Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Is anosmia the price to pay in an immune-induced scorched-earth policy against COVID-19?

S.D. Le Bon*, M. Horoi

Department of Otorhinolaryngology, St. Peter's Hospital, Brussels, Belgium

A B S T R A C T

Since the outbreak of Coronavirus Disease 2019 (COVID-19), loss of smell has increasingly been reported as a frequent clinical sign. Understanding the underlying mechanism and the prognostic value of this symptom will help better manage patients. SARS-CoV-2, as SARS-CoV-1, may likely spread to the central nervous system (CNS) via the olfactory nerve, a known gateway for respiratory neurotropic viruses. We hypothesise that sudden loss of smell due to COVID-19 is the consequence of a protective host defence mechanism involving apoptosis of olfactory receptor neurons. Sacrificing smelling over neuroprotection is a logical strategy, even more so as olfaction is the only sense with the ability to regenerate in adults. Induced apoptosis of olfactory neurons has been shown in mice, successfully preventing neuroinvasion. On the other hand, adult olfactory neurogenesis has been shown to be regulated in part by the immune system, allowing to restore olfactory function. Understanding anosmia as part of a defence mechanism would support the concept of sudden anosmia as being a positive prognostic factor in the short term. Also, it may orient research to investigate the risk of future neurodegenerative disease linked to persisting coronavirus in neurons.

Introduction

The olfactory nerve is a known gateway to the brain as it is the only cranial nerve whose neurons are directly exposed to the external world, thus potentially leading to a security breach. While retinal ganglion cells and inner ear hair cells receive external stimuli behind some physical barrier, olfactory receptor neurons (ORNs) are directly embedded in the upper olfactory mucosa ready to bind odour molecules as they enter nasal fossae. The advantage is having a direct sensor of our chemical environment but the downside is having a vulnerable entry point to the brain for inhaled pathogens and toxins. In humans, many neurotropic viruses are naturally neuroinvasive, often primarily via this olfactory route, such as poliovirus, influenza, HSV and, more importantly, coronaviruses [1]. Netland et al. showed that SARS-CoV-1 spread in murine central nervous system primarily through the olfactory bulb, inducing neuronal loss [2]. In humans, presence of SARS-CoV-1 was found in brain autopsies – in neurons –, and in CSF of living patients [2,3]. Other human coronaviruses have shown to result in encephalitis, acute paralysis and other neurological complications [4]. As for COVID-19, the extent of neurological involvement is still unknown, although preliminary studies report neurological manifestations in 36.4% of infected patients and a case of meningo-encephalitis was reported in which SARS-CoV-2 RNA was detected in CSF [5,6].

Since the COVID-19 epidemic broke out in late December 2019 in Wuhan, China, doctors and patients progressively started to report sudden total loss of smell, or anosmia, as a frequent clinical symptom [7,8]. A European study reported early on that 72% of patients complained of persisting loss of smell after the acute phase. Post-viral olfactory dysfunction is indeed a well-known sequela of common colds by respiratory viruses, such as influenza, rhinovirus, and other coronaviruses, but unlike COVID-19, it has always been a rare event given the high incidence of common colds in the population [9]. Although the mechanism underlying post-viral olfactory dysfunction is still unknown, human biopsies showed disordered or absent olfactory neuroepithelium with signs of loss of sensory cilia, neuronal apoptosis, excessive cicatrisation and respiratory metaplasia. These pathological observations led to think that post-viral loss of smell is an unfortunate consequence of virus-induced damage to the olfactory neuroepithelium [10].

The neuroprotective hypothesis

We propose to look at COVID-19-related olfactory dysfunction in a different way. Although rare, viral spread to the brain is a serious danger to survival. We wonder whether beyond a certain threshold, when local barriers are overwhelmed by viral spread, an immune-mediated self-defence mechanism in ORNs is triggered in order to cut off the road to the brain? Could it be that some people lose smell not because the virus destroyed olfactory neurons but because our body evolved to bomb the bridge in a scorched-earth strategy?

The notion that apoptosis is a protective host response to viral replication and spread is not a new concept in animal studies [11,12]. In mice, Mori et al. suggested that influenza-induced apoptosis could be a

* Corresponding author.
E-mail address: sergelebon@gmail.com (S.D. Le Bon).

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protective host response to curtail viral replication in olfactory cells [13]. They showed that influenza viral components were trapped in apoptotic bodies later to be phagocytised by macrophages, effectively preventing lethal spread to the central nervous system. Perlman et al. showed in mice that intranasal inoculation of a neurotropic coronavirus led to central nervous system infection via the olfactory nerve; and that it did not, when the olfactory bulb was ablated, suggesting that cutting off the road can be an effective protective mechanism against coronaviruses [14].

As Levine et al. pointed out, neuronal apoptosis is a thorny dilemma as the vast majority of neurons are life-long not-renewable key cells, limiting the benefit of large-scale apoptosis for each infection by a respiratory virus [15]. This is totally different if neurons have the capacity for self-renewal. ORNs are very special neurons as they self-renew continuously through life every 30–120 days [16]. Lifelong regulated apoptosis is therefore a normal turnover phenomenon for ORNs. People do not perceive any olfactory change in a permanent controlled apoptosis mechanism, whereas brutal large-scale apoptosis of ORNs could in contrast lead to sudden loss of smell. Teleologically it would make sense for nature to be able to continuously regenerate parts of the only cranial nerve it can knock down, thereby allowing restoration of the ability to smell after the threat has passed.

Over the last decade, mounting evidence has shown the critical modulatory role of immune cells and cytokines in regulating apoptosis and neurogenesis in the olfactory neuroepithelium. Borders et al. showed in mice that activated macrophages, secreting cytokines and growth factors, upregulate ORN regeneration and that their absence led to a decrease in neurogenesis [17]. In late 2019, olfactory mucosa samples from living adult humans showed the presence of many immature neurons alongside leukocytes, suggesting that (a) olfactory neurogenesis is a robust process in adult humans, and that (b) cells from the immune system play a key role in olfactory epithelium homeostasis [18].

COVID-19-related olfactory dysfunction

As aforementioned, loss of smell is now accepted as a diagnostic clinical symptom for COVID-19 infection [19]. As of now, it remains still controversial where exactly loss of smell stands in COVID-19 clinical picture in terms of severity. Preliminary studies show that patients reporting anosmia seem to be younger and have less serious symptoms [7]. Conversely, it seems that hospitalised patients may be less subject to olfactory impairment [30]. Mao et al. found only 5% out of 214 hospitalised patients complained of loss of smell with a mean age of 52.7 [5]. This suggests that losing smell could turn out to be a positive prognostic factor, corroborating the concept that anosmia could reflect an effective defence strategy against the virus. Moreover, beyond the acute phase, time will tell if COVID-19-related anosmia or its absence will also be linked to long-term neurological disease. Human coronaviruses have indeed been found persisting in neurons of living patients, some with neurological sequelae [2,20]. They have been suggested as potential etiological agents or triggers for many neurological diseases in genetically predisposed individuals, such as multiple sclerosis, Alzheimer's disease, and Parkinson's disease [20,21]. This is part of the still debated "olfactory vector hypothesis" which posits that with time inhaled pathogens and toxins lead to or participate in neurodegeneration as they pass via a porous olfactory nerve [22,23].

The question remains as to why anosmia only affects an unknown portion of COVID-19 patient, with published results still ranging from 5 to 89% of patients [5,7]. This is true also for other COVID-19 symptoms, as we discover that clinical pictures are very much age-dependent and can be dominated by many different symptoms, such as abdominal complaints, strokes, or cutaneous reactions. The disease phenotype depends on the interaction between the host and the virus, rather than the virus only, as it has been shown for SARS-CoV-1 [21]. Mouse models showed that the intensity of viral propagation through the olfactory route and the induction of apoptosis depended on the animal's age and immune response [11,24,25].

It cannot be excluded that apoptosis and anosmia may be the consequence of an unwanted excessive reaction from the immune system, rather than a triggered innate strategy, as some have put forward [1,26,27]. The immune system loss of control and cytokine storm seem indeed to play a bigger role than previously thought in the morbidity and mortality of COVID-19, but this contradicts the observation that loss of smell seems to concern patients with predominantly mild to moderate symptoms [28]. It may be that older or more vulnerable patients lack an effective and regenerative immuno-olfactory barrier which eventually let viruses pass through and without successfully triggering immune-induced apoptosis.

Evaluating the hypothesis

To date, the only experimental study to investigate sudden olfactory dysfunction due to SARS-CoV-2 was conducted by Brann et al. They analysed the expression of ACE2 in olfactory mucosa, a known receptor SARS-CoV-2 uses to infect human cells [29]. They showed that ACE2 can be sparsely found in support cells, pericytes and stem cells but not in olfactory neurons. They speculated therefore that olfactory dysfunction was not due to direct ORN infection by the virus and could be due to secondary infection or inflammation of olfactory neurons. Paradoxically, they observed that infecting the rat olfactory epithelium with a strain of coronavirus led to loss of neurosensory cilia from ORNs and rather limited infection of supporting cells. These results support the idea that ORNs may be affected in an ACE2-independent manner and that the subsequent olfactory dysfunction may be due to an immune response towards SARS-CoV-2 rather than direct damage by the virus.

Understanding the exact underlying mechanisms behind COVID-19-related olfactory dysfunction will require further molecular experiments on animal models. However, even though most biological pathways may be very similar among mammals, olfaction is much more important for mice than humans in terms of impact on survival. This means that to fully explore the interactions between coronavirus neuroinvasion, immune reaction, apoptosis and neurogenesis, future research will have to be conducted on fresh human olfactory mucosa sampling. This can be done by excision of a portion of the olfactory cleft as part of a transnasal endoscopic surgery performed for an unrelated rhinological condition.

Conclusion

As SARS-CoV-2 may continue to infect millions of people in the years to come, the prognostic implication of a frequent symptom may turn out to be paramount in managing patients early on in their clinical course. Besides, identifying the mechanism underlying potential immune-induced apoptosis of the olfactory route could help prevent neuroinvasion in vulnerable patients and raise concern about possible long-term neurodegenerative implications.

To sum up, we posit that COVID-19-related anosmia may be the consequence of a programmed immune-mediated self-defence mechanism by olfactory nerve deaffarentation, as it is a known royal path to the brain. Besides, such a drastic protective strategy is all the more worth the risk since the olfactory nerve has the rare ability to regenerate. Consistent with this hypothesis and as anosmia also seems to be part of the mild-to-moderate clinical presentation of COVID-19, we suspect it to be a positive prognostic factor.

Contributors

SDLB put forward the hypothesis and drafted the paper. MH helped with the literature search and revised the manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.109881.

References

[1] van Riel D, Verdijk R, Kuiken T. The olfactory nerve: a shortcut for influenza and other viral diseases into the central nervous system. J Pathol 2015;235(2):277–87.
[2] Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe Acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J Virol 2008;82(15):7264–75.
[3] Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, et al. Multiple organ infection and the pathogenesis of SARS. J Exp Med 2005;202(3):415–24.
[4] Dubé M, Le Coupanec A, Wong AHM, Rini JM, Desforges M, Talbot PJ. Axonal transport enables neuron-to-neuron propagation of human coronavirus OC43. J Virol 2018.
[5] Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020.
[6] Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-coronavirus-2. Int J Infect Dis 2020;94:55–8.
[7] Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID- 19): a multicenter European study. Eur Arch Oto-Rhino-Laryngology 2020;6.
[8] Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 Virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci 2020;11:995–8.
[9] Suzuki M, Saito K, Min W-P, Vladau C, Toida K, Itoh H, et al. Identification of viruses in patients with postviral olfactory dysfunction. Laryngoscope 2007;117(2):272–7.
[10] Welge-Lüssen A, Wolfensberger M. Olfactory Disorders following Upper Respiratory Tract Infections. In: Taste and Smell. Basel: KARGER; 2006. p. 125–32.
[11] Loseva E, Yuan T-F, Karnup S. Neurogliogenesis in the mature olfactory system: a possible protective role against infection and toxic dust. Brain Res Rev 2009;59(2):374–87.
[12] O'Brien V. Viruses and apoptosis. J Gen Virol 1998;79(8):1833–45.
[13] Mori I, Nishiyama Y, Yokochi T, Kimura Y. Virus-induced neuronal apoptosis as pathological and protective responses of the host. Rev Med Virol 2004;14:209–16.
[14] Perlman S, Evans G, Afifi A. Effect of olfactory bulb ablation on spread of a neurotropic coronavirus into the mouse brain. J Exp Med 1990;172(4):1127–32.
[15] Levine B. Apoptosis in Viral Infections of Neurons: a Protective or Pathologic Host Response? In: Current Topics in Microbiology and Immunology. 2002. p. 95–118.
[16] Mori I. Transolfactory neuroinvasion by viruses threatens the human brain. Acta Virol 2015;59(4):338–49.
[17] Borders AS, Getchell ML, Etscheidt JT, van Rooijen N, Cohen DA, Getchell TV. Macrophage depletion in the murine olfactory epithelium leads to increased neuronal death and decreased neurogenesis. J Comp Neurol 2007;501(2):206–18.
[18] Durante MA, Kurtenbach S, Sargi ZB, Harbour JW, Choi R, Kurtenbach S, et al. Single-cell analysis of olfactory neurogenesis and differentiation in adult humans. Nat Neurosci 2020;23(3):323–6.
[19] Carolyn Crist. CDC Adds Six Symptoms to COVID-19 List [Internet]. 2020 [cited 2020 May 1]. Available from: https://www.medscape.com/viewarticle/929636.
[20] Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dubé M, et al. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? Viruses 2019;12(1):14.
[21] Arbour N, Day R, Newcombe J, Talbot PJ. Neuroinvasion by human respiratory coronaviruses. J Virol 2000;74(19):8913–21.
[22] Crespo C, Liberia T, Blasco-Ibáñez JM, Nácher J, Varea E. Cranial Pair I: The Olfactory Nerve. Anat Rec 2019;302(3):405–27.
[23] Doty RL. The olfactory vector hypothesis of neurodegenerative disease: Is it viable? Ann Neurol 2008;63(1):7–15.
[24] Mori I, Nishiyama Y, Yokochi T, Kimura Y. Olfactory transmission of neurotropic viruses. J Neurovirol 2005;11:129–237.
[25] Kondo K, Watanabe K, Sakamoto T, Suzukawa K, Nibu K, Kaga K, et al. Distribution and severity of spontaneous lesions in the neuroepithelium and Bowman's glands in mouse olfactory mucosa: age-related progression. Cell Tissue Res 2009;335(3):489–503.
[26] Kanaya K, Kondo K, Suzukawa K, Sakamoto T, Kikuta S, Okada K, et al. Innate immune responses and neuroepithelial degeneration and regeneration in the mouse olfactory mucosa induced by intranasal administration of Poly(I:C). Cell Tissue Res 2014;357(1):279–99.
[27] Durrant DM, Ghosh S, Klein RS. The olfactory bulb: an immunosensory effector organ during neurotropic viral infections. ACS Chem Neurosci 2016;7(4):464–9.
[28] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395(10229):1033–4.
[29] Brann DH, Tsukahara T, Weinreb C, Lipovsek M, Van den Berge K, Gong B, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. BioRxiv 2020.
[30] Yan Carol H, Faraji F, Prajapati Divya P, Ostrander Benjamin T, DeConde Adam S. Self-reported olfactory loss associates with outpatient clinical course in Covid-19. Int Forum Allergy Rhinol 2020 Apr 24. https://doi.org/10.1002/alr.22592. In preparation.