·综述·

COVID–19患者嗅觉障碍的研究现状

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【摘要】COVID–19 是由 SARS–CoV–2 引起的以呼吸系统为主要感染靶标的传染病。越来越多的学者发现神经系统也可能是 SARS–CoV–2 感染的靶标之一，主要表现为嗅觉障碍，常伴有味觉丧失。本文旨在对 SARS–CoV–2 感染引起的嗅觉障碍相关研究加以综述，总结出 COVID–19 嗅觉障碍的原因、发病率、发病特点和目前的治疗情况，以加深临床医护人员对 COVID–19 的认识，促进对具有嗅觉障碍症状患者的早期识别、诊断和管理。

【关键词】新型冠状病毒肺炎；嗅觉障碍；症状；早期诊断

Current status of research on olfactory dysfunction in COVID-19 patients

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【Abstract】COVID-19 is caused by SARS-CoV-2, and the infection mainly targets the respiratory system. Recently, more and more reports have highlighted nervous system effects of SARS-CoV-2 infection, mainly manifested as olfactory dysfunction, often accompanied by ageusia. The purpose of this article is to review the relevant studies on olfactory dysfunction caused by SARS-CoV-2 infection, and to summarize its causes, incidence, characteristics and current treatments in COVID-19, so as to deepen clinical medical staff's understanding of COVID-19, and to promote the identification, diagnosis and management of patients with these symptoms.

【Keywords】COVID-19; Olfactory dysfunction; Symptom; Early diagnose

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新型冠状病毒肺炎（COVID-19）的出现给全球公共卫生和经济发展造成了严重负担[1]。发热、咳嗽、疲乏等已被证实是 COVID-19 患者常见的临床表现[2-3]，然而一些不具备这些常见症状的患者则很容易被忽视，成为疾病传播和持续的媒介。有研究指出嗅觉功能障碍可能是无症状感染者的一个重要预测指标[4-5]。嗅觉障碍通常作为轻中度 COVID-19 患者的伴随症状或者唯一症状，也可作为首发症状出现[6]。另有证据表明，那些仅出现嗅觉障碍的 COVID-19 患者也可能具有传播病毒的能力[7]，因此有学者建议，对新发或突发嗅觉丧失的人群应进行自我隔离和相关验证性检查[8]。目前，WHO 已将嗅觉障碍列为 COVID-19 的一个潜在筛查症状，这将有助于检测疑似病例和指导患者隔离[9]。本文系统回顾了 COVID-19 嗅觉障碍的现有文献，总结了 COVID-19 嗅觉障碍的原因、发病率、发病特点和目前的治疗情况，为 COVID-19 患者的早期筛查提供一定的帮助。

1 嗅觉系统的解剖学特点

嗅觉系统具有外围和中央的分支。外周嗅觉系统由嗅上皮和神经束组成，中央嗅觉系统由嗅球及其中枢连接组成[10]。嗅觉器官在人体内是独一无二的，因为它们含有再生的神经上皮。然而，这些脆弱的神经纤维也可能被损坏或永久性丧失[11]。人类大约有 350 个有功能的气味基因编码特定的蛋白质受体，它们与自身的化学物质或物质子集相互作用，形成了复杂的嗅觉识别机制[12]。现普遍认为，嗅觉系统在一定程度上反映了人类进化的适应性，对人类的生存至关重要。

2 COVID-19的流行病学特点

COVID-19 是本世纪人类经历的第三次致命性的冠状病毒感染。飞沫传播、接触传播和气溶胶传播是 COVID-19 最常见的三种感染途径[13]。普通成人 COVID-19 患者最常见的临床表现为发热和咳嗽（以干咳为主），常伴有疲劳、肌肉酸痛、呼吸困难和咳痰[2-3,14]。部分患者也可能会出现腹泻、恶心、呕吐等胃肠道症状[15]。目前诊断 COVID-19 的主要手段有核酸检测（RT-PCR）、抗体检测（IgM 和 IgG）、胸部 CT 和 X 线等。常见的实验室检查指标变化为淋巴细胞、血小板计数和中性粒细胞减少，以及乳酸脱氢酶、白细胞介素 -6 和 D- 二聚体升高等[16-19]。常见的影像学表现为磨玻璃影（GGO）、小叶间隔增厚、铺路石征、肺实变征及支气管充气征等[20-21]。

3 嗅觉障碍与COVID-19

3.1 COVID-19患者嗅觉障碍的发生率

自 2020 年 3 月以来，国际上关于 COVID-19 患者嗅觉障碍的报道大幅增加。一项来自英国的报道称，在 2020 年 2 月至 3 月之间，嗅觉障碍的发病率呈指数增长，与 COVID-19 的发病率有相似的趋势[22]。有学者发现在英国伦敦的 COVID-19 住院患者、社区患者及其家庭接触者中，半数以上均报告了嗅觉和味觉障碍，他们建议将嗅觉和味觉障碍加入到确认病例和指导隔离的方案中[23]。Bagheri 等的研究显示，自 COVID-19 疫情暴发以来，伊朗 31 个省份患者报告的嗅觉障碍发病率与同期 COVID-19 的发病率呈高度相关[24]。一项来自意大利的研究比较了住院患者和居家隔离患者嗅觉障碍的患病率，发现居家隔离患者嗅觉障碍发生率高于住院患者[25]。这一发现与 Boscolo 等的研究一致，他们表示在居家隔离的 SARS-CoV-2 感染者的家庭接触者中嗅觉障碍是普遍存在的症状，患病率高达 63.0%[26]。另一项来自西班牙的病例对照研究发现嗅觉和味觉障碍在 COVID-19 患者中的发生率明显高于流感患者，并且通常是患者的首发症状[27]。在亚洲的病例队列中也有相似的发现，有学者指出，与其他呼吸道病毒感染者相比，SARS-CoV-2 感染者出现嗅觉和味觉障碍的几率更高[28]。Lechien 等调查了欧洲 12 家医院的 COVID-19 患者，发现分别有 85.6% 和 88.0% 的患者报告嗅觉和味觉功能障碍，并且这两者之间存在显著的相关性[29]。另一项同样来自欧洲的报道称三分之二的 COVID-19 患者出现了嗅觉和味觉功能障碍，提示这一症状在早期诊断中的重要意义[30]。另外一项基于 202 名 COVID-19 患者的横断面调查显示，在整个研究人群中有 64.4% 的患者出现了嗅觉和味觉障碍，并且其中有 24 名患者以嗅觉和味觉障碍为首发症状，6 名患者以嗅觉和味觉障碍为唯一症状[31]。

3.2 COVID-19患者嗅觉障碍的特点

大量报道表明，嗅觉障碍已成为 COVID-19 的重要症状之一，该症状好发于轻中度患者、年

轻患者和女性患者，并且发病早、症状严重，常伴有味觉丧失。Moein 等对 60 名 COVID-19 住院患者进行了宾夕法尼亚大学嗅觉识别测验，发现 98% 的患者出现了嗅觉障碍，表明嗅觉功能障碍是 SARS-CoV-2 感染的主要标志之一，且通常症状较重 [32]。Hopkins 团队发表的病例报告等证据也证明了嗅觉丧失与 SARS-CoV-2 感染的高度相关性 [5]。在居家隔离的轻症 COVID-19 患者中，嗅觉障碍非常普遍 [26]。来自韩国的一项前瞻性研究发现，在 3 191 名患者中分别有 15.3% 和 15.7% 的患者出现了急性嗅觉和味觉丧失，并且均发生在 COVID-19 早期和无症状及轻度症状患者中 [33]。也有研究支持了此观点，他们认为嗅觉缺失可能与较温和的临床病程有关并且一般出现较早 [34-35]。由于嗅觉障碍这一感官症状通常发生在呼吸道症状之前，所以有学者将其定义为 COVID-19 的“前哨”症状 [36]。嗅觉障碍在 COVID-19 患者中的性别和年龄差异已被多项研究证实。两项来自意大利的研究发现嗅觉和味觉障碍在居家隔离患者中更为普遍并且与较小的年龄和女性独立相关 [25,31]。另外一项大型横断面研究指出嗅觉功能障碍是轻中度 COVID-19 患者的一个重要的被低估的症状，并且女性患者在 COVID-19 病程中自我报告的嗅觉或味觉障碍的频率明显高于男性 [37]。部分研究指出，COVID-19 患者的嗅觉缺失与鼻塞、鼻漏和炎症无关 [38-39]，且大多数 COVID-19 患者在嗅觉或味觉丧失时都伴有其他提示 COVID-19 的症状 [6]，少数以嗅觉和（或）味觉障碍为首发或唯一表现 [40-41]。另外，嗅觉功能障碍的患者也可能经历更严重的呼吸短促 [42]。

3.3 COVID-19患者出现嗅觉障碍的原因

在病毒感染后出现嗅觉功能障碍并不罕见。诸多病毒可以通过鼻粘膜的炎症反应导致嗅觉障碍，并进一步发展为鼻漏，最常见的病原体包括鼻病毒、副流感病毒、人类疱疹病毒 4 型和一些冠状病毒 [43]。但是病毒感染后出现嗅觉障碍的确切病理生理机制目前尚不清楚。SARS-CoV-2 与许多其他呼吸道病毒一样，附着和感染的主要部位是呼吸道上皮，因此不难想象 COVID-19 通过影响嗅觉神经上皮进而影响嗅觉 [24]。在 COVID-19 暴发初期，血管紧张素转移酶 2（angiotensin-converting enzyme 2, ACE2）就已被证实是 SARS-CoV-2 的功能受体 [44]，其存在于人体的多个器官，包括神经系统，所以 SARS-CoV-2 可能通过直接或间接的机制引起某些神经系统表现。部分学者认为鼻腔嗅上皮可能是增强结合 SARS-CoV-2 的位点 [45-48]。因为嗅觉上皮细胞中存在多种非神经元细胞，它们通过表达 ACE2 和 TMPRSS2 蛋白酶这两种宿主受体，从而促进 SARS-CoV-2 的结合、复制和积累。Bilinska 等使用小鼠模型，通过转录组测序技术、RT-PCR、原位杂交、蛋白印迹和免疫细胞化学来测定嗅上皮细胞是否表达 SARS-CoV-2 病毒的特异性受体，发现细胞表面蛋白 ACE2 和蛋白酶 TMPRSS2 在嗅上皮的支持细胞中表达，但在大多数嗅觉受器神经元中不表达或表达很少，表明支持细胞参与了 COVID-19 患者的 SARS-CoV-2 病毒侵入和嗅觉受损 [49]。也有学者认为 COVID-19 患者嗅觉障碍的起源可能与嗅球的中央受累和鼻神经上皮的嗅觉受器细胞的周边损伤有关，并且常伴随味觉障碍 [50]。另外，诱导凋亡小鼠的嗅觉神经元可以阻止神经入侵，并且嗅觉是成年人唯一具有再生能力的感官。基于这两点，Le 等推测 COVID-19 导致的突发性嗅觉丧失可能是一种涉及嗅觉受体神经元凋亡的宿主保护机制 [51]。有研究人员在对 COVID-19 患者进行尸检时，在其脑脊液及脑组织中检测到了 SARS-CoV-2 核酸，说明该病毒也可能通过血源性或逆行性神经元途径进入中枢神经系统，从而引起嗅觉障碍 [52]。Kirschenbaum 等报告了 2 例在尸检时观察到了炎症性嗅神经病变的 COVID-19 患者，但目前尚不清楚这种炎症性神经病变是病毒直接破坏的结果还是通过对支持性非神经细胞的损伤来介导的，尚需进一步的研究来阐明 SARS-CoV-2 的神经侵袭特性对 COVID-19 患者产生的影响 [53]。

3.4 COVID-19患者嗅觉障碍的治疗

目前，国际上 COVID-19 治疗标准仍未成熟，暂无强有力的证据证明有药物能治疗 COVID-19 引起的嗅觉障碍。对于病毒感染引起的嗅觉丧失已经有研究者提出了许多不同的治疗药物，例如皮质类固醇、α-硫辛酸、维生素 A 等，而病毒性嗅觉障碍又是 COVID-19 最常见的原因，基于此，有学者建议遵循相同的治疗策略 [54-57]。然而，在一项关于嗅觉功能障碍药物治疗的系统评价中未能找到任何高水平的证据证明这些治疗药物的

有效性，研究指出这些药物的研究大多规模小，无对照组，并且忽略了一定程度的疾病自发性恢复，所以对于是否应将这些治疗病毒性嗅觉障碍的药物应用于 COVID-19 仍存在争论[58]。尽管 COVID-19 患者嗅觉障碍的发病率较高，但有学者指出这一症状是短暂的并且可以随着病程自行恢复[36]。已有多项研究表明，大多数 COVID-19 患者的嗅觉障碍在症状出现后 1~4 周内基本消失[23,27,33,39,59-60]。但 Otte 等发现，以嗅觉丧失为症状之一的 COVID-19 患者中，有一半的患者在两个月后仍存在嗅觉障碍[61]。嗅觉障碍持续时间的差异可能是由于没有使用有效的嗅觉测试导致的，很多关于嗅觉障碍的研究都是通过问卷调查和回忆数据得到的结果[22,29-30,34,39,62-63]，而那些主观上没有发现自己存在嗅觉障碍的患者可能并没有完全康复，必须通过长期有效的嗅觉测试来确认 COVID-19 患者的嗅觉是否完全恢复。

4 结语

嗅觉功能障碍可以作为 SARS-CoV-2 感染的一个预测因子，其发生率较高，好发于轻中度患者的疾病早期，常伴有味觉障碍，且与年龄和性别相关。充分了解这一症状有利于医务人员对 COVID-19 患者的早诊断、早隔离和早治疗，从而减少病毒携带者数量，避免病毒传播。当患者在没有过敏性鼻炎、急慢性鼻窦炎等其他呼吸道疾病的情况下，突然出现的嗅觉障碍，应警惕 SARS-CoV-2 阳性的可能。虽然不能用嗅觉障碍来代替检测，但可以将其与发热和咳嗽等常见症状相结合作为确定 COVID-19 的预测性症状。临床医务人员应提高对嗅觉障碍这一神经系统症状的重视，做到严谨而科学地防治。

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