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FACULDADE DE ODONTOLOGIA DE PIRACICABA

RENATO TOGNOLI MISSON

ANOSMIA CAUSADA PELO SARS-CoV-2 E A ANATOMIA DO NERVO OLFATÓRIO: REVISÃO DE LITERATURA

ANOSMIA CAUSED BY SARS-CoV-2 AND THE OLFACTORY NERVE ANATOMY: LITERATURE REVIEW

PIRACICABA
2021

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Trabalho de Conclusão de Curso apresentado à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para obtenção do título de Cirurgião Dentista.

Undergraduate final work presented to the Piracicaba Dental School of the University of Campinas in partial fulfillment of the requirements for the degree of Dental Surgeon

Orientadora: Profª Drª Ana Cláudia Rossi

ESTE EXEMPLAR CORRESPONDE À VERSÃO FINAL DO TRABALHO DE CONCLUSÃO DE CURSO APRESENTADO PELO ALUNO RENATO TOGNOLI MISSON E ORIENTADO PELA PROFª DRª. ANA CLÁUDIA ROSSI

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DEDICATÓRIA

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RESUMO

O objetivo do presente estudo foi revisar a literatura sobre a anatomia do nervo olfatório e correlacioná-la com as possíveis causas de anosmia por SARS-CoV-2. A revisão da literatura foi realizada na base de dados internacional PubMed Central. As palavras-chave consideradas foram “SARS-CoV-2”, “anosmia”, “nervo olfatório”, “cheiro”. Os critérios de inclusão dos artigos na revisão foram o ano (2020 e 2021), o tema abordado e apenas os financiados pelo National Institutes of Health (NIH). Foram considerados apenas os artigos publicados em inglês. Todos os tipos de artigos foram considerados (relato de caso, revisão da literatura e artigo original). Em conclusão, o papel do vírus na anosmia ainda não está claro, mas estudos apontam para um mecanismo de ação indireta nas células olfativas por meio das células sustentaculares.

Palavras-chave: SARS-CoV-2. Anosmia. Nervo Olfatório.

ABSTRACT

The aim of the present study was to review the literature on the anatomy of the olfactory nerve and to correlate it with the possible causes of anosmia caused by SARS-CoV-2. The literature review was effectuated on the international database PubMed Central. The key-words considerated were “SARS-CoV-2", “anosmia”, “olfactory nerve”, “smell”. The criteria for inclusion of articles in the review were the year (2020 and 2021), the topic approach and only those funded by the National Institutes of Health (NIH). Only articles published in English were considered. All types of articles were considered (case report, literature review and original article). In conclusion, role of the virus in anosmia is still unclear, but studies points to an indirect action mechanism in olfactory cells through sustentacular cells.

Key words: SARS-CoV-2. Anosmia. Olfactory nerve.

SUMÁRIO

1 INTRODUÇÃO

Coronaviridae é uma larga família de vírus de RNA envelopado com virulenta capacidade observada entre várias espécies. Os primeiros relatos da doença originada pelo atual SARS-CoV-2 foram reportados como casos de pneumonia adquiridos por uma comunidade concentrada na província de Hubei, na República Popular da China, em 31 de dezembro de 2019 (World Health Organization, 2020). Em 7 de Janeiro de 2020, foi identificado o patógeno causador, denominado provisoriamente de “2019-nCoVID”, seu nome foi alterado após um mês, através de uma declaração da Organização Mundial da Saúde (OMS), anunciando que a emergência de saúde pública era de interesse internacional. A designação do vírus foi oficialmente dada como Coronavírus de Síndrome Respiratória Aguda Grave 2 (SARS-CoV-2), devido à sua semelhança genética ao SARS-CoV-1 (World Health Organization, 2020). Inicialmente, os típicos sintomas associados à COVID-19 eram de febre, tosse, diarreia e fadiga, mas não haviam sido relatados pacientes com manifestações neurológicas (Mao et al., 2020). Posteriormente, o envolvimento neurológico começou a ser reconhecido entre adultos acometidos pela COVID-19, sendo possível o desenvolvimento de desordens sensoriais do olfato e do paladar, delírios, encefalopatias, dores de cabeça, apoplexia e desordens do sistema nervoso periférico. Tal acometimento apresenta característica neuro invasiva e pode desencadear consequências médicas e neuropsiquiátricas de longo termo (Butowt et al., 2020).

A anosmia, caracterizada pela perda do olfato, estava presente em somente 5% dos pacientes acometidos pela COVID-19, no início dos estudos (Mao et al., 2020), mas atualmente, a deficiência olfatória causada pela doença apresenta uma taxa calculada em 44,1% nos pacientes ao redor do mundo (Butowt et al., 2020). A redução ou perda do olfato ou paladar são um dos principais acometimentos da doença, sendo reconhecidos hoje como os sintomas cardinais da COVID-19. A deficiência possui característica transitória, com a recuperação do olfato e paladar após alguns dias ou semanas (Butowt et al., 2020).

Diante do exposto, o objetivo do presente estudo foi revisar a literatura sobre a anatomia do nervo olfatório e correlacionar com as possíveis causas da anosmia ocasionada pelo SARS-CoV-2.

2 ARTIGO: ANOSMIA CAUSED BY SARS-CoV-2 AND THE OLFACTORY NERVE ANATOMY: LITERATURE REVIEW

ANOSMIA CAUSADA PELO SARS-CoV-2 E A ANATOMIA DO NERVO OLFATÓRIO: REVISÃO DE LITERATURA

Submetido no periódico Revista Sul Brasileira de Odontologia - RSBO (Anexo 2)

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Abstract

The aim of the present study was to review the literature on the anatomy of the olfactory nerve and to correlate it with the possible causes of anosmia caused by SARS-CoV-2. The literature review was effectuated on the international database PubMed Central. The key-words considerated were “SARS-CoV-2", “anosmia”, “olfactory nerve”, “smell”. The criteria for inclusion of articles in the review were the year (2020 and 2021), the topic approach and only those funded by the National Institutes of Health (NIH). Only articles published in English were considered. All types of articles were considered (case report, literature review and original article). In conclusion, role of the virus in anosmia is still unclear, but studies points to an indirect action mechanism in olfactory cells through sustentacular cells.

Key words: SARS-CoV-2. Anosmia. Olfactory nerve.

Introduction

Recent studies indicate that the SARS-CoV-2 can promote reduction of smell in a considerable portion of patients and this symptom is often one of the earliest and, eventually, one of the only signs in asymptomatic people with SARS-CoV-2 virus [4]. Still, it is enigmatic how the virus affects the olfactory system and new researches are beggining to explain the

molecular and cellular mechanisms of anosmia caused by SARS-CoV-2 infection [4]. These works started to provide new understandings of cell types in the olfactory epithelium that can manifest virus entry proteins and that can compile the SARS-CoV-2 after infection. A study [4] suggests that a distinctive cascade of cellular events can elucidate the transitory anosmia in COVID-19 and that the virus might use a course from nose to infect the brain.

Anosmia is an olfactory dysfunction that causes the inability to smell. Chronic sinonasal and neurodegenerative diseases, severe head trauma, upper respiratory infections, or even aging can be sources to anosmia. It can interfere in the ability to sense threatening odors in foods and in the surroundings. Researchers [11] found out that patients with anosmia were three times more likely to be at risk of experiencing a hazardous event when compared with normosmics, and between one quarter and half of anosmics reported eating rotten or spoiled food by accident [14]. Olfactory dysfunctions can decrease appetite and enjoyment of eating and even arise difficulties with maintaining personal hygiene and social relationships [15]. The consequences of anosmia can interfere with the quality of life related to eating and feelings of wellbeing.

The olfactory loss caused by anosmia can lead to reorganization processes in the brain. Our visual and auditory systems have been reported in detail, but, disparately, our olfactory system remains undetermined when it comes to how particularly the neuronal mechanism happens after the loss of olfact [9].

SARS viruses can enter and deslocate beyond sustentacular cells and get to the brain. A suggested mechanism for the transfering of the virus from sustentacular cells to olfactory neurons or to structures that permit the entry to cerebrospinal fluid is by organelle exchange system connecting support cells and neurons [4]. An additional one is that the virus can possibly advance from sustentacular cells to stem cells and when the immature olfactory receptor neurons formed by stem cells become mature, with axons elongating into the ofactory bulb, they could move the virus straight to the olfactory bulb and beyond [4].

The aim of the present study was to review the literature on the anatomy of the olfactory nerve and to correlate it with the possible causes of anosmia caused by SARS-CoV-2.

Methods

The literature review was effectuated on the international database PubMed Central. The key-words considerated were “SARS-CoV-2", “anosmia”, “olfactory nerve”, “smell”. The criteria for inclusion of articles in the review were the year (2020 and 2021), the topic approach and only those funded by the National Institutes of Health (NIH). Only articles

published in English were considered. All types of articles were considered (case report, literature review and original article).

Literature review

The olfactory nerve

Neurons of the olfact sense are bipolar neurons that can perceive and bind odorant molecules. The olfactory nerve is the cranial nerve I and it is established with the coalescence of axons of these neurons. This first cranial nerve cross the cribriform plate of the etmoid bone and extend to the ipsilateral olfactory bulb, the local where the axons synapse on central neurons. Sustentacular cells or supporting cells enclose olfactory sensory neurons that are provided with radiating cilia emanating from their dendrites. As opposed to, there is microvilli at the apical surface of sustentacular cells [10]. In the inferior part of the epithelium, basal cells are found and they serve as precursor cells that will vigorously divide to replace olfactory sensory neurons. This ceaseless substitution is necessary because of the brief life span of olfactory sensory neurons of 30 to 60 days. Underlying the olfactory epithelium in the connective tissue is located the Bowman's glands [10]. They secrete a serous fluid with ducts that move to the surface of the epithelium and immerses the cilia of olfactory sensory neurons in a mucus layer to cage odorant molecules and to prevent frequent olfactory stimulation. Bowman's glands secretion generates a fluid environment through the olfactory cilia to clear the cilia assisting the entering of new odor substances. Moreover, the mucus creates an ionic milieu across the cilia trapping odorants with odorant-binding proteins conducting to the cilia [10].

A research [7] suggests that SARS-CoV-2 probably reaches the central nervous system along the way of olfactory nerves into the olfactory bulb or across the subarachnoid space alongside olfactory nerves towards the brain's cerebrospinal fluid compartment and subsequently inside the brain's interstitial space.

There is detailed evidence that SARS viruses can surpass sustentacular cells and then get to the brain. It is known that the virus can effortlessly enter sustentacular cells, however, further researches are necessary to clarify how the SARS-CoV-2 can probably transfer from sustentacular cells to either olfactory neurons or structures or to another cells that permit the virus to the cerebrospinal fluid [4].

Anosmia

Losing chemical senses is one of the symptoms that a person with SARS-CoV-2 disease, COVID-19, can show [10]. The decrease of smell is now acknowledged as one of the principal symptoms of COVID-19 [4] and the new abrupt loss of the senses of smell, denominated anosmia, is included in the diverse symptoms described. In addition, a new study revealed that 98% of COVID-19 patients manifestated some smell dysfunction, implying that a great number of patients lost totally or partially their olfactory sense when the outbreak of COVID-19 was occurring. Latter reports on the variants of SARS-CoV-2 coronavirus also proposes differences that depend of virus variants in chemosensory dysfunction induced by COVID-19 [10].

To recover the sense of smell, there is a clinical urge to elaborate medication treatments and methods. Still, smell training is a example of treatment technique used for decades in subjects with pots-viral anosmia. This strategy uses essential oils, and the frequently essential oil types used by tradiction have been those of lemon, eucalyptus, rose and clove, but there are also several other options accessible to use [10].

Detecting further signs of COVID-19 is helpful to diagnosticate this disease. Reports of loss of smell in asymptomatic individuals that follow a positive test for COVID-19 are increasing [8]. Latest studies implied that up to 85.6% of affected individuals experience anosmia and in at least 11.8% of cases, anosmia is one of the first existing signs [8]. In addition, news case studies described the loss of smell as one of the only symptom of COVID-19 [8]. Consequently, anosmia is frequent but as of now under-recognized initial symptom of COVID-19 and possibly unnoticeable because of the similarities with manifestations from cough or fatigue. Nonetheless, anosmia can be a early warning sign to recognize asymptomatic patients that would not be detected past the protocols of the healthcare system because of the lack of common symptoms (fever, dyspnea) and could pass through COVID-19 protocols. Thereby, molecular testing could be effectively prioritized to other patients and clinical progress could be better evaluated. Additionally, patients with dysfunction of olfactory sense might be candidates for wearing masks and reinforced social distancing until testing is avaiable in underdeveloped or rural areas [8].

Nevertheless, it is still necessary to emphasize that the recognition of anosmia do not replace appropriate molecular testing in the diagnosis of COVID-19 that can detect low copies of the virus in the collected material. Moreover, anosmia is also present in upper respiratory infections, chronic rhinosinusitis, allergic rhinitis, head trauma and even as a rare side effects of conventional medications (diuretics, angiotensin-converting enzyme (ACE)

inhibitors). Thus, it is necessary to know the medical history of patients with anosmia for the possible suspicion of infection with SARS-CoV-2 [8].

Neurobiological and neuroanatomical mechanism that affects the olfactory nerve in anosmia

As the causative of atual SARS (Severe Acute Respiratory Syndrome) novel, SARS-CoV-2 shows genetic similarity with it's predecessor SARS-CoV-1, featuring the same entry cell mechanism that consists in binding the spike protein expressed on it's surface to ACE2 proteins and TMPRSS2 priming, entrey proteins expressed on several types of human cells [2], [12].

The upset of chemosensory disturbances in olfactory and taste caused by SARS-CoV-2 may be associated to different possible mechanisms of infection. A possible mechanism suggests nasal inflammation or obstruction caused by upper respiratory infection of SARS-CoV-2 would be the causative of chemosensory disturbances [6], this could be plausible due the inflamation caused by microvillous cells of olfactory epithelium involved in innate immune response generated by working cells from immune response system when epithelium cells are infected by SARS-CoV-2 [1].

Other possible mechanism of chemosensory disturbance involves sustentacular cells, olfactory epithelium microvillar cells and Bowman's gland cells due it's expression of both ACE2 and TMPRSS2, possibly being directly infected by SARS-CoV-2, causing changes in olfactory mucus or ionic imbalance inhibiting olfactory signaling [6].

In fact, high expression of ACE2 and TMPRSS2 were reported in sustentacular cells while less or none expression on neuronal olfactory cells [2]. The plausibility of support cells being primary targets of SARS-CoV-2 [6] and the possible neurobiological mechanism of anosmia, relies on the fact that olfactory receptor neurons do not express entry proteins (ACE2 and TMPRSS2) [5], being essential for maintenance and normal function of cilia in olfactory cells [4]. The accumulation of SARS-CoV-2 on sustentacular cells may disrupt the sustentacular cells essential functions of maintaining epithelial integrity and the cilia of mature olfactory neurons possibly causing disturbances on olfactory system, but it's also unknown wheter the virus may directly act in olfactory neurons by transfering from sustentacular cells to mature olfactory neurons which lack expression of entry proteins (ACE2 and TMPRSS2) [4].

The comparision of sustentacular cells and olfactory neurons shows that, altough both being possible to be replaced for stem cells, sustentacular cells replacement are much faster than olfactory neurons, where stem cells first generates immature olfactory neurons whose axons have to grow through cribform plate, brain and then maturate [4]. Damages caused to olfactory sensory neurons takes up 10 to 20 days to fully regenerate and maturate [4]. This may explain which cells are danified in previously cited mechanisms of SARS-CoV-2 induced anosmia. The two major inconsistencies related to directly damage to olfactory neuron are lack of entry proteins expression on olfactory neuron cells and longer regeneration time when damaged [4] while compared to the duration of anosmia.

Many authors cites the possibility to direct action of the virus on olfactory bulb or direct neuronal damage after a route of invasion taken by the SARS-CoV-2. It is possible a route to SARS-CoV-2 directly infect the olfactory sensory neurons in the olfactory epithelium and then be transported into the CNS through the olfactory nerve [12]. Moreover, some mechanisms of neurotropism, immunoresponse or systematic effects could be answers to neurological effects, being the systematic mechanism based on binding in ACE2 proteins of olfactory epithelium and invading central nervous system through cribriform plate [13]. Controversially, brain infection route of SARS-CoV-2 through cribriform plate or neuron-hopping, starting in olfactory neurons, isn't a possibility due wide consensus about olfactory receptor neurons which do not expresses cells entry protein, possibility of false positive when observing these cells even with specific cell type markers because of the fact that sustentacular cells thightly wraps neurons, reports shows immature olfactory receptor neurons infected which lacks axonal projections to cribriform plate impossibiliting the virus to reach the brain and the timeline of neuro-invasion in animals models that explains alternative routes may be taken rather than virus transfer between olfactory neurons or neuro-hopping [5]. Although, as already cited, directly damages to axons after CNS invasion through cribriform plate would imply in long-lasting anosmia due the time to regenerate and maturate olfactory receptor neurons, taking up 10 to 20 days [4] what does not match with the olfactory disturbs duration found in literature, the average of 9.3 days of duration. The large majority of patients recover their smell usually in 1 to 3 weeks but reports of some patients reported anosmia or hyposmia that lasted for months or more. The possible explanation for that is a larger area of olfactory nerves affected and deep destruction of epithelium including death of large amount of olfactory nerves [4].

Several phytochemicals shows anti-inflammation or anti-viral effects and also the recovery of COVID-19 induced anosmia through smell training using essential oils due their bioactive properties is effective [10].

Up to current publishing date of this article no positive effects of COVID-19 induced anosmia reversing drugs or COVID-19 induced anosmia treatments were found.

Conclusion

In conclusion, role of the virus in anosmia is still unclear, but studies points to an indirect action mechanism in olfactory cells through sustentacular cells.

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3 CONCLUSÃO

A revisão de literatura realizada possibilitou concluir que o papel do coronavírus na anosmia ainda não está claro, mas estudos apontam para um mecanismo de ação indireta nas células olfatórias por meio das células sustentaculares.

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ANEXOS

Anexo 1 – Verificação de originalidade e prevenção de plágio

ANOSMIA CAUSADA PELO SARS-CoV-2 E A ANATOMIA DO NERVO OLFATÓRIO: REVISÃO DE LITERATURA

RELATÓRIO DE ORIGINALIDADE

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3	Igor Santana de Melo, Robinson Sabino-Silva, Thúlio Marquez Cunha, Luiz Ricardo Goulart et al. "Hydroelectrolytic Disorder in COVID-19 patients: Evidence Supporting the	1%

Anexo 2 – Comprovante de submissão do Artigo