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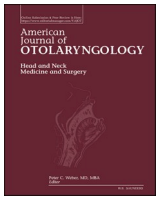

How does Covid-19 infection affect smell?

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Loss of smell is a common sequela after a patient experiences Covid-19 infection; as many as 68% of patients who experience Covid-19 infection have loss of smell [1]. While this symptom is commonly transient and can occur in absence of any other clinical symptoms many patients develop a chronic loss of smell. How does this occur?

Loss of smell following a viral infection was first described clinically in 1975 [2]. After a viral infection many patients report a chronic loss of smell. Indeed this patient group represents the majority among several pathological entities that cause smell loss accounting for about 25% of all patients who reported smell loss [3]. However, the type of virus which caused the smell loss was not previously determined nor was the mechanism which caused this loss [2]. In order to understand this symptom and how it is related to Covid-19 infection, a systematic evaluation of this sensory system was explored.

The smell system is comprised of three major components – brain, nerves and receptors. Although each portion of this system can exhibit pathology which can inhibit smell, the major component through which pathology occurs is through pathogenesis in the olfactory receptors. Olfactory receptors are unique since they do not contain blood vessels, lymphatics or exhibit mitosis [4]. These receptors, which turn over frequently, as often as every 24 h, depend upon stem cells which respond to growth or transcription factors secreted into nasal mucus from nasal serous glands [5]. These growth factors then activate stem cells to mature and generate the olfactory receptors by which the smell response is initiated [5]. Indeed, nasal mucus secreted from serous glands in the nasal cavity is the critical fluid through which these receptors grow and mature to maintain smell function. Indeed, failure to produce nasal mucus or salivary secretions (saliva), as occurs in Sjogren's syndrome, causes loss of sensory receptors with subsequent loss of smell and taste [6]. Restoration of these secretions is associated with the restoration of the sensory receptors and subsequent return of sensory function.

In order to understand the nature of these nasal mucus growth factors a total protein analysis of the components of nasal mucus was undertaken [7]. This analysis demonstrated the presence of several moieties which can be considered as the growth factors that stimulate these stem cells. These moieties include cyclic AMP and cGMP [8] and sonic hedgehog [9]. Inhibition of secretion of these growth factors is associated with inhibition of stem cell activity with subsequent inhibition of stimulation of olfactory receptor cells [5] and subsequent loss of smell. While the immune and other systems may eventually inhibit the general viremia associated with Covid-19 infection, the Covid-19 virus attacks the nasal serous glands directly and inhibits secretion of these growth factors which are necessary for stem cell activation.

Since these olfactory receptors turn over rapidly [4], they require continued stimulation by these growth factors. If this stimulation is inhibited these receptors do not grow or mature leading to smell loss. Even transient inhibition of these growth factors causes inhibition of receptor development with subsequent loss of smell. This common transient loss of growth-factor secretion may relate to the transient loss of smell observed in many patients after Covid-19 infection. Persistent secretion loss causes continued inhibition of stem cell activity with resulting loss of receptor growth with persistent loss of smell.

Other studies have considered that neural factors involving the brain and the olfactory neurons themselves are responsible for the smell loss following Covid-19 infection [10]. In a recent report specific insight into the mechanism of the loss suggested that smell loss was mediated by transient dysfunction of the olfactory epithelium [11]. This observation is consistent with the mechanism presented in the present formulation.

Studies in other hyposmic patients indicate that restoration of secretion of these affected growth factors is associated with restoration of stem cell activation, olfactory receptor growth and development, and return of smell function [12]. This stimulation occurs by two mutually dependent mechanisms – the action of cAMP, cGMP [7] and sonic hedgehog [8] on olfactory receptor function, and direct stimulation of stem cells which initiate growth of these sensory receptors [12]. The present formulation of transient smell loss is more consistent with a metabolic rather than a direct neural cause of smell loss after Covid-19 infection. Indeed stimulation of these growth factors in other hyposmic patients, demonstrated by the use of phosphodiesterase inhibition, such as theophylline administration [12], activated nasal mucus cAMP, cGMP [7] and sonic hedgehog secretion [8] which in turn activated smell function.

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