

Meige 综合征脑深部电刺激术治疗进展

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【摘要】 Meige 综合征是一种以眼睑痉挛和口-下颌肌张力障碍为主要特征的节段型肌张力障碍,早期药物治疗或局部注射肉毒毒素可取得一定疗效,但长期应用导致疗效下降和不良反应给治疗带来挑战。脑深部电刺激术因其安全、有效、微创、可逆、可调控等特征,成为一种新型 Meige 综合征治疗方法。本文对 Meige 综合征的临床表现和发病机制以及脑深部电刺激术治疗机制和疗效进展进行综述,以提高临床对脑深部电刺激术治疗 Meige 综合征的认识。

【关键词】 Meige 综合征; 深部脑刺激法; 综述

Clinical research progress of deep brain stimulation for Meige's syndrome

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【Abstract】 Meige's syndrome (MS) is a segmental dystonia characterized by blepharospasm and oromandibular dystonia. Early treatment with medication or local injection of botulinum toxin can achieve certain therapeutic effects, but long-term use leads to decreased efficacy and adverse reactions, posing challenges to the treatment of the disease. Deep brain stimulation (DBS) has become a new treatment method for Meige's syndrome due to its safety, effectiveness, minimally invasive nature, reversibility, and controllability. This article reviews the clinical manifestations, pathogenesis of Meige's syndrome, as well as the mechanism and efficacy of DBS treatment, to improve clinical understanding of DBS treatment for Meige's syndrome.

【Key words】 Meige syndrome; Deep brain stimulation; Review

This study was supported by National High Level Hospital Clinical Research Funding (No. 2023-NHLHCRF-YYPP-TS-05).

Conflicts of interest: none declared

Meige 综合征(MS)是临床罕见的节段型肌张力障碍性疾病,临床主要表现为双侧眼睑痉挛和口-下颌、颈部肌肉不随意运动,亦称眼睑痉挛-口下颌肌张力障碍综合征^[1]。主要发生在 40~70 岁人群,女性患病率高于男性(2:1),不仅显著降低患者工作能力和生活质量,还对情绪和社会交往产生负面影响^[1-2]。发病机制目前尚不清楚,早期治疗主要为药

物治疗和局部注射肉毒毒素(BTX)等对症治疗,但长期药物不良反应和疗效下降给治疗带来挑战^[3-4]。脑深部电刺激术(DBS)不仅可以有效缓解肌张力障碍,而且具有微创、安全的特点,为 Meige 综合征的治疗带来新的希望^[5]。本文拟全面综述 Meige 综合征临床表现和发病机制以及脑深部电刺激术治疗机制和疗效进展,以期提高临床对脑深部电刺激术治疗 Meige 综合征的认识。

一、Meige 综合征的临床表现

Meige 综合征主要累及双侧眼轮匝肌、口-下颌肌肉和颈部肌肉致受累肌肉出现不随意运动,表现为眼睑痉挛和(或)口-下颌肌肉不自主抽动^[1-2]。少数患者并不局限于头颈部,可能扩展至躯干、四肢等远隔部位^[1]。根据受累部位,Meige 综合征可分为

doi:10.3969/j.issn.1672-6731.2024.07.003

基金项目:中央高水平医院临床科研业务费资助(项目编号:2023-NHLHCRF-YYPP-TS-05)

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4种类型^[6]:(1)眼睑痉挛型,表现为不自主眨眼或阵发性或持续性眼睑痉挛。大多数患者同时存在双侧眼睑痉挛,约25%患者首发症状为单侧眼睑痉挛,随病情进展逐渐累及双侧眼睑^[7],甚至部分患者出现功能性失明。此型患者的典型眼睑痉挛出现之前常有眼睑灼烧感和异物感、眼干、畏光、畏风等症状^[8],早期易误诊为“干眼症”。(2)眼睑痉挛合并口-下颌肌张力障碍型,表现为眼睑痉挛同时合并口-下颌肌肉不自主抽动。此型患者眼睑痉挛逐渐加重,累及口-下颌、颈部和四肢肌肉,尤以口-下颌肌肉受累最早、最常出现^[9],表现出噤嘴、缩唇、张口、伸舌等症状,累及咽喉部肌肉还可出现构音障碍和吞咽困难^[10-11]。(3)口-下颌肌张力障碍型,仅表现为口唇部、下颌肌肉不自主抽动,不伴眼睑痉挛。(4)其他型,表现为头面部肌张力障碍合并颈部、躯干和四肢等部位肌张力障碍,患者可以出现颈项前屈、斜颈、躯干肌痉挛、上肢肌张力障碍震颤、呼吸困难等症状^[12-13]。Meige综合征除引起受累肌肉不自主运动外,还可导致感觉异常、精神心理异常和认知功能障碍等非运动症状^[14-16]。

二、Meige综合征的发病机制

Meige综合征的发病机制尚未完全阐明,针对其病理生理学机制的研究支持其发病与环境因素和遗传易感性共同作用导致神经可塑性异常和中枢抑制减弱有关^[17]。

1. 环境因素引起神经递质功能紊乱 环境因素和机体应激反应可影响中脑边缘系统多巴胺能神经元和多巴胺水平^[18],轻至中度短期应激促进多巴胺释放,强烈或长期慢性应激则抑制多巴胺释放。动物模型显示,肌张力障碍可能与纹状体胆碱能和多巴胺能信号失衡相关:Scarduzio等^[19]直接检测到TORIA基因敲入小鼠纹状体细胞外乙酰胆碱水平升高,证实纹状体内高胆碱能状态;Tassone等^[20]发现TORIA基因敲入小鼠纹状体囊泡乙酰胆碱转运体(VACHT)水平显著升高,该蛋白负责将乙酰胆碱自细胞质装载至突触囊泡中,进一步揭示纹状体内高胆碱能状态的作用机制。但临床研究则得出相反结论,Mazere等^[21]发现,DYT1型肌张力障碍患者纹状体乙酰胆碱转运体水平下降。

2. 遗传易感性 尽管肌张力障碍的遗传学机制尚未完全阐明,但仍有约17%患者特别是成人局灶性肌张力障碍患者存在家族史^[22]。目前已在某些家系中确定原发性肌张力障碍的致病基因,包括

TORIA变异引发的DYT1型肌张力障碍、THAPI变异引发的DYT6型肌张力障碍、GNAL变异引发的DYT25型肌张力障碍等^[23]。Zech等^[24]的全外显子组测序(WES)研究显示,728个家系中135个家系(18.54%)发现致病或可能的致病变异,涉及78种单基因遗传病。尽管目前尚未确定原发性Meige综合征的致病基因,但随着近年基因测序技术在Meige综合征中的应用,REEP4、TORIA、THAPI被认为可能是潜在致病基因^[25-26]。

3. 大脑皮质抑制性减弱 大脑皮质抑制性神经元活动减弱是Meige综合征的病理生理学机制之一。经颅磁刺激(TMS)研究显示,头面部肌张力障碍患者皮质静息期(CSP)显著缩短,且眼睑痉挛合并口-下颌肌张力障碍型患者皮质静息期缩短程度大于眼睑痉挛型,提示肌张力障碍患者存在大脑皮质抑制性神经元兴奋性降低^[27]。Meta分析亦支持这一结论^[28]。静息态fMRI研究显示,Meige综合征患者做吹哨动作时口唇区初级运动皮质(M1)和腹侧前运动皮质(PMv)激活不足,提示口-下颌肌肉运动执行过程中运动区和前运动区皮质抑制减弱^[29]。

三、Meige综合征的治疗

Meige综合征主要采取对症治疗,未经治疗者自行缓解的概率很小。早期轻型患者可予以药物联合治疗,但长期药物不良反应使多数患者中断治疗^[3]。临床常用药物包括抗胆碱能药物、γ-氨基丁酸(GABA)受体激动药、苯二氮草类药物、多巴胺受体阻断药等^[7]。对于药物疗效欠佳或难以耐受药物不良反应的患者,局部注射A型肉毒毒素是重要的替代方案^[30-31]。A型肉毒毒素局部注射可通过高选择性结合胆碱能神经元,阻断乙酰胆碱的转运和释放^[32],缓解肌肉痉挛,但需定期注射以应对神经支配再生及毒素代谢,避免痉挛复发。然而,长期局部注射A型肉毒毒素可使机体产生免疫抗体,导致疗效降低甚至失效^[33]。近年来,以脑深部电刺激术为代表的神经调控技术因其安全、有效、微创、可逆、可调节等优势成为探索肌张力障碍性疾病治疗的前沿^[34]。

1. 脑深部电刺激术的作用机制 业已证实,脑深部电刺激术治疗Meige综合征具有很好疗效并广泛应用,但其确切作用机制尚未完全阐明。关于脑深部电刺激术作用机制的研究主要集中于帕金森病动物模型和帕金森病患者,目前已形成多种假说,包括抑制假说、兴奋假说和干扰假说^[35]。(1)抑

制假说:脑深部电刺激术可以产生类似神经核团毁损手术的效果,因此抑制假说最初认为主要通过抑制局部神经元活动以发挥作用。然而,Filali等^[36]在帕金森病患者中发现,丘脑底核脑深部电刺激术(STN-DBS)刺激靶点周围神经元活动受到抑制,放电频率显著下降,而刺激靶点神经元仍残留电活动。Lafreniere-Roula等^[37]亦发现,帕金森病患者苍白球内侧部脑深部电刺激术(GPi-DBS)刺激靶点周围神经元活动明显减弱。上述研究进一步发展了抑制假说,即脑深部电刺激术主要通过抑制刺激靶点周围神经元活动,降低其放电频率而发挥作用。(2)兴奋假说:兴奋假说认为,电刺激信号直接激活局部兴奋性或抑制性神经元,并沿传出通路至下游靶点或逆向激活上游区域。Johnson和McIntyre^[38]在帕金森病患者中发现,GPi-DBS可直接诱发苍白球内侧部神经元产生动作电位。Montgomery^[39]认为,GPi-DBS可兴奋抑制性苍白球内侧部-丘脑投射,减少帕金森病患者丘脑神经元放电。Miocinovic等^[40]发现,STN-DBS可通过透镜状束(苍白球内侧部-丘脑投射的一部分)逆向激活苍白球内侧部神经元。(3)干扰假说:干扰假说主张电刺激诱导的规律神经元活动模式可以中断并替代丘脑和基底神经节的异常振荡活动。Chicken和Nambu^[41]电刺激正常猴(3只日本猴,1只恒河猴)苍白球外侧部(GPe),可同时检测到苍白球内侧部和外侧部的神经元活动,发现GPi-DBS可以阻断流经苍白球内侧部的信息流,完全抑制神经元的皮质诱发电位和自发放电。Maurice等^[42]通过研究正常大鼠黑质网状部(SNr)神经元的皮质诱发电位,发现STN-DBS可以阻断经丘脑底核的信息传递。由于基底节异常放电模式或异常放电增加可传递至丘脑和运动皮质,并最终诱发运动症状,因此阻断流经苍白球内侧部和丘脑底核的信息流可以抑制运动症状。关于脑深部电刺激术治疗Meige综合症的机制,更多学者倾向干扰假说^[6],即通过阻断丘脑和基底节的低频振荡,同时激活下游神经核团,促进其产生规律的电活动。Zhang等^[43]对28例Meige综合症患者行GPi-DBS时的局部场电位研究发现,苍白球内侧部存在异常 θ 振荡(4~8 Hz),且振荡爆发持续时间与疾病严重程度相关。此外,在其他类型肌张力障碍中也观察到类似的低频振荡^[44],进一步支持干扰假说。近年有学者提出脑深部电刺激术治疗Meige综合症的机制可能与脑代谢改善相关,¹⁸F-FDG PET显

像显示,Meige综合症患者苍白球和丘脑均呈低代谢改变^[45],脑深部电刺激术后脑代谢显著提高^[46]。

2. 不同靶点脑深部电刺激术的治疗效果 脑深部电刺激术治疗Meige综合症的靶点主要包括苍白球内侧部和丘脑底核。(1)GPi-DBS:郝庆沛等^[47]回顾分析15例接受双侧GPi-DBS的Meige综合症患者的临床资料,术后3、6、12个月Burke-Fahn-Marsden肌张力障碍量表(BFMDRS)中眼部、口-下颌、言语和吞咽、颈部评分均较术前明显降低,且随着时间延长评分呈降低趋势。Zheng等^[5]对35例行双侧GPi-DBS的Meige综合症患者进行长期随访发现,术后1年BFMDRS运动和功能障碍评分平均改善率分别为65%和49%,术后3年平均改善率为72%和57%。Hao等^[48]报告22例行双侧GPi-DBS的Meige综合症患者,术后12个月BFMDRS运动评分平均改善率为78%、功能障碍评分平均改善率为56%,术后36条简明健康状况调查表(SF-36)评分亦显著改善。因此认为,双侧GPi-DBS是治疗难治性Meige综合症的有效方法,可以改善运动功能,提高生活质量。(2)STN-DBS:双侧STN-DBS治疗Meige综合症同样表现出令人满意的效果,尤其对于曾行苍白球切开术的患者。王宁等^[49]回顾分析14例行双侧STN-DBS的Meige综合症患者的临床资料,至末次随访[(28.4±9.5)个月]时BFMDRS运动评分平均改善率为79%,功能障碍评分平均改善率为73%。Hao等^[50]对30例Meige综合症患者双侧STN-DBS术后进行长期随访,术后12和48个月BFMDRS运动评分平均改善率为63.0%和66.8%,功能障碍评分平均改善率为60.8%和63.3%。对比不同靶点脑深部电刺激术治疗效果的研究显示,STN-DBS治疗Meige综合症的效果与GPi-DBS相当^[51-54],但这些研究样本量较小,尚待大样本随机对照试验的验证。尽管脑深部电刺激术在治疗Meige综合症的有效性方面已得到越来越多研究的证实,但其同样可以引起运动迟缓、冻结步态、肢体异动等并发症^[55-57],值得临床医师关注。

3. 脑深部电刺激术疗效的预测因素 目前尚无可靠指标预测脑深部电刺激术治疗Meige综合症的疗效。术前BFMDRS评分^[58]、左侧小脑小叶VIIIb区灰质体积^[59]、术后出现微毁损效应^[60]均与术后症状改善相关,可作为脑深部电刺激术疗效的潜在预测因素,但尚待更多研究验证;此外,电极植入部位及刺激靶点周围神经元活性也可能是脑深部电刺激

术疗效的关键影响因素。有研究分析 Meige 综合征患者 GPi-DBS 术后刺激靶点周围的电生理学特征,结果显示,苍白球内侧部后下区具有更高的神经元活性,刺激该部位可获得更佳临床效果^[61]。亦有研究显示,患者丘脑底核背外侧活化组织体积与 STN-DBS 术后症状改善率显著相关^[62-63]。

综上所述,Meige 综合征是临床罕见的头面部肌张力障碍性疾病,临床症状复杂多样,发病机制尚不完全清楚,目前主要侧重对症治疗。大多数早期 Meige 综合征患者药物治疗和局部注射肉毒毒素可取得一定疗效,对于药物和肉毒毒素治疗效果欠佳或无法耐受药物不良反应的患者,脑深部电刺激术成为最佳替代选择。脑深部电刺激术治疗 Meige 综合征的有效性和安全性已经初步验证,尚待更大规模的随机对照试验进一步确认其疗效和安全性,以及确定最佳刺激靶点和预测因素。

利益冲突 无

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(收稿日期:2024-05-22)

(本文编辑:彭一帆)

· 小词典 ·

中英文对照名词词汇(一)

- γ-氨基丁酸 γ-aminobutyric acid(GABA)
- γ-氨基丁酸 B 型受体
γ-aminobutyric acid receptor type B(GABA_BR)
- α-氨基-3-羟基-5-甲基-4-异噁唑丙酸受体
α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor(AMPA)
- 半高全宽 full width half maximum(FWHM)
- 变频刺激 variable frequency stimulation(VFS)
- 丙型肝炎病毒 hepatitis C virus(HCV)
- 苍白球内侧部 globus pallidus internus(GPi)
- 苍白球外侧部 globus pallidus externus(GPe)
- 长时程增强 long-term potentiation(LTP)
- 齿状核 dentate nucleus(DN)
- 齿状核-丘脑-皮质 dentate thalamus cortex(DTC)
- 重复神经电刺激 repetitive nerve stimulation(RNS)
- 重复时间 repetition time(TR)
- 初级运动皮质 primary motor cortex(M1)
- 磁化准备快速梯度回波
magnetization-prepared rapid gradient echo(MPRAGE)
- 错误发现率 false discovery rate(FDR)
- 单纯部分性发作 simple partial seizure(PS)
- 电压门控性钾离子通道
voltage-gated potassium channel(VGKC)
- 动脉瘤性蛛网膜下腔出血
aneurysmal subarachnoid hemorrhage(aSAH)
- 冻结步态 freezing of gait(FOG)
- 冻结步态问卷 The Freezing of Gait-Questionnaire(FOG-Q)
- 翻转角 flip angle(FA)
- 反转时间 inversion time(TI)
- 非运动症状 non-motor symptoms(NMS)
- 非运动症状量表 Non-Motor Symptom Scale(NMSS)
- 复杂部分性发作 complex partial seizure(CPS)
- 副肿瘤性眼阵挛-肌阵挛-共济失调综合征
paraneoplastic opsoclonus-myoclonus-ataxia syndrome (P-OMAS)
- 富亮氨酸胶质瘤失活蛋白 1
leucine-rich glioma-inactivated 1(LGI1)
- 改良 Rankin 量表 modified Rankin Scale(mRS)
- 钙/钙调素依赖性蛋白激酶 II
calcium/calmodulin-dependent protein kinase II (CaMK II)
- 感兴趣区 region of interest(ROI)
- 高频刺激 high frequency stimulation(HFS)
- 功能连接 functional connectivity(FC)
- 功能性神经系统疾病 functional neurological disorder(FND)
- 功能性运动障碍 functional movement disorder(FMD)
- 共济失调等级量表
Scale for the Assessment and Rating of Ataxia(SARA)
- 谷氨酸脱羧酶 65 glutamic acid decarboxylase 65(GAD65)
- 光学相干断层扫描术 optical coherence tomography(OCT)
- 光学相干断层扫描血管成像
optical coherence tomography angiography(OCTA)
- 国际抗癫痫联盟
International League Against Epilepsy(ILAE)
- 国际前列腺症状评分
International Prostate Symptom Score(IPSS)
- 国际运动障碍协会 The Movement Disorder Society(MDS)