Smell Changes in COVID-19 and Other Diseases: Summary of Pathophysiology Mechanism

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ABSTRACT

Olfactory alteration during common rhinitis component of upper respiratory tract is common observation. Smell changes leads to its own consequences on the human body affecting taste, social interactions and affecting the overall quality of life. Alterations in smell may be qualitative or quantitative and depending on the etiology, pathophysiologic mechanisms involve either the conduction part of the olfactory pathway or sensorinnural component. Sensorinnural component may be peripheral or central. With emergence of corona epidemic researchers are looking for reasons behind changes in smell during COVID-19 infection, so that better management can be planned for the patient involved. This article aims to present summary of pathomechanisms behind the smell changes during known inflammatory, traumatic and tumors of nasal cavity. We tried to summaries information available in literature related to the main factors responsible for olfactory sensation changes during COVID-19 infection and how this is slightly different from other known causes. Author hope that present article will serve as quick and easy reference for revision of pathophysiologic mechanisms for smell changes during various diseases involving the nasal cavity.

Keywords: COVID19, smell changes, pathophysiology.

I. INTRODUCTION

A. Importance of Revision of Smell Knowledge in Current Scenario

Surprisingly when we compare smell with other senses of vision, hearing, touch, and taste is not given that much importance as it should have been with better research and studies, considering smell affect human behaviour, health, productivity, and interaction with fellow human being. We all aware of role of pheromones used for mating in animal world.

WHO was informed on 31st January 2019 of pneumonia cases in Chinese city of Wuhan, which as later identified by Chinese authorities as novel corona virus infection. Ultimately on 30th January 2020 WHO declared corona infection outbreak as public health emergency of international concern (PHEIC) [1]. In the almost near 2-year period of COVID19 outbreak patients developed symptoms and signs limited to upper respiratory tract and developed severe clinical manifestations when disease spread to lower respiratory tract. URTI symptoms include related to rhinitis and pharyngitis, smell change is a common complaint in rhinitis cases of different severity depending on the disease severity. Some studies on COVID-19 have discussed diagnostic and prognostic importance of smell changes during the illness.

B. Brief Historical Facts

Among all special senses, smell was the first with good knowledge of anatomy and physiology associated. First descriptive study publication [2] noted that though majority aware of the fact that organ of smell is present inside nose, but no one is sure about the exact reason. He proposed first time that there is one olfactory nerve coming from brain by crossing, and responsible for smell. Reference [3] described anatomy and physiology of smell in his doctoral thesis. Clouquet was the first physician who attempted to describe science behind smell.

C. Anatomy of smell [4], [5]

For easy understating we can divide the anatomy of smell into peripheral and central component [4].

1) Peripheral component of Olfactory Pathway

Historically it is well known that olfactory area is present in the superior most par of nasal cavity where odorants (smell producer) must reach and attach to the olfactory receptor. Classically in many publications that olfactory area measurement mentioned is 2.5 cm², these receptors are covered my mucus which is secreted locally by bowman’s gland [5]. Thus, odorants need to be soluble enough to cross the mucosal barrier for smell sensation. These olfactory receptor in previous literature are mentioned to be locate along the cribriform plate in the superior most region of the nasal cavity, and superior as well as medial to the superior turbinate [6]. Recently studies have proven more wide
extension of olfactory neuroepithelium including anterolateral middle turbinate and posterosuperior location of nasal septum [7].

2) Central component of Olfactory Pathway:

Central olfactory structures are important the further transmission and processing of olfactory signals from olfactory neuroepithelium where receptors for odors are in the superior most regions of the nasal cavity. Recent advances in the radio imaging have added in understanding of the central anatomical structures involved in the smell. Compared to peripheral olfactory system which is located extracranially in nasal cavity and olfactory receptor present in the neuroepithelium bind with smell producing odorants. This stimulate olfactory and information is carried intracranially to the central component of the olfactory pathway [8]. Anatomical connection from olfactory receptor goes to [9]:

a) Olfactory bulb which relays information by neural connections, some of which are direct and many intertwined and complex

b) Primary olfactory regions [10], [11]: With availability of better radio imaging techniques like magnetic resonance imaging, diffusion tensor imaging and tractography, our understanding of the central olfactory pathway has become more refined. Primary olfactory cortex includes Pyriform cortex, Olfactory nucleus, entorhinal cortex, and amygdala. They receive processed olfactory information from the olfactory bulb. The new radio imaging techniques has helped us in better neuroanatomical comparative studies.

c) Secondary olfactory regions [12], [13]: They are responsible in the emotional components associated with olfactory sensations, which has important ramifications on the human behavior. This includes, Orbitofrontal, Cerebellum, hypothalamus, thalamus, and hippocampal region.

D. Physiology of Smell [14]-[16]

Simplified way we can explain the physiology of smell in diagram given below:

**Fig. 1. Simplified physiology of olfaction.**

E. Classification of Smell Disorders

1) Based on the Pathomechanism olfactory disorders can be classified as [17], [18]

a) Conductive:
When inflammatory disease pathologies obstruct the odorants (smell producing particles or substances) from reaching the olfactory region and attachment to receptors. This is most important Pathomechanism as only 10 % of inspired air reach olfactory cleft situated in superior most region of nasal cavity [19].

b) Sensorineural

In this category there is no obstruction to airflow inside the nasal cavity, pathology mechanism is directly attacking the olfactory neural pathway. Which include olfactory neuroepithelium to olfactory bulb and organs located higher up in the central nervous system. So sensorineural type of olfactory disturbance can be subclassified into further two types [18]:

- Peripheral: Diseases involving olfactory neuroepithelium.
- Central: Diseases affecting components of central olfactory system starting from olfactory bulb.

2) Based on subjective perception by the patients [20]-[23]

Patients describe their smell problems in so many ways that clinicians have used that descriptive part of history to subclassify type of olfactory disturbances

- Quantitative: Patients describe their smell disturbances as complete loss of smell (Anosmia), partial loss (Hyposmia).
- Qualitative (Dysosmia) (22,23): Usually three common perceptive changes smell include.

a) Parosmia (Different from normal odour): In the presence of odorants, patient’s perception of the normal smell is altered. For example, when presented with coffee powder to smell, patient response may be of vanilla but not smell of coffee.

b) Phantosmia (ghost odour): Patient can smell in the absence of any smell producing odorants.

F. Aetiology of Smell Disturbances

Some important points to remember in the aetiology includes:

a) Most of the aetiologic factors associated with the smell alteration affect the conduction of odorants to the olfactory receptor: i.e., All the Sinonasal diseases: infection, neoplastic conditions involving nasal cavity, sinonasal surgeries and anatomical deformities of nasal cavities obstructing odorants passage to olfactory clefts present in superior most part of the nasal cavity. Treatment outcome is predictable.

b) Sensorineurral smell loss, many aetiologic factors are associate with this type of the smell change which affects:

- Peripheral [24]-[28]: Upper respiratory tract infections (URTI), Head trauma, Drugs, and toxins, Sinonasal surgeries and age-related changes in the nerve functions.
- Central [29]-[32]: Early diagnosis of central sensorineural smell disorders can help better
management of Alzheimer’s disease, and other neurodegenerative disorders. In 1975 first neurodegenerative disease found to be associated with olfactory sensation degradation was Parkinson’s disease, later in 1984 neurologists begin to report smell impairment in Alzheimer’s disease patients [31]-[32]. So, considering the increasing prevalence and diagnosis of neurogenerative disorders, early diagnosis is possible if treating clinician is careful regarding smell change.

G. Smell Changes during COVID-19 Infection
We have discussed in previously the basic mechanisms involved in smell related changes in rhinitis cases include
1) Conductive pathway: increase mucous discharge by inflammation, obstructing odorants that smell producing particles from binding to olfactory neuroepithelium.
2) Neurosensory pathway: this is the most interesting component in studies on causes of olfactory changes in SARS-CoV2 infections.
SARS-Corona virus binds to angiotensin converting enzyme -2 receptor, which is expressed on the respiratory epithelial cells (columnar cells).
It is well established that SARS-CoV2 virus causes upper respiratory tract infections symptoms and signs, by entering human cells via angiotensin converting enzyme-2 receptors (ACE-2 receptor protein) [33], [34]. Same receptors are important for severe acute respiratory syndrome (ARDS) clinical manifestations [35].
Recently in study done by a team researcher from Harvard Medical School, Department of Neurobiology, other institutions from USA and Europe, published in science advances July 2020 edition. Researchers have reported that ACE-2 receptor, which is present on respiratory epithelial cells, is not found on olfactory neuroepithelium. ACE2 is expressed in cells sustentacular which provide structural as well as metabolic support to the olfactory sensory neurons, and certain populations of stem cells like basal cells and blood vessel endothelial cells [36].
Finding of this study can explain, why it takes months to recover from post viral anosmia. where olfactory neuroepithelium is directly damaged by viral infection [37]-[39]. While in COVID-19 it takes weeks for olfactory sensation to come back to normal [40], [41].

H. Summary of Pathomechanisms involved in Smell Changes during Different Diseases
1) COVID-19 infection: inflammatory to injuries to olfactory support cells like sustentacular cells, basal cells: This is the reason most patients regain the olfactory sensation in 1-3 weeks.
2) Inflammatory process induced direct trauma to olfactory neuroepithelium: This explains why this pathomechanism needs months to heal and patients start to feel better.
3) Oedema: Rhinitis because of any etiology manifest with oedema inside the nasal cavity and that will block odorants from binding to olfactory neuroepithelium.
4) Growth: both benign as well as malignant growth will prevent odorants (smell producing chemicals) from attaching to the olfactory receptors.
5) Trauma: both iatrogenic and no-iatrogenic known cause disruptive injuries to sensorineural component of olfactory pathway, site of injury may be peripheral, central or both. This type of smell loss takes long time to recover and many times permanent loss of smell.
6) Neurodegenerative changes in central nervous system: Still moderately understood and area of recent focused research considering change in smell is one of the important clinical presentations of Alzheimer’s and Parkinson’s disease. These changes involve a) degeneration of protein like Tau in olfactory bulb and other central component of olfactory pathway b) loss of neurotransmitters, c) amyloid deposition. 

II. Conclusion
Smell is as important for better quality of life when we compare with other special senses of human body. Historically we knew early about details of anatomy and physiology by the researchers of 17th and 18th century. We lost momentum into further research to know better about olfactory system. Since few decades interest have emerged again for studies on smell and early diagnosis of diseases like Alzheimer’s and Parkinson’s. COVID-19 pandemic is giving booster effect to the olfactory system studies. Now we know that smell changes in COVID-19 cases are due to involvement of olfactory supporting cells like sustentacular cells. Further research is need of the hour to know more about the olfactory system problems early diagnosis and the diagnostic and prognostic importance of the qualitative and quantitative changes in the smell sensation.

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