

嗅觉障碍的文献学习总结综述

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摘要

嗅觉障碍(OD)是一种发病原因尚不明确的嗅觉疾病, 以嗅觉下降或完全丧失为主要临床表现。嗅觉是人的基本感知觉之一, 在识别气味、预警危险及影响情绪等方面有着重要作用。嗅觉疾病逐渐被各国学者关注、OD是一种较为常见的嗅觉疾病, 尽管目前在OD的诊断及发病机制上有所研究, 但其临床诊疗工作仍十分具有挑战性。本文通过总结目前国内外关于OD的文献报道, 对嗅觉系统、发病情况、病因、治疗进行学习整合, 为OD的临床诊疗工作提供参考。

关键词

嗅觉障碍, 药物治疗, 针灸治疗, 嗅觉训练, 生长因子治疗

Integrated Review of the Literature on Olfactory Disorders

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Abstract

Olfactory dysfunction (OD) is a kind of olfactory disease. It is still unclear for the pathogenesis of IOD. The main clinical manifestation is the decrease or complete loss of olfactory dysfunction. The olfactory sensation is one of the basic senses of human beings, which plays an important role in identifying odors, warning dangers and affecting emotions. Olfactory diseases have gradually attracted the attention of scholars all over the world. OD is a relatively common olfactory disease.

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Despite the current research on the diagnosis and pathogenesis of IOD, the clinical diagnosis and treatment is still very challenging. In this paper, the domestic and foreign academic literatures on OD summarized about the Olfactory System disease onset, incidence, treatment were reviewed. It is expected to provide a reference for the olfactory system clinical diagnosis and treatment of OD.

Keywords

Olfaction Disorders, Drug Therapy, Acupuncture Train, Olfactory Train, Growing Gene Therapy

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1. 嗅觉系统和嗅觉障碍

1.1. 嗅觉系统

嗅上皮位于鼻孔后上方约 7 cm 处的鼻腔末端, 覆盖了部分鼻中隔、筛状板和上鼻甲[1], 是产生人类嗅觉的关键部位。嗅上皮中主要有嗅觉感觉神经元、支持细胞和基底细胞、刷细胞、微绒毛细胞。其中, 基底细胞又分为两种: 水平基底细胞和球形基底细胞。此外还有分泌黏液的嗅腺细胞和嗅鞘细胞(又名嗅觉胶质细胞)等[2]。支持细胞构成上皮的主体构架, 为维持神经元的兴奋性和上皮的主体性做出重要作用, 当支持细胞受到破坏, 嗅细胞的功能就会受到损伤[3]。而嗅腺细胞不仅可以通过导管将黏液分泌至嗅上皮表面, 浸润嗅觉感觉神经元的树突末梢和嗅觉纤毛, 对嗅觉感觉神经元起到保护作用, 还含有大量免疫球蛋白, 具有重要的免疫功能[3]。

嗅质是指能够被嗅觉系统感知并产生气味感觉的挥发性化学物质[4]。人类嗅上皮存在 1~2 千万个嗅觉感觉神经元, 每个成熟的嗅觉感觉神经元只特异性表达一种受体[5]。嗅质与嗅觉受体结合是产生嗅觉的开始。一个受体可以对多种嗅质产生反应, 一种嗅质也可以激活多个受体[6]。在嗅上皮区域, 嗅质会被结合蛋白运输至嗅觉感觉神经元树突端的嗅觉纤毛上, 与嗅觉受体相结合, 使化学信号转化为电信号[7]。之后嗅觉信息再通过嗅觉感觉神经元轴突形成的嗅丝传出, 穿过筛状板, 进入颅内[8], 到达嗅球[9]。随后通过嗅球中的轴突投射到大脑皮层, 并终止于额叶和内侧颞叶的几个区域, 包括梨状皮质、杏仁核和前杏仁核以及前额叶内侧皮质[10]。

1.2. 嗅觉障碍

嗅觉障碍是患者对气味感知异常, 患者嗅觉通路出现器质性或功能性病变, 导致对气味的觉察、传导和中枢整合信息异常[11][12]。嗅觉障碍的定量障碍主要包括嗅觉丧失、嗅觉减退、嗅觉过敏, 是基于嗅觉阈限、嗅觉分辨和嗅觉识别 3 种不同的嗅觉能力[13]。嗅觉定性障碍分为嗅觉倒错、幻嗅和嗅觉不耐受[14]。

2. 嗅觉障碍发病情况与病因

2.1. 嗅觉障碍的发病情况

嗅觉障碍在成年人的患病率为 1.4%~19.1% [15], 65 岁以上患病率高达 24.5% [16]。1989 年, Frank 曾报道 150 万被调查者中永久性嗅觉丧失者占 1.2%, 暂时性嗅觉丧失者占 62.4%。国外有学者称嗅觉障

碍整体发病率为 19%，其中约 13% 为嗅觉减退，6% 为嗅觉丧失[17]。在国内具体到嗅觉障碍在慢性鼻窦炎中的患病率为 48%~83%，慢性鼻窦炎伴鼻息肉甚至高达 95% [18]。流行病学调查显示[19]，多数帕金森患者早期表现有不同程度嗅觉障碍，发生率高达 45.0%~96.7%，故嗅觉障碍被认为是神经退行性病变首发症状和早期诊断的临床指标之一[20]。在 2019 年新冠患者的众多急性期症状中，嗅觉障碍尤其受到关注，被视作提示感染的早期指标[21]，研究报告显示新冠患者在急性期出现嗅觉障碍的比率相差很大，在 5%~85% 之间[22]。关于嗅觉障碍的大样本研究不多，结论不一。

2.2. 嗅觉障碍常见病因

约有超过 200 多种疾病和 120 种物质可导致嗅觉障碍[23]，临床最常见引起嗅觉障碍的原因为：头部创伤、上呼吸道感染、鼻 - 鼻窦疾病(慢性鼻窦炎)，上述占临床病因的 2/3。嗅觉减退程度与鼻 - 鼻窦疾病严重程度呈正相关，其中以慢性鼻窦炎、鼻息肉引起的嗅觉障碍较重[23]；其余病因包括神经退行性病变、先天畸形、精神疾病、自身免疫疾病、手术、中毒及营养不良等诸多因素。年龄被认为是引起人群嗅觉减退的最明显因素，大约在 60 岁时，嗅觉识别能力开始下降，65 岁后出现明显的嗅觉减退[24]，男性比女性下降快；上呼吸道感染尤其是病毒感染，发生嗅觉障碍的发生率为 16%，上呼吸道感染后嗅觉障碍的预后较好，大约有 1/3 的患者可望在感染后的半年内恢复[25]；神经退行性病变中，阿尔茨海默病多以嗅觉障碍为首发症状，并伴不同程度嗅觉减退，嗅觉丧失及嗅觉系统活检可作为早期诊断依据[26]。研究报道，有 10% 存在原发性嗅觉减退的帕金森病的一级亲属会发展为临床帕金森病[27]，因此嗅觉测试可作为帕金森病的早期诊断依据之一；外科手术也是影响嗅觉障碍发生的病因，有报道 1% 鼻腔术后患者可出现嗅觉丧失，另有数据表明，6% 的鼻整形患者和 3% 功能性鼻内镜手术患者术后出现嗅觉减退[28]。

3. 嗅觉障碍的治疗

嗅觉治疗的临床进展从 20 世纪 70 年代以后并不大[29]，并且嗅觉障碍并无其他阳性体征，病因的治疗仍是首要原则。

3.1. 药物治疗

文献表明糖皮质激素几乎可改善所有类型的嗅觉障碍[30]，被视为最普遍的治疗嗅觉障碍的药物，包括局部和全身使用[31]，有证据表明糖皮质激素受体和三磷酸腺苷酶可能在其中发挥作用[32]。但是针对新型冠状病毒感染后的嗅觉障碍使用糖皮质激素治疗的有效性还存在商讨[33]。

卡罗维林是钙离子通道阻滞剂，具有抗氧化作用，激发轴突和树突的修复机制的作用[34]。Quint 研究卡罗维林和硫辛酸，表明口服 4 周的卡罗维林患者气味识别能力显著提高，而服用硫辛酸组嗅觉没有改变[35]。

银杏叶提取物也可改善病毒感染后的嗅觉障碍，银杏叶可提高动物实验中嗅觉障碍模型小鼠的血供、抗氧化剂生成，与嗅觉再生有关[36]；也有硫辛酸、维生素 C、维生素 E 用于治疗嗅功能障碍的报道；锌参与物质代谢、酶的构成，调控突触性神经传递并能促进神经细胞再生，缺乏后可以导致嗅觉障碍，目前锌剂被广泛应用于味觉及嗅觉障碍；米诺环素属于四环素类抗生素，抗感染同时还具有抑制嗅感觉神经元凋亡的能力，有研究表明其也可能对治疗周围性嗅觉障碍有效[37]。

3.2. 中药治疗

嗅觉定量障碍在中医中可归为“鼻不闻香臭”“鼻聋”等范畴，嗅觉定性障碍并无明确的病名[38]。关于嗅觉的产生机理，中医上有“宗气上出于鼻而为臭”“五脏各有声色臭味”“心主臭”三种说法。对于宗气的认识，普遍认为其是由从肺吸入的自然界清气以及脾胃运化的水谷精气结合而成。《黄帝内经

灵枢集注》载“宗气者, 阳明之所生……是阳明之气, 上出于鼻而为臭”因此从生理上看, 嗅觉的产生主要依赖于肺、脾、胃的运化。而在《难经》三十七难中有对五脏之气的论述: “五脏之气, 于何发起, 通于何许, 可晓以不? 然: 五脏者, 当上关于九窍也。”

由此可见, 嗅觉的产生依赖于肺气上通于鼻, 而味道的不同则源于“肝臊、心焦、脾香、肺腥、肾腐”五脏之气的不同。

中医治疗只是阅读古籍对嗅觉以及嗅觉障碍的初步探索, 将嗅觉与五脏六腑相联系, 从而找出治疗的新出口, 但缺乏临床病例, 不能笼统概括, 研究效果有待验证。针对中医的病机基于黄帝内经分析[39]分为以下几种治法。

3.2.1. 宗气不能上达

宗气不能上达[40]的原因当责之有二: 其一为脾胃运化功能失常, 水谷之精气产生障碍。治疗可以四君子汤健脾益气为主进行加减, 配伍山药、白扁豆等增加运脾之效, 或配伍柴胡、升麻、葛根等提高升清之能。若因气弱不能上升而致宗气不能上达者, 可服用补中益气汤[41]; 其二为肺之宣发肃降功能失常[42], 《灵枢·脉度》言: “肺气通于鼻, 肺和鼻能知臭香矣。若肺气不和, 宣发失常, 故治疗可用辛味药如细辛、辛夷、麻黄等助肺之宣发。若肃降不能, 则肺气上逆, 气机郁闭[43], 治疗可以降气之药(如旋覆花、霜桑叶、枳壳、厚朴等)助肺之肃降。

3.2.2. 心肺有病, 而鼻为之不利也

心肺有病的原因当责之有三: 其一为“若心经移热于肺, 致肺脏不和, 则其窍亦无以宣达”[44], 可予栀子、黄连等清心火; 其二为宗气积于胸中, 其升清也有赖于心阳之温煦[41], 故心阳不足, 也会导致宗气不能上达, 可以桂枝甘草汤为主进行加减; 其三为心神失养, 心血不足[38], 治疗可以当归、丹参等养心血为主。

3.3. 针灸治疗

针灸治疗嗅觉障碍取穴以肺、胃、大肠三经为主, 其与督脉紧密联系。督脉为“阳脉之海”, 统摄诸阳、运行营气, 与脏腑经脉气血和鼻窍密切相关。督脉阳气运行顺畅, 促使肺、脾、肾阳气正常运行输布, 通利鼻窍之目的[45]。

手阳明大肠经循行于鼻腔两侧, 根据“经络所过, 主治所及”的治疗原则, 治疗取手阳明大肠经穴、手足阳明之迎香穴, 迎香具有散风清热、宣通鼻窍之功, 针刺迎香可使肺、鼻功能协调。合谷为手阳明经原穴, 可调节鼻腔气血, 为远道取穴法, 与迎香同用可增强疗效。列缺为手太阴肺经络穴, 针之具有调和肺气、宣通鼻窍的作用。

相对于督脉来说, 印堂和上星为督脉治疗嗅觉障碍的两大要穴。印堂位于两眉之间, 邻近于鼻, 为局部取穴; 上星在头部, 前发际正中直上 1 寸处, 一切上焦沉阴、头目不清之症, 悉可取此穴。除了上述迎香、印堂之外, 还可取位于鼻翼周边的内迎香、上迎香、鼻根等穴。

在 2023 年新冠期间, 李飞团队选取 28 例新冠后嗅觉障碍患者, 予通调法针灸治疗, 总有效率为 96.4% (27/28)[46], 通调法针灸可改善新冠后嗅觉障碍患者的症状, 升高血清皮质醇含量, 缓解焦虑抑郁情绪。

3.4. 嗅觉训练

嗅觉训练是指通过定期、重复地主动吸嗅暴露的各种类型气味, 从而改善嗅觉功能和嗅觉灵敏度[47]。嗅觉训练的效果受患者年龄、性别、病程、治疗时间等因素影响, 总体有效率为 30%~50% [48]。嗅觉训练可改善与上呼吸道感染、头部创伤[49]和特发性相关的嗅觉障碍[50], 神经退行性疾病[51]。也被用于改善老年人的嗅觉障碍, 在嗅觉功能得到改善的同时, 老年人的主观幸福感也有所提升, 抑郁症状

有所减轻[52]。

Hummel [53]最早将嗅觉训练用于改善嗅觉丧失患者的嗅觉功能。Pellegrino [54]的嗅觉训练可促进患者嗅觉识别能力的快速恢复。Konstantinidis 的研究[55]发现重复的气味暴露提高了患者嗅觉上皮的敏感性,可以改善患者对气味的识别和辨别力。Altundag [56]发现增加嗅觉训练的时间和改变嗅觉训练的气味种类对患者嗅觉识别能力的改善效果更明显。

3.5. 生物治疗

生长因子刺激细胞生长、增殖,对调节细胞再生的过程很重要[57]。不同的生长因子在嗅觉障碍嗅觉恢复中起到重要的作用。Nishikawa [58]使用碱性成纤维细胞生长因子对小鼠经鼻给药结果显示嗅觉标记蛋白数量增多;Fukuda [59]研究表明,胰岛素样生长因子-1和成纤维细胞生长因子-2均可促进小鼠退化嗅上皮的基底细胞增殖和嗅感觉神经元的分化。Beecher [60]联合应用血管内皮生长因子和血小板衍生生长因子对小鼠经鼻滴入结果表明有可能改善嗅觉障碍。中国医科大学耳鼻喉科团队[61]的研究表明嗅觉训练联合神经生长因子治疗上呼吸道感染及外伤后嗅觉障碍疗效优于单纯嗅觉障碍,可以作为感觉神经性嗅觉障碍的治疗方法应用于临床。并且有团队研究表明[62]糖皮质激素雾化吸入联合鼠神经生长因子能安全有效地治疗感冒后的嗅觉障碍。总之,生长因子以及生长因子的联合治疗在嗅觉障碍中发挥了重大作用,为嗅觉障碍的临床也增加了补充治疗。

在生物制剂方面,发现度普利尤单抗、奥马珠单抗和美泊利单抗均能明显改善慢性鼻窦炎伴鼻息肉患者的嗅觉功能[63]。当前开发的生物制剂也主要针对靶向2型炎症。抗Ig-E生物制剂Omalizumab,研究表明奥马珠单抗不仅可以降低合并哮喘的慢性鼻窦炎伴鼻息肉鼻内镜下鼻息肉评分[64]也可以提高患者的自报嗅觉;抗IL-5生物制剂Reslizumab和Mepolizumab以及Benralizumab,其中Bachert等[65]研究则证明,Mepolizumab单抗组在严重的双侧鼻息肉患者中,VAS评分改善显著提高;抗IL-4/IL-13生物制剂Dupilumab,有三期临床试验表明慢性鼻窦炎伴鼻息肉患者用Dupilumab治疗后UPSIT评分及自报嗅觉的改善与安慰剂组有显著差异。上述单抗均对嗅觉障碍有所改善,Oykhmanb研究表明,Dupilumba的改善最明显[63]。

单抗已逐渐走向难治性鼻炎患者的视野,但其对嗅觉障碍这一症状的改善还缺乏大量的数据作为支撑背景。同时我国还缺乏在生长因子方面大量的样本和随访实验,距离生物制剂成为难治性、炎症性嗅觉障碍常规诊疗方法,还有很长的路要走。

3.6. 间充质干细胞治疗

间充质干细胞是一种来源于中胚层的多能干细胞,可以分化为多种细胞类型,包括脂肪细胞、成骨细胞、心肌细胞、神经细胞,骨髓间充质干细胞有强大的修复能力。Jo等[66]在诱导的嗅上皮变性小鼠中鼻内移植骨髓间充质干细胞,4周后,嗅上皮厚度和细胞组成恢复正常,并且神经生长因子的表达水平显著增加,有助于嗅感觉神经元的再生。针对感觉神经性嗅觉功能障碍,还有神经干细胞移植以及球状基底细胞[67]移植被证明可促进嗅觉功能的恢复;水平基底细胞[68]激活对治疗老年人的嗅觉障碍方面有着显著改善。

针对新冠病毒后的嗅觉障碍,专家们研发出间充质干细胞治疗。嗅上皮中的支持细胞是唯一表达角蛋白K18(keratin-18)的细胞类型,在患者嗅上皮局部注射与K18结合的间充质干细胞,减少患者嗅上皮炎症环境,加速嗅觉功能的恢复[69]。富血小板血浆内含有大量生长因子及蛋白质,有研究者将其注射到新冠患者的嗅液中,3个月后,患者的嗅觉辨别能力得到明显改善[70]。

目前各项研究报告中嗅觉障碍以主观方法计算、群体研究对象略少居多,都以探索式为嗅觉障碍治

疗开辟新道路, 新型的研究方法需要更多采用客观测量的方法收集的样本数据, 并且研究未系统的对安全、伦理进行临床试验。

4. 总结

关于嗅觉障碍的病因、治疗还未形成系统化体系, 但对于嗅觉障碍的研究从未停止, 以上综述仅阅读相关文献后进行的关于嗅觉障碍的知识总和, 给予学习和研究参考。

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