory dysfunction (from [39])</th>
</tr>
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<tbody>
<tr>
<td><strong>Quantitative</strong></td>
</tr>
<tr>
<td>Hyperosmia</td>
</tr>
<tr>
<td>Oversensitivity</td>
</tr>
<tr>
<td>Normosmia</td>
</tr>
<tr>
<td>Normal sensitivity</td>
</tr>
<tr>
<td>Hyposmia</td>
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<tr>
<td>Reduced sensitivity</td>
</tr>
<tr>
<td>Anosmia (functional anosmia, specific anosmia)</td>
</tr>
<tr>
<td><strong>Complete anosmia</strong>: absolute loss of olfactory function; no sense of smell detectable</td>
</tr>
<tr>
<td><strong>Functional anosmia</strong>: severe limitation of olfactory function; includes complete loss as well as residual odor perception</td>
</tr>
<tr>
<td><strong>Partial anosmia</strong>: greatly reduced sensitivity to a particular odoriferous substance/group of substances compared with the general population, usually not viewed as pathological</td>
</tr>
<tr>
<td><strong>Qualitative</strong></td>
</tr>
<tr>
<td>Parosmia</td>
</tr>
<tr>
<td>Altered perception of odors in the presence of a stimulus</td>
</tr>
<tr>
<td>Phantosmia</td>
</tr>
<tr>
<td>Perception of odors in the absence of a stimulus</td>
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</tbody>
</table>

Prevalence of olfactory dysfunction

19% of the population over the age of 20
25% of the population over the age of 53
From aging alone, one out of eight people between the ages of 53 and 91 will acquire an olfactory impairment over a 5-year period.
Olfaction as a Function of Age

Decreased and Distorted Olfaction

• “Life for the person with anosmia has a very ‘flat’ quality to it”
• “People with smell loss struggle with the blandness of meals and have difficulty with the appropriate use of bodily hygiene products or perfumes”
• “Some state, for example, that they must identify sour milk from its lumpy character”
• “Many express concern regarding fire and noxious or dangerous gases”
Decreased and Distorted Olfaction

• “...in fact, most anosmic patients have been involved in at least one accident stemming from this problem”
Olfactory Dysfunction and QOL

Figure 1 Daily life problems in patients with smell disorders. Results of 8 studies are included. The bars visualize the mean percentage of patients affected, weighted by the number of participants per study. The error bars show the lowest and highest reported percentage in the studies. The calculation is based on the following studies: Temmel et al. (2002), n = 278 (items 4–6, 8, 11); Tennen et al. (1991), n = 66 (item 8); Miwa et al. (2001), n = 420 (items 5–8); Nordin et al. (2011), n = 50 (item 4); Ferris and Duffy (1989), n = 230 (item 1–4); Brämerson et al. (2007), n = 102, (items 9–11); Blomqvist et al. (2004), n = 72 (item 4); Aschenbrenner et al. (2008), n = 176 (items 2,3).

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Olfactory Anatomy

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Olfactory Epithelium

• Classically, the olfactory epithelium is located in the most superior-posterior part of the nose, at the cribriform plate, the superior turbinate, and the corresponding nasal septum, the olfactory cleft
  – Distribution of the olfactory epithelium is much broader
  – May be found on the anterior part of the middle turbinate and also along the middle portion of the nasal septum.

• Bipolar neurons are exposed through dendrites and cilia and project to the olfactory bulb

Holbrook, EH, Leopold, DA. Chapter 24 –Olfaction. Baileys Otolaryngology Head and Neck Surgery
Kalogjera, L, Dzepina, D. Management of Smell Dysfunction. Curr Allergy Asthma Rep 2012 12;154-62
Olfactory Epithelium

• Although animals and fetuses show a solid sheet of olfactory mucosa, there is mixing of olfactory and respiratory epithelia in adults, which increases with age
  – This area is variable in size and variable in the extensiveness of small patches of respiratory epithelial replacement.
    • Speculated to be caused by cumulative environmental insult and subsequently a source for olfactory loss with aging
  – The overall area averages 1 to 2 cm² in adults (some sources indicate up to 10 cm²), but covers a much larger region in infants
Olfactory Epithelium

- The epithelium is pseudostratified columnar and rests on a lamina propria without submucosa
- Four main cell types have been identified: ciliated olfactory receptors, microvillar cells, supporting (sustentacular) cells, and basal cells
  - The olfactory receptor neuron is bipolar and has a club-shaped peripheral “knob” that bears the cilia
  - There are no dynein arms on these cilia
  - Axons travel to the olfactory bulb via the cribriform plate

Olfactory Epithelium

• Interestingly, olfactory neurons show the ability to regenerate and make functional synapses on the olfactory bulb
  – Ongoing study about use of this epithelium to repair nerve/spinal cord injuries
• The microvillar cell function is not well understood but felt to function at least in part by uptake of some odorants
• Sustentacular cells seem play a role in ion and water regulation and likely contribute to odor metabolism
• Basal cells responsible for replacement of olfactory receptor neurons

Figure 24.1 Human olfactory mucosa. A: Hematoxylin and eosin stain of human olfactory mucosa (200x). The epithelium can be divided into a basal cell layer (bc), neuronal layer (n), and supporting cell layer (s) where the cell bodies of each of these cell types typically reside. The underlying lamina propria contains Bowman glands (b) and fila olfactoria (arrows) with multiple olfactory receptor axons. B: Immunohistochemical staining of human olfactory epithelium (400x). Olfactory neurons with their dendrites and axons are labeled red with an antibody directed against PGP9.5. The fine dendrites are seen extending between supporting cells and ending in knobs at the apical surface, while the axons exit through the basal lamina (white arrowhead) to converge and join the fila olfactoria. Horizontal basal cells (HBCs) are labeled green with antibodies against keratin 5 and reside on top of the basal lamina. Unstained cells between the HBCs and neurons are likely globose basal cells (arrow). Supporting cell nuclei are seen as the row of blue (DAPI stained) nuclei above the neuronal layer.
Olfactory Epithelium

• The axons extending from bipolar cells extend through the basal lamina and converge with other olfactory axons to form bundles that transverse the cribriform plate and innervate the brain within the olfactory bulbs at synaptic collections termed glomeruli.

• These axons are unique in several aspects: they are true receptor neurons with direct synapses to the brain, they are the only cranial nerve (CN I) with direct exposure to the environment, and they are continually replaced throughout our lifetime.

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Figure 17–3 Olfactory mucosa.
Olfactory Bulb

- First relay station of olfactory nerves
- Structures called glomeruli contain aggregates of neural tissue
- Connects to multiple structures in the brain
  - Olfactory tubercle, the prepiriform cortex, part of the amygdaloid nuclei, and the nucleus of the terminal stria, with further projections to a number of structures, including the hypothalamus.
Nasal Airflow

- For olfactory input, odorant must reach olfactory mucosa
  - Airflow
    - Approximately 50% of the total airflow passes through the middle meatus, 35% flowing through the inferior meatus, leaving about 15% through the olfactory region
    - Retronasal flow with eating

Nasal Airflow

• https://www.youtube.com/watch?v=0FjSvttkHMk
Olfactory Mucus

- Odorants reaching the olfactory region must interact with mucous overlying the receptor cells
  - Mixture from Bowman’s glands (lamina propria) and goblet cells (respiratory mucosa)
  - Odorants must be soluble in the mucus but also traverse it to interact with the receptors
  - A variety of factors influence the character of the mucus such as adrenergic, cholinergic and peptidergic agents through impacting secretory glands
  - Variable clearance has also been demonstrated for different compounds

Factors Impacting Olfaction

- The sorption of molecules to these mucus-lined walls extracts some of them from the air stream and increases their travel time.
- The sorption of molecules may separate or sort the odorants before they reach the olfactory mucosa.
  - Highly sorbable chemicals may have minimal or no odor simply because they sorb to the nasal walls before they reach the olfactory cleft, thereby accentuating the trigeminal component.

Factors Impacting Olfaction

• Soluble odorant binding protein (Bowman’s glands) is believed to enhance access to odorants to the odorant binding receptors
Factors Impacting Olfaction

• Olfactory ability is best when this epithelium is moderately congested, wet, and red, such as during an upper respiratory infection.

• Olfactory ability seems to improve with narrowed nasal chambers
  – Nasal cycle does not have any effect on olfactory ability.

Vomeronasal (Jacobson’s) Organ

• Most animals have an identifiable pit or groove in the septum where a nerve can be identified connecting these cells to the central nervous system, often to an accessory olfactory bulb.
  – In some situations, this system has been receptive to pheromones.
• Biopsy studies of the nasal mucosa in the small pit often seen along the anteroinferior nasal septum (Jacobson’s organ) show olfactory-like histology but no central connection in humans.
• Electrophysiologic studies have shown negative action potentials from this vomeronasal area in response to specific chemical stimuli but without a subjective response from individuals tested.
• Similar electrical activity elicited by certain compounds directly delivered to the vomeronasal area has been shown to cause changes in blood pressure, heart rate, and hormonal levels.
• No identified central brain connection seems to exist, and an accessory olfactory bulb seen in other mammals has never been identified in humans.
• Positron emission tomography (PET) scanning after presentation of a putative pheromone show detection of the compound executed in higher cortical regions different from those usually activated in the perception of odors.
  – Show gender differences.

Vomeronasal Organ In Humans

• Several studies argue for a chemosensory communication system that seems to occur in humans
  – One example of the type of human biologic activity on which chemosensory control can be exerted is menstrual cycle synchrony
    • A mixture of alcohol and underarm secretion from one woman was placed on the upper-lip skin of five women subjects and alcohol only on the skin of six control women subjects
    • Over 5 months, there was a statistically significant (0.01) greater tendency for menstrual synchrony with the woman who donated the axillary secretions among the experimental group than in the control group.
  – Male axillary extract was applied to upper lips of a group of women and observed changes in luteinizing hormone pulses
• At present, no good evidence for symptom-related importance of the human vomeronasal organ exists, but prudence suggests that this anatomic area should not be disturbed during surgery unless it is necessary

Overview

• Background
• Nasal Anatomy & Physiology
• Diagnostic Assessment
• Pathophysiology
• Selected Disorders & Management
Diagnostic Assessment

• “The most important thing the physician can offer the patient with an olfactory dysfunction is an accurate diagnosis and concern for his or her plight”

Case

• 51 y/o male presents to clinic with olfactory loss
History?
History

- Estimate the severity of olfactory loss
- The time over which the loss occurred (e.g., days, weeks, or months)
- Events that occurred around the time of the loss, such as trauma or URI
- Fluctuation in symptoms
- Steroid trial and effect
- Nasal breathing obstruction
- Epistaxis
- Neurologic losses such as diplopia, vision changes, and motor/sensory dysfunction
- Review of systems and general medical health
  - Medications
  - All current and prior medical conditions
  - Cognitive function/memory
  - Previous surgeries
  - Toxin exposure
  - Drug use such as cocaine
Physical

- Thorough head and neck examination with assessment of cranial nerve function
  - Important to avoid excessive manipulation of the nose or application of nasal anesthetic agents prior to olfactory testing
Testing?
"Mandatory" Testing

– Testing of their gustatory and olfactory abilities
  • Identification tests have been more useful than threshold tests in the clinical situation

– Nasal endoscopy
  • Particularly useful in assessing the nasal airways in the region just below the olfactory cleft
  • Anterior rhinoscopy alone is insufficient
Measurement of Olfaction

- Careful clinical practice demands quantitative, repeatable tests that can be used to document olfactory ability during the course of medical management or over time.
- The two aspects of olfaction commonly tested: threshold and identification ability.
- Threshold: odorants are presented from lowest to highest concentration until the subject correctly identifies four odorants at a given concentration.
  - Order of presentation avoids adaptation
  - In the test situation, the subject is presented with two bottles, one containing the odorant and the other a blank.
  - Test-retest reliability of this test has been reported to be low
- Identification tests allow the subject to smell a number of odorants and name them correctly.
  - Suprathreshold test
  - Presume normal cognitive ability.
- Identification is more closely related to everyday olfactory functioning.

Measurement of Olfaction

• The most widely used test of olfactory ability is the University of Pennsylvania Smell Identification Test (UPSIT40)
  – Self-administered microencapsulated beads that release an odor with scratching
  – Subjects are required to choose odors from a list of four possibilities

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University of Pennsylvania Smell Identification Test

• Material accompanying the booklets allows percentile score ranking of test results by age and gender, which are known determinants of olfactory ability
What is the most likely etiology of olfactory loss in an individual who suffered an occupational injury and scored 4/40 on the University of Pennsylvania Smell Identification Test?

- Neuronal shearing
- Olfactory mucosal damage
- Parosmia
- Olfactory bulb degeneration
- Nasal obstruction
- None of the above
University of Pennsylvania Smell Identification Test

• None!

• Because the subject is asked to choose the correct answer from a list of four possible answers, a chance performance would be 25% correct
  – Anyone scoring much less than this should be considered for malingering
Figure 24.2 Olfactory tests. A: The butanol threshold test consists of a series of progressively stronger butanol dilutions (outer 10 bottles) and blank controls (center four bottles). Patients are asked to identify the bottle containing butanol after smelling a puff of air squeezed from the dilution and a blank. The concentration consistently identified is compared with what responses are known for the normal population and for those with olfactory loss. (Photo courtesy of R. Costanzo, VCUHS Smell and Taste Disorders Center, Richmond, VA.) B: The 40-item SIT (Sansonics, Inc., Haddon Heights, NJ) consists of 40 scratch-and-sniff samples matched with the names of four possible odors the patient can choose from. The number of correct responses correlates with the degree of olfactory ability.
Measurement of Olfaction

- Many other tests available
- Others that I found noteworthy:
  - Pierce and Halpern developed a clinical testing kit to assess retronasal olfactory function with oral stimulus presentation
  - A Japanese group included “intravenous smell testing” in their olfactory evaluation
    - The subject is asked to perceive the mercaptan (garlic) smell of injected Alinamin, a thiol-type derivative of vitamin B1.
    - Mechanism of the test by the discharge of Alinamin’s metabolic by-products from the blood stream into the pulmonary alveoli, from which it reaches the olfactory receptors via the nasopharynx through the exhaled air stream.
  - Electroolfactogram (EOG)
    - Placement of an electrode directly on the olfactory epithelium and recording voltage changes within receptor cells
  - Peanut butter test
    - Measure the distance from the nose where an individual can identify peanut butter odor

Factors Affecting Olfactory Testing

• Age: Testing is difficult in children
  – 14+ equal performance to adults
  – Successful testing in those 8+ with pictures
  – Not possible in demented individuals

• Adaptation: 1-5 minutes after stimulus
Adjuvant Testing

- Imaging
- Others:
  - Blood
    - Ex thyroid hormone levels
    - Routine blood tests have not been useful
  - Rhinomanometry
    - If the upper nasal airways are patent, any small nasal airflow allows olfaction to occur
  - Olfactory biopsies
    - Considered research tools
Imaging

• CT:
  – If an anatomic deformity or obstruction is suspected
  – If there is any history of nasal or sinus disease
  – If the diagnosis is not perfectly clear
• MRI of this region does not permit visualization of the fine bony detail of the upper nasal cavity, but it can be useful for soft tissues, sometimes including the olfactory sulci.
  – Consider MRI:
    • Absence of a clear etiology
    • Unusual presentation
    • Suspicion of intracranial lesion
    • Suspicion of a neurodegenerative process
    • Congenital anosmia
### TABLE I.

<table>
<thead>
<tr>
<th>Finding</th>
<th>Potential Diagnoses</th>
<th>Recommended Imaging Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory infection at onset</td>
<td>Post-URI hyposmia/anosmia</td>
<td>CT scan of sinuses</td>
</tr>
<tr>
<td>Head trauma</td>
<td>Traumatic olfactory nerve sheering injury</td>
<td>CT scan of sinuses</td>
</tr>
<tr>
<td>After sinus surgery</td>
<td>Iatrogenic or recurrent sinusitis</td>
<td>CT scan of sinuses</td>
</tr>
<tr>
<td>Family history of neurogenerative disease</td>
<td>Alzheimer's, Parkinson's, Huntington's</td>
<td>MRI brain or other neuroimaging study</td>
</tr>
<tr>
<td>Other neurologic deficits (motor or cognitive deficits, headaches, vision impairment)</td>
<td>CVA, intracranial tumor, neurogenerative process, schizophrenia</td>
<td>MRI brain or other neuroimaging study</td>
</tr>
<tr>
<td>Olfactory hallucinations</td>
<td>Temporal lobe mass or process, schizophrenia</td>
<td>MRI brain or other neuroimaging study</td>
</tr>
<tr>
<td>Hypogonadism or lifelong anosmia</td>
<td>Congenital etiology (e.g., Kallman’s syndrome, encephalocele)</td>
<td>MRI brain or other neuroimaging study</td>
</tr>
</tbody>
</table>

CT = computed tomography; CVA = cerebrovascular accident; MRI = magnetic resonance imaging; URI = upper respiratory infection.

Overview

• Background
• Nasal Anatomy & Physiology
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• Pathophysiology
• Selected Disorders & Management
Clinical Olfactory Disorders

• >200 conditions associated with changes in chemosensory ability

Table 41.1
Spectrum of Olfactory Loss as Reported at Four Chemosensory Centers

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<tr>
<th></th>
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<tbody>
<tr>
<td>Total no. patients</td>
<td>441</td>
<td>63</td>
<td>198</td>
<td>133</td>
</tr>
<tr>
<td>Obstructive nasal and sinus disease</td>
<td>30</td>
<td>33</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>Post-upper respiratory infection</td>
<td>19</td>
<td>32</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Head trauma</td>
<td>9</td>
<td>10</td>
<td>19</td>
<td>32</td>
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<tr>
<td>Aging</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Congenital</td>
<td>0</td>
<td>5</td>
<td>8</td>
<td>0</td>
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<tr>
<td>Toxins</td>
<td>1</td>
<td>11</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>14</td>
<td>10</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>26</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Obstructive Nasal and Sinus Disease

- Total obstruction (absent airflow) causes anosmia  
  - Chronic rhinosinusitis/polyps, extreme nasal swelling, tumors, nasal bony deformities, scarring  
    - Critical site of anatomic blockage is felt to be medial and anterior to the middle turbinate  
  - Total laryngectomy and tracheostomy  
- Radiologic evidence of mucosal thickening, specifically in the olfactory region, significantly correlates with subjective and objective hyposmia  
- Precise degree of flow necessary for sensation is not known  
  - Obstruction may occur even when the lower nasal cavity seems normal  
- Although proposed that traumatic nasal cavity deformity can cause olfactory loss, the scientific rigor of such studies is criticized  
- Risk of olfactory loss from nasal surgery is low but patients should be counseled about possible worsening/loss

Olfactory Epithelial Damage

• Absent/diseased olfactory epithelia results in anosmia/hyposmia
  – Aging, chronic rhinosinusitis, toxins, URI, congenital degeneration, surgical injury
• Toxins such as cigarette smoke, cadmium, mercury, formaldehyde etc as well as OCT topical zinc nasal spray have been implicated in causing smell loss
  – These patients may describe intense nasal burning after use and rapid onset of anosmia

Neural Transmission or Processing Deficits

• Loss of neural transmission centrally or poor processing leads to hyposmia/anosmia
  – Head trauma, neurodegenerative disorders, congenital disorders, masses, aging
• Aging is associated with a linear decline of mitral cells that averaged 520 cells per year. Likewise, from a total olfactory bulb volume declined with increasing age.
• Alzheimer’s disease and Parkinson’s disease are particularly associated with olfactory loss
  – “involvement by the olfactory system contrasts strikingly with the minimal abnormality seen in other areas of the brain”

Functional Smell Disorders

• Phantosmias
  – Olfactory auras may be associated with epilepsy
    • Prevalence of olfactory auras has been estimated to be between less than 1% and less than 30%
    • Auras often last for only a few minutes or less and are often unpleasant in character
  – Patients with depression, schizophrenia, and hallucinations may have olfactory complaints

• Parosmias
  – Adverse odors may be intermittent or continuous and can be brought on by specific triggers, such as strong odors, loud sounds, and stress.
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Aging

• Most common cause of olfactory loss overall
• Significant loss in 50% of patients with some degree of loss in most otherwise healthy older individuals
• Secondary to losses in quality and quantity of olfactory receptors and possibly ossification of the cribriform plate foramina
  – Degree and rate of olfactory loss are odorant specific and vary from individual to individual
• Progressive
  – Use of lipid-lowering medication, exercise, and oral steroid use were associated with a decreased risk of hyposmia

Impact of Age on Cribriform Anatomy

FIGURE 11 | Left: left and right halves of the cribriform plate of a 25-year-old female in superior view. Right: left half of cribriform plate of a 66-year-old male in superior view. Note the difference in size and number of patent foramina that transmit cranial nerve 1 between the young and old cribriform plates. Anterior is toward top. From Kalmey et al. (1998), with permission. Copyright ©1998, Wiley-Liss, Inc.

Richard L. Doty1* and Vidyulata Kamath1,2 The influences of age on olfaction: a review Frontiers in Psychology February 2014 | Volume 5 | Article 20
Head Trauma

- Olfactory loss in up to 15% of cases
- Arises from cribriform plate injury and olfactory neuron shearing
- Frontal blows most frequently cause olfactory loss; however, total anosmia is five times more likely with an occipital blow
- Onset of a traumatic olfactory loss is generally immediate
  - In some instances the patient either does not appreciate the loss or does not experience the loss until months after the injury
- Rate of recovery of olfactory function is less than 10% according to most large studies
  - Up to one third of patients might have slight to moderate improvement in identification ability after the trauma
- Usually, if return of function occurs, it generally begins within a year of the trauma.
- Parosmia may develop
Upper Respiratory Tract Infection

- Many people have short term losses due to obstruction that will spontaneously improve over 1-3 days
- Less than 1% of individuals with URIs develop lasting olfactory losses
  - Tend to be otherwise healthy individuals in the fourth, fifth, or sixth decade of life
  - Overwhelmingly women (70%-80%)
- Most common cause of permanent smell loss in adulthood
- Loss due to viral damage of olfactory epithelium and neurons (Parainfluenza 3)
- The prognosis for recovery from this olfactory loss is generally poor
  - Most studies show approximately one third of the patients recovered their olfactory ability, regardless of treatment
  - Late improvement is possible
- Parosmia frequently develops

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Kalogjera, L, Dzepina, D. Management of Smell Dysfunction. *Curr Allergy Asthma Rep* 2012 12;154-62
Upper Respiratory Tract Infections

- Oral steroids, zinc, vitamin A, vitamin B and minocycline may be used
  - There is no strong objective data for improvement
- Ginko has also been studied without proven benefit
Olfactory Training for URTI and Trauma Associated Olfactory Losses

• Prospective study of 119 patients with postinfectious and post-traumatic olfactory dysfunction

• Patients exposed themselves twice daily to four odors: phenyl ethyl alcohol (rose), eucalyptol (eucalyptus), citronellal (lemon), and eugenol (clove) twice per day for 5 minutes. Every session included rotated exposure to each odorant for 10 seconds, with time intervals of 10 seconds between odors for 16 weeks
Olfactory Training for URTI and Trauma Associated Olfactory Losses

Fig. 1. Percentages of individual improvement, no change, or worsening within the study groups (change in the threshold/discrimination/identification score of olfactory function of ≥6). URTI = upper respiratory tract infection.
Parosmia

- After an average of 12 months, almost a third of the parosmic patients reported relief
- Another study of 5-year result
  - 1/3 with phantosmia lost the bad smell
  - 1/4 had improvement
  - Less than 5% were worse
- A limited number of resections of the fila olfactoria have been reported with subjective improvement in most patients
  - Much less morbid than olfactory bulb surgery

Kalogjera, L, Dzepina, D. Management of Smell Dysfunction. *Curr Allergy Asthma Rep* 2012 12;154-62
Chronic Rhinosinusitis

- Olfactory dysfunction affects 65-80% of individuals with nasal chronic rhinosinusitis.
- Obstruction of flow caused by mucosal hypertrophy and polyps.
- Inflammation leads to olfactory epithelial damage including apoptosis.
- Characteristically fluctuating ability to smell with periods of complete return.
  - Response to steroids in the past suggests this diagnosis.
- Natural history of olfactory epithelium damage supports aggressive medical and/or surgical management to prevent long-term damage.
- Prognosis for improvement is good but full recovery is not typically achieved.

Kalogjera, L, Dzepina, D. Management of Smell Dysfunction. Curr Allergy Asthma Rep 2012 12;154-62
Medical Treatment of Olfactory Dysfunction in Chronic Rhinosinusitis

• The treatment of CRS with and without polyps with saline washings and long-term topical steroid therapy improves symptoms of rhinosinusitis but has a minor impact on smell improvement
  – Meta analysis showed improvement in 3 studies, not effective in 2 others

• Greater smell improvement may be achieved through the use of oral steroids or a combination of oral and topical steroids
Surgical Treatment of Olfactory Dysfunction in Chronic Rhinosinusitis

- Non-randomized clinical trial study that was done on 60 patients with CRS AND polyposis who were divided into two groups (medical and surgical). Patients were matched based on age, history of smoking, and the severity of obstruction.
- Patients in surgery groups underwent functional endoscopic sinus surgery under general anesthesia and then received Fluticasone propionate nasal spray for 8 weeks (400 mcg bd). Patients in the medical group were only prescribed with Fluticasone propionate with the same duration and same dose as mentioned.

Mohammad Hossein Baradaranfar • Zeynab Sadat Ahmadi • Mohammad Hossein Dadgarnia • Mohammad Hossein Bemanian • Saeid Atighechi • Ghasem Karimi • Abolhasan Halvani • Nasim Behniafard • Amin Baradaranfar • Tohid Emami Meybodi Comparison of the effect of endoscopic sinus surgery versus medical therapy on olfaction in nasal polyposis Eur Arch Otorhinolaryngol (2014) 271:311–316
Surgical Treatment of Olfactory Dysfunction in Chronic Rhinosinusitis

- Prospective consecutive patients at a tertiary institution who were undergoing FESS; for these patients prolonged medical therapy for chronic rhinosinusitis had failed
- 89 patients who had undergone sinus surgery. Postoperative olfactory function was 77% improved for all subjects as a group
- Patients’ olfaction was significantly related to polyp pathology, duration of disease, age, smoking habits and history of asthma
- After surgery, the change in ability to smell significantly correlated with nasal polyposis (Chi square, P = 0.001), which shows that patients without polyposis had better changing in subjective smell rating
Other Reports of Olfactory Changes Following ESS

• Litvack et al. reported a prospective trial of 111 patients with olfactory impairment undergoing ESS for medically refractory CRS
  – Olfactory impairment improved following ESS for anosmic patients but not for patients with hyposmia
  – Stable after 1 year follow-up
  – The only predictive factor for post-ESS olfactory improvement was the presence of nasal polyposis

• Prospective study by Pade et al. evaluated 206 patients with olfactory impairment who elected ESS for CRS
  – 23% of patients received improvement, 68% received no change, and 9% got worse after ESS

• Jiang et al. evaluated the impact of ESS on olfactory outcomes in patients with medically refractory CRS
  – They demonstrated that ESS had no impact on olfactory improvement
  – No predicative correlation between olfactory improvement following ESS and the degree of nasal obstruction, severity of CRS, presence of nasal polyposis, or allergy status.
Postsurgical Loss of Smell

• In many reports at least some portion of the patients show worsening of olfaction
• “Olfactory testing is crucial for accurately diagnosing chemosensory problems and before nasal surgery as a medical-legal safeguard for a medical practice.”
• Mechanisms:
  – Scar tissue
  – Granulation tissue
  – Persistent mucosal edema
  – Inflammation and olfactory neuroepithelial damage
• Septoplasty, turbinectomy or reduction, rhinoplasty, functional sinus surgery, and laryngectomy are among the more common surgical procedures whereby olfaction can be worsened.
Postsurgical Loss of Smell

• Middle Turbinate Resection
  – One study showed loss in 1/198 with resection and similar rate without resection

• Septoplasty
  – Unlikely to improve olfaction in most cases
  – Long term postsurgical anosmia 0.3-2.9% and hyposmia 1%

• Rhinoplasty
  – Subjective losses reported in 22/200 cases by one author and 3% of cases by another
Another study of 94 patients undergoing a variety of nasal procedures showed 34% had decreased smell.
Congenital

• Kallmann’s syndrome
  – Affects approximately 1 in 8000 males and 1 in 40,000 females
  – Sporadic
    • X chromosome–located KAL1 gene, which encodes the protein anosmin-1, accounts for 11% to 14% of cases
    • Autosomal dominant mutation in the KAL2 gene for fibroblast growth factor receptor-1 (FGFR-1) is accounts for another 10% of cases
  – Some patients with Kallmann’s syndrome have been shown to have agenesis of the olfactory bulbs and stalks and incomplete development of the hypothalamus
  – Also associated with absent/abnormal olfactory epithelium
  – Other defects sometimes seen in Kallmann’s syndrome are renal abnormalities, cryptorchidism, deafness, midline facial deformities, and diabetes.

• Hypoplastic or absent olfactory bulbs has also been associated with CHARGE syndrome

Normal MRI

Kallman Syndrome

Figure 4. Patient with Kallmann syndrome: exploration by MRI. a: front section T2: olfactory sulcus not very deep. Absence of olfactory bulbs; b: median sagittal section: small pituitary gland.
Medications

Table 41-2

<table>
<thead>
<tr>
<th>Drugs Affecting Taste and Smell</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classification</strong></td>
</tr>
<tr>
<td>Amebicides and anthelmintics</td>
</tr>
<tr>
<td>Anesthetics, local</td>
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<tr>
<td>Anticoagulants</td>
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<tr>
<td>Anticholesterolics</td>
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<tr>
<td>Antihistamines</td>
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<tr>
<td>Antimicrobial agents</td>
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<tr>
<td>Antiproliferatives, including immunosuppressive agents</td>
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<tr>
<td>Antirheumatic, analgesic-antipyretic, anti-inflammatory agents</td>
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<tr>
<td>Antiseptics</td>
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</table>

<table>
<thead>
<tr>
<th>Classification</th>
<th>Drug(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithyroid agents</td>
<td>Carbimazole; methimazole; methylthiouracil; propylthiouracil; thiouracil</td>
</tr>
<tr>
<td>Agents for dental hygiene</td>
<td>Sodium lauryl sulfate (toothpaste)</td>
</tr>
<tr>
<td>Diuretics and antihypertensive agents</td>
<td>Captopril; diazoxide; ethacrynic acid</td>
</tr>
<tr>
<td>Hypoglycemic drugs</td>
<td>Glipizide; phenformin and derivatives</td>
</tr>
<tr>
<td>Muscle relaxants and drugs for treatment of Parkinson’s disease</td>
<td>Baclofen; chlorpromazine; levodopa</td>
</tr>
<tr>
<td>Opiates</td>
<td>Codeine; hydromorphone hydrochloride; morphine</td>
</tr>
<tr>
<td>Psychopharmacologic, including antiepileptic drugs</td>
<td>Carbamazepine; lithium carbonate; phenytoin; psiloycin; trifluoperazine</td>
</tr>
<tr>
<td>Sympathomimetic drugs</td>
<td>Amphetamines; phenmetrazine theoclate and fenbutrazate hydrochloride (combined)</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>Oxyfedrine; barnylline hydrochloride</td>
</tr>
<tr>
<td>Others</td>
<td>Germaine monoacetate; idoxuridine; iron sorbit; vitamin D; industrial chemicals, including insecticides</td>
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</tbody>
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Toxins

• Cessation of smoking leads to improvement inversely proportional to the duration of smoking history
Management of Olfactory Disorders

• Counseling to protect the anosmic or hyposmic patient is an important responsibility of the physician.

• Once patients have been identified as having one of the olfactory losses for which we have no assured treatments, they should be reassured that there are others with similar deficits.

• Use of smoke and natural gas detectors in their homes and offices — Converting to an “all electric” home would be a good option.

• Educating patients’ family members so that they are able to inform the patient if the milk in the refrigerator smells foul are extra safeguards the anosmic patient should practice.

• Particularly important to use proper refrigeration and storage techniques and remove food at their expiration dates.

• Training to appreciate remaining sensory modalities such as texture of food, color, pungency, residual taste, and mouth sensation is beneficial.

• Training the patient to think about the proximity of the smell and intensify the smell by bringing it closer offers value.

• The use of excess sweeteners or salt is a natural adaptation by many patients with smell loss, and they need to be aware of the detrimental health effects that can result.
