

Ageusia as a Manifestation of Long Covid

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Abstract

We define "Long-COVID" as that phase of the disease following SARS-Cov2 infection which clinically continues for months after infection. It is considered to affect approximately 1 in 10 patients. Long-COVID presents a very broad and heterogeneous clinical picture that ranges from general manifestations such as fatigue and malaise to both central and peripheral neurological symptoms, from cardiovascular manifestations to ENT symptoms, from gastrointestinal symptoms to musculoskeletal manifestations. In this work, through a concise review of the literature, we have focused attention on the etiopathogenetic and clinical aspects of ageusia, one of the most frequent and important consequences of long-COVID.

Keywords: Ageusia, Long Covid, SARS Cov2, Life quality.

Introduction

We first learned of SARS-Cov 2 infection in December 2019. Since then, COVID-19 has spread rapidly across the globe causing a heavy pandemic. Most of the affected subjects develop a pseudo-influenza syndrome with mild symptoms (fever, asthenia, cough, nasal congestion, anosmia, ageusia) but about 15% progress towards more severe clinical pictures and 5% even towards critical forms. Much has been studied and written about the acute phase of the disease, but today more than ever the need to deepen the knowledge about that post-acute disease whose consequences continue for many months after the infection and which we now call " Long COVID ".

We do not have a real definition for this stage of the disease. Nabavi *et al.*^[1] define it as "non-recovery for many weeks or months after the onset of symptoms". Other authors have distinguished various forms of chronicization of COVID-19. Greenhalg *et al.*^[2] distinguishes a form of post-acute COVID that occurs between the third and twelfth week of infection and a form of chronic COVID (Long COVID) that persists beyond the twelfth week of infection.

In the review published by Cabrera Martimbianco *et al.*^[3], the term Long COVID is used to describe the condition presented by individuals who have passed the acute phase of the disease but who still have lasting effects of the infection or who have presented the traditional clinical picture for a much longer than expected or they develop new signs and symptoms. According to the UK's Office for National Statistics, approximately 1 in 10 patients would be affected by a form of Long-Covid^[4].

The clinical aspects that characterize Long-COVID are broad and diversified. The outcomes of acute disease can in fact affect various organs and therefore determine multiple syndromes. Two of the symptoms mainly encountered are fatigue and general malaise persisting for many months after infection. Furthermore, patients often report difficulty concentrating and wheezing. Many of them report the persistence of a chemosensory deficit (anosmia or ageusia). The onset of this chronic condition leads to a decline in the quality of life in affected patients. This aspect is nowadays extremely important also for the psychological implications (anxiety and depression) that it entails in the affected subjects^[5]. The extensive

symptom set of Long COVID also includes cardiovascular symptoms (chest pain, cough, tachycardia), ENT symptoms (sore throat and nasal congestion), gastrointestinal symptoms (nausea, vomiting, diarrhea, weight loss), musculoskeletal symptoms (myalgia, arthralgia) and neurological manifestations. Grisanti *et al.*^[6] studied the neurological clinical aspects of Long COVID and distinguished 2 patient subtypes. They describe a "Type 1" that group of patients presenting central neurological manifestations including cognitive, memory, headache, anosmia and ageusia disorders, while they define "Type 2" that subset of patients with neurological Long COVID characterized by involvement of the peripheral nervous system (inflammatory neuropathies, compressive neuropathies, cranial mononeuropathies).

Even today we know little about the frequency and criteria for defining the diagnosis of Long COVID as well as we have little experience in the therapeutic field. We therefore believe it is necessary to deepen the knowledge regarding this pathology given the great diffusion and the numerous sequelae that it entails in the population with an inevitable deterioration in the quality of life.

The goal of our work was to focus attention on the ageusia of Long COVID trying to describe the physiopathological and clinical aspects, the frequency with which it occurs, the risk factors, the main manifestations, the implications and the impact that these disorders exert in the lives of patients based on the data currently available in the literature.

Discussion

Since the beginning of the pandemic, a strong correlation has been observed between the onset of chemosensory changes and infection with SARS-Cov 2^[7,8]. As of December 3, 2020, the European Center for Disease Prevention and Control has included the sudden onset of anosmia and ageusia as clinical criteria for case definition of COVID-19.

Since then, many studies have been performed to monitor the evolution of chemosensory changes in progress and after recovery from COVID-19^[3]. However, only a few authors have described the behavior of anosmia and ageusia in follow-up longer than 6 months^[9-14].

The data currently available in the literature indicate that the recovery of the gustatory function occurs mainly and spontaneously in the first month following the infection. However, a significant part of patients continue to suffer from ageusia even after 6 months and more after the infection.

Fortunato *et al.*^[19] describe a population of 201 cases of paucisymptomatic COVID patients with chemosensory dysfunction. After 12 months, 21.3% of these patients reported persistence of ageusia.

According to Alghatani *et al.*, ageusia and anosmia represent the symptoms with the highest probability of persisting over time following COVID-19. This trend has been described above all in the female population which seems to be more prone to developing chemosensory deficits in the condition that we now define as Long-Covid^[15]. This aspect is confirmed in many other studies including that of Lee *et al.*^[16].

The pathogenetic mechanisms that determine the onset of ageusia are still unknown today. Vaira *et al.*^[17], suggest some possible explanations regarding this issue. On the one hand, they indicate the possible role of ACE2 receptors to which SARS-Cov2 binds with great affinity, present in different types of cells in our body (alveolar, intestinal, renal, myocardial, epithelial cells). It was observed that the epithelial cells of the oral mucosa and in particular of the lingual mucosa are also particularly rich in these receptors. On the other hand, a possible participation in the pathogenetic mechanism of ageusia by the sialic acid receptors to which SARS-Cov2 would have a strong affinity is hypothesized. As indicated by Park *et al.*^[18], and by Milanetti *et al.*^[19] sialic acid represents a fundamental component of saliva with the aim of preserving the taste molecules with respect to a premature degradation by salivary enzymes. The binding of the Coronavirus with the sialic acid receptors would result in a lack of action of the acid itself and therefore a rapid degradation of the taste molecules that would not be able to reach the taste pores. This would result in an elevation of the taste threshold (hypogeusia) or a complete loss of function (ageusia).

In modern society, the increase in voluptuous habits and the increasingly careful search for social moments of leisure attribute a fundamental role to the sense of taste in determining the quality of life. Several publications demonstrate the relationship between a decline in quality of life and taste dysfunctions^[20-24]. Speth *et al.*^[25] correlates gustatory dysfunction to the onset of anxiety and depression confirming the observations of Yom-Tov *et al.*^[26]. The impact of ageusia on the quality of life therefore represents a particularly topical and delicate issue in subjects suffering from long COVID for whom it is not yet known whether to envisage a possible recovery of the function. However, the effects of ageusia on the quality of life in these patients are still largely to be studied.

Burges Watson *et al.*^[27] conducted an important study on 9000 patients thanks to the support of social networks with the aim of evaluating the impact of taste-olfactory alterations in long COVID. The results, in addition to confirming the importance of the role of anosmia and ageusia in deteriorating the quality of life of these patients, bring out important reflections on some aspects not considered in other works. In fact, the relationship between taste alteration and food alteration is considered. Patients with ageusia have in fact been shown to experience a loss of pleasure and interest in food that leads them to weight loss or on the contrary to overweight and reduced socialization due to the loss of interest in moments of conviviality and commensality. The study also highlights the profound psychological distress that affects subjects suffering from chemosensory dysfunctions who find themselves experiencing an anomalous situation of altered relationship with the surrounding world.

The importance of ageusia in long COVID is also demonstrated by the interesting work by Damiano *et al.*^[28]. The author in a cohort study on 701 patients describes the correlation

between the onset and persistence of ageusia and neuropsychiatric morbidity. In particular, from the proposed data, the association between ageusia and reduced performance in some neuropsychiatric tests would seem evident. The Author observes how in Long COVID the persistence of ageusia can in some way favor a reduction in cognitive and memory abilities.

The significant impact of ageusia on the quality of life in patients suffering from Long COVID involves the need to understand another fundamental aspect. How will the condition of patients who are still ageusic evolve after many months? What should we expect to happen in these subjects? One possible answer is provided by Fernandez-De La Pena *et al.*^[29]. In this multicenter study, a population of 2000 individuals admitted to 5 different Spanish hospitals for COVID was studied. The prevalence of ageusia was calculated at T0 (time of hospital admission), at T1 (8.4 months) and T2 (13.2 months). The study provides us with the first trajectory curve for the recovery of taste-olfactory loss in the Long COVID^[29,30]. According to what emerged from this study, chemosensory dysfunctions tend to recover spontaneously in the 3 years following the infection.

In conclusion ageusia represents one of the most frequent clinical manifestations associated with long-COVID. The pathogenetic mechanism from which it originates is still unclear. We know that the onset of this deficit correlates with a significant worsening in the quality of life, causing both psychological repercussions such as anxiety and depression and also reduced cognitive performance in affected patients. Some studies believe that in the population affected by ageusia following SARS-Cov2 infection, the deficit may persist even after 12 months in over 20% of subjects. This difficulty in recovery and the important impact on the quality of life make the problem of great importance and relevance.

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Conflict of interest

The Author certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Author Contributions

The Author assert that all procedure contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation, and with the Helsinki Declaration of 1975, as revised in 2008.

Marco Capelli made all contributions to study: conception, data acquisition, analysis and interpretation, manuscript writing.

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