·专题综述·

行为异常型额颞叶痴呆研究进展

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【摘要】 鉴于我国目前尚无额颞叶痴呆的流行病学资料，行为异常型额颞叶痴呆国际标准联盟公布的新的诊断标准与我国专家共识、多模态影像学和生物学标志物研究有望提高临床对行为异常型额颞叶痴呆的认识，多种干预措施可能延缓病情进展。

【关键词】 痴呆； 额叶； 颞叶； 生物学标记； 综述

Research progress of behavioral variant frontotemporal dementia

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【Abstract】 There is no epidemiological data of frontotemporal dementia (FTD) in China. The application of updated diagnostic criteria, publishing of frontotemporal lobar degeneration (FTLD) consensus in China, development of multimodal imaging and biomarkers promote the clinical understanding on behavioral variant frontotemporal dementia (bvFTD). There is still no drugs treating FTD approved by U.S. Food and Drug Administration (FDA). Multidisciplinary intervention may delay the progression of bvFTD.

【Key words】 Dementia; Frontal lobe; Temporal lobe; Biological markers; Review

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额颞叶痴呆（FTD）是一组临床表现、组织病理学和遗传学均具有异质性的神经变性病，其中行为异常型额颞叶痴呆（bvFTD）为临床常见亚型，约占70%[1]。近年来，有关行为异常型额颞叶痴呆临床特征、早期诊断与治疗、生物学标志物等方面的研究取得了重大成果，笔者拟对其相关研究进展进行简要概述。

一、流行病学

流行病学调查研究显示，额颞叶痴呆是仅次于阿尔茨海默病（AD）的痴呆常见病因[2-3]。我国目前尚无翔实的流行病学数据，仅有一些小样本临床研究[4-5]。来自英国的两项独立的流行病学调查资料显示，额颞叶痴呆患病率约15/10万，发病年龄45～64岁[3]。一般认为，额颞叶痴呆是老年人晚发型痴呆（>65岁）的罕见病因，其实不尽然，目前研究强烈提示，额颞叶痴呆并非罕见，究其原因是老年患者病理学检查资料不完善且通常不行尸检[3]。

行为异常型额颞叶痴呆患者的病情较阿尔茨海默病进展迅速，中位生存期（自首诊开始）为3～

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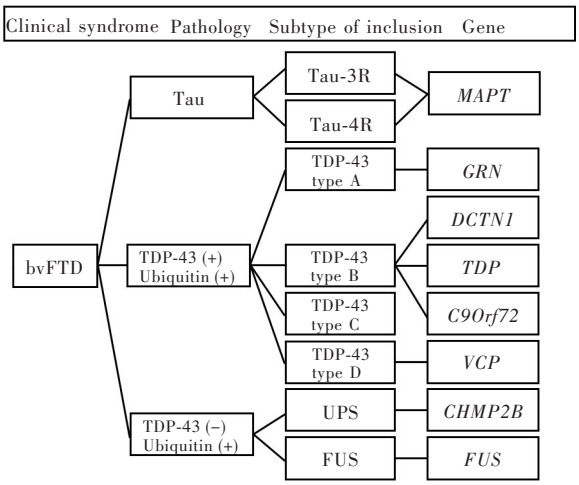
4.50年[6-7]，其中伴运动神经元病（MND）、肌萎缩侧索硬化症（ALS）或言语障碍者生存期可能更短[7]；其神经病理学分型与生存期间的关系尚不明确[3]。

二、病理学与遗传学特征

典型病理表现为双侧额颞叶萎缩，伴神经元缺失、微空泡形成和不同程度的神经胶质细胞增生[8]；萎缩自额叶近中线部位和眶额部开始，逐渐累及颞极、海马、背外侧额叶皮质和基底节，萎缩进展顺序与皮质和皮质下区域体积和底层神经元缺失相关[9-10]。组织病理学将其称为额颞叶变性（FTLD），根据免疫组织化学染色和细胞内包涵体特点可以分为：微管相关蛋白tau蛋白包涵体（FTLD-tau），tau蛋白阴性、泛素（ubiquitin）阳性、由TAR DNA结合蛋白43（TDP-43）组成的包涵体（FTLD-TDP），含泛素-蛋白酶体系统的包涵体（FTLD-UPS），含肉瘤融合蛋白的包涵体（FTLD-FUS），无特异性病理学特征的额颞叶变性，嗜碱性包涵体等罕见类型[11]。该病的分子病理学表现具有异质性，FTLD-tau和FTLD-TDP比例各占50%[12-13]，另有小部分为FTLD-FUS[14]。

约40%的额颞叶痴呆患者有阳性家族史[3]，其中10%为常染色体显性遗传[15]，常见突变基因有微管相关蛋白tau（*MAPT*）、前颗粒蛋白（*GRN*），各占5%～11%，其他基因型有动力蛋白激活蛋白1（*DCTN1*）、*TDP*、9号染色体开放阅读框72（*C9Orf72*）、含缬酪肽蛋白（*VCP*）、带电荷的多囊泡体蛋白2B（*CHMP2B*）等[16-17]。*C9Orf72*为常见致病基因，约占家族性额颞叶痴呆患者的1/3，在欧洲人群中十分常见，亚洲相对少见[18]。*C9Orf72*基因突变是第9号染色体内含子区域较大的6核苷酸重复扩增序列，导致RNA核内聚集，抑制基因表达。疾病亚型并不依赖于重复序列的长度，初步研究证据显示，重复序列的长短可以影响患者生存期。携带*C9Orf72*基因者多伴运动神经元病，其表型与散发性运动神经元病相似，但早期不出现下肢无力症状与体征[19]。行为异常型额颞叶痴呆是额颞叶痴呆异质性最典型的亚型，其临床表现不典型和病理学异质性均增加诊断难度，因此遗传学检测有助于预测隐藏的组织病理学改变（图1）。



bvFTD，behavioral variant frontotemporal dementia，行为异常型额颞叶痴呆；TDP-43，transactive response DNA-binding protein 43，TAR DNA结合蛋白43；UPS，ubiquitin proteasome system，泛素-蛋白酶体系统；FUS，fusion in sarcoma，肉瘤融合蛋白；MAPT，microtubule-associated protein tau，微管相关蛋白tau；GRN，progranulin，前颗粒蛋白；DCTN1，dynactin 1，动力蛋白激活蛋白1；C9Orf72，chromosome 9 open reading frame 72，9号染色体开放阅读框72；VCP，valosin-containing protein，含缬酪肽蛋白；CHMP2B，charged multivesicular body protein 2B，带电荷的多囊泡体蛋白2B

图1　行为异常型额颞叶痴呆病理学与分子遗传学的联系

Figure 1　The relation between pathologies and molecular genetics in bvFTD.

三、临床特征

根据行为异常型额颞叶痴呆国际标准联盟（FTDC）公布的相关诊断标准[20]，行为异常型额颞叶痴呆定义为早期出现的人际沟通能力和（或）执行功能下降，具有提示意义的症状与体征还包括早期去抑制、淡漠、同情心丧失、固定和刻板行为、异食癖等。其中淡漠较为常见，逾85%的患者首发症状为淡漠、主动性减少，如进行性缺乏动机、失去以往的爱好兴趣，甚至社会隔离；约76%的患者伴行为去抑制表现，产生一系列冲动行为，如过度消费、粗鲁或不恰当的性言论，以及一系列尴尬行为[20]，亦可表现为病理性赌博、过度宗教倾向[21-22]。同情心丧失主要表现为冷淡，临床证据显示，额中回前角萎缩或退化与患者精神状态、关心和理解他人损害有关[23]。行为异常型额颞叶痴呆患者可出现重复刻板行为，如抓挠、舌头舔拭、拍手、反复做某种固定动作、重复句子、讲述同样故事、固定路线游荡、咆哮等，这些不正确、重复的行为可能与眶额回环路和前扣带回皮质损伤有关，也包括基底节和丘脑[24]；强迫行为可以从轻度简单重复性动作进展为更复杂的强迫症。随着前额叶背外侧皮质（DLPFC）退行性变程度逐渐加重，开始出现执行功能、工作记忆和注意力转换障碍等[25]。照料者常反映患者

有收藏癖，且通常收集较脏物品，如垃圾。饮食习惯的改变表现为食物偏好改变、暴饮暴食等。晚近研究显示，与正常对照者或阿尔茨海默病患者相比，行为异常型额颞叶痴呆患者更喜食碳水化合物和糖果，伴体重增加、吞咽困难，其进食增加并非因为饥饿，而是与下丘脑病理改变有关[26]；由于异常进食行为导致患者高密度脂蛋白胆固醇（HDL-C）降低、总胆固醇（TC）/高密度脂蛋白胆固醇比值增加，以及甘油三酯和胰岛素升高等外周胰岛素抵抗现象[27]。因此，行为异常型额颞叶痴呆患者应定期监测进食状况和代谢指标。

行为异常型额颞叶痴呆患者情绪变化表现为情感迟钝和情感反应减弱，或类似轻度躁狂症的情绪高涨[28]。精神症状如幻觉、妄想等较为少见，但若合并运动神经元病或青年期起病经病理证实的FTLD-FUS，伴精神症状的比例可达50%[29-30]。此类患者发病较早（≤40岁），且以丰富的行为症状为主要表现[14]。此外，行为异常型额颞叶痴呆患者与额叶脑卒中患者具有相似的社会认知功能障碍，表现为道德和推理能力受损，且二者道德评判能力损害程度相似。

随着病程进展，约19%的患者可出现心血管功能障碍和体位性低血压等自主神经功能障碍症状，但不能排除心血管自主神经功能障碍，也不能作为行为异常型额颞叶痴呆与阿尔茨海默病的鉴别特点[31]。Carlino等[32]比较不同类型痴呆患者对疼痛的反应，发现额颞叶痴呆患者的疼痛阈值和耐受性均增加，而阿尔茨海默病患者的疼痛耐受性增加、疼痛阈值无变化，这一差异可能与二者受累部位不同有关。仅部分文献报道，额颞叶痴呆患者可伴睡眠障碍，然而，有证据提示，患者相位前移与白天过度嗜睡发病率增加有关[33]。

在上述行为学特征中，社会行为不当、刻板和异常行为、饮食习惯改变是行为异常型额颞叶痴呆区别于阿尔茨海默病的显著特征[34-35]，但在不同病程阶段，其症状谱也有所变化。行为学变化增加与疾病严重程度相关[36]，激越、去抑制、易激惹等症状与体征主要出现在病程晚期，躁动不安和口语亢进则在病程的不同阶段均可出现。发病年龄亦是重要影响因素之一，淡漠在晚发型患者中表现得更为突出[37]，但此观点尚存争议[38]。

四、早期诊断

2011年，FTDC公布新版诊断标准[20]，提出“可能（possible）”、“很可能（probable）”和“确诊（definite）”行为异常型额颞叶痴呆的3项标准，新标准诊断早发型和晚发型行为异常型额颞叶痴呆具有较好的敏感性和特异性[39-41]。

1. 神经心理学诊断　行为异常型额颞叶痴呆早期症状与精神病或其他类型痴呆存在重叠，故诊断较为困难[42]。而行为学评价是其重要诊断方法，而且鉴别诊断行为异常型额颞叶痴呆与阿尔茨海默病的敏感性优于认知功能测验。虽然行为异常型额颞叶痴呆的所有症状在其他类型痴呆中均可出现，但在疾病早期即出现的以行为学改变为主的症状，高度提示行为异常型额颞叶痴呆。基于其以行为损害为主的临床特征，系列知情者量表有助于明确诊断，如神经精神科问卷（NPI）、额叶行为量表（FBI）[43]、额叶系统行为评分（FrSBe）[44]，其中FBI量表较NPI量表信效度更佳。采用FBI量表鉴别诊断行为异常型额颞叶痴呆与阿尔茨海默病，准确率达88.30%[45]。尽管行为异常型额颞叶痴呆患者在病程早期即表现出显著的性格和行为改变，但神经心理学测验仍可正常[46]。其中以简易智能状态检查量表（MMSE）筛查敏感性较差，而改良Addenbrooke认知评价量表（ACE-R）首诊阳性率可达90%，甚至更高[47]。行为异常型额颞叶痴呆患者在疾病早期是否存在执行功能障碍尚存争议[48]。严重的情景记忆障碍被认为是排除标准[20]，但也有10%～15%经病理证实的额颞叶痴呆患者临床表现有严重的遗忘[49]；最近的一项临床研究提示，情景记忆损害在行为异常型额颞叶痴呆患者中也较为常见，经校正疾病严重程度后，与阿尔茨海默病患者情景记忆测验表现无差异[50]。随着疾病进展，前颞叶萎缩、认知域损伤类型与额颞叶痴呆其他亚型间的差异逐渐缩小，认知功能障碍尤与语义性痴呆（SD）临床表现相似。由于行为异常型额颞叶痴呆特异性损害的认知域尚存争议，因此近年来，对其社会认知、情感认同和解决复杂问题能力的研究备受重视[51]。行为异常型额颞叶痴呆患者在病程早期即出现明显的情感认同损害，尤其对负面情绪的识别（恐惧、悲伤、愤怒和厌恶）[52]，但情感识别能力损害并非其所特有，其他痴呆亚型如语义性痴呆也可出现，在静态（照片）或动态（电影）视觉刺激、声音或音乐刺激时，可发现行为异常型额颞叶痴呆患者存在情感认同缺陷，但对情绪刺激所产生的生理反应（通过皮肤电导检测）仍保留[53]。有研究显示，

行为异常型额颞叶痴呆患者还可出现复杂情感损害(如尴尬),社会认知也显著受损(如失礼、缺乏同情心、冷漠、无法区分真诚交流与讽刺)[54-55]。尽管,大多数评价社会认知、情感认同和解决复杂问题能力的测试工具仍处于开发阶段,但今后有望成为行为异常型额颞叶痴呆认知功能评价的一部分。

2.影像学诊断 行为异常型额颞叶痴呆的典型MRI表现为大脑半球前部不对称性额叶和颞叶萎缩,以近中线额部、眶额部和岛叶前部显著,基底节亦可受累[56],但MRI表现正常者不能排除诊断,因为在疾病早期阶段,影像学改变不明显。脑电图除轻度额区慢波外无特征性改变。脑萎缩部位不仅局限于皮质,还包括杏仁核、海马、尾状核、纹状体、壳核、丘脑和下丘脑等皮质下结构,其中杏仁核萎缩是与阿尔茨海默病的鉴别诊断要点之一[57]。灰质萎缩还可预测潜在的病理改变,如双侧背外侧前额叶萎缩提示Pick病,颞叶萎缩分别与FTLD-TDP和FTLD-tau病理改变相关[58],尾状核萎缩更可能与FTLD-FUS病理改变有关[59]。然而,与特征性病理改变相比,萎缩类型与临床特点更具有关联性[60]。近年对行为异常型额颞叶痴呆患者脑白质异常的关注日益增多,扩散张量成像(DTI)能够反映白质纤维束结构的完整性,病程早期即可出现选择性白质纤维束减少,包括上纵束、钩束、扣带束、胼胝体压部和膝部,其中以额叶传导束(胼胝体膝部)、连接额叶与颞叶传导束(钩束)更为显著[61],且可发生于无症状的突变基因携带者,故较结构性MRI能够提供更加准确的诊断信息。DTI可以鉴别行为异常型额颞叶痴呆与阿尔茨海默病、额颞叶痴呆其他亚型。行为异常型额颞叶痴呆患者所表现的淡漠症状与左侧钩束部分各向异性(FA)值下降、去抑制症状与右侧放射冠FA值下降相关[62]。定量影像学技术,如基于体素的形态学分析(VBM)和皮质厚度测定在疾病早期即可发现前扣带回和额叶萎缩[63]。行为异常型额颞叶痴呆患者脑萎缩进展速度较阿尔茨海默病快,后者年进展率为0.50%~4.70%、平均为2.40%,前者年进展率为0.30%~8.00%、平均为3.70%[64]。SPECT和PET有助于诊断与鉴别诊断,行为异常型额颞叶痴呆SPECT显像呈现额叶低灌注,而阿尔茨海默病则为颞顶叶和后扣带回低灌注。尽管,SPECT对早期病理改变较结构性MRI更为敏感,但其准确性和特异性尚待进一步验证[65]。^{18}F-脱氧葡萄糖(^{18}F-FDG)PET在行为异常型额颞叶痴呆病程早期即呈现出额叶低代谢,而阿尔茨海默病则表现为后扣带回低代谢[5,66],^{11}C-匹兹堡复合物B(^{11}C-PIB)PET用于鉴别额颞叶痴呆与阿尔茨海默病的前景十分广泛[67],未来将会出现针对tau蛋白、TDP-43或FUS的PET显像技术应用于临床[68]。

3.生物学标志物 目前尚缺乏明确的额颞叶痴呆或行为异常型额颞叶痴呆生物学标志物,对于疑似常染色体显性遗传者需行基因学检测[69]。目前认为,脑脊液生物学标志物对区分额颞叶痴呆与阿尔茨海默病有一定应用前景:额颞叶痴呆患者脑脊液tau蛋白与β-淀粉样蛋白1~42($A\beta_{1\sim42}$)比值低于阿尔茨海默病患者[70],携带突变*GRN*基因的额颞叶痴呆患者血清GRN水平降低,既往研究业已证实该方法的敏感性和特异性[71]。

五、临床试验

目前,尚无有效的治疗方法能够终止行为异常型额颞叶痴呆的病情进展,现有治疗原则为延缓病情进展、控制临床症状、提高患者生活质量,包括药物治疗和非药物治疗[72]两种方法。药物治疗效果尚不明确,多数研究为小样本、开放标签研究或病例报道(表1)[73-91]。其中大多数药物耐受性较好,如选择性5-羟色胺再摄取抑制药(SSRI)曲唑酮、抗精神病药物安非他命对控制部分行为症状有一定疗效,但多巴胺能药物对行为症状无效。目前尚无能够明确改善认知功能的药物,现有证据均不支持美金刚治疗,胆碱酯酶抑制剂可能加重患者行为症状。考虑到非典型抗精神病药物的锥体外系不良反应,对于有严重激惹症状与体征的患者应慎用。伴帕金森综合征表现者,可考虑应用左旋多巴,尤其适用于疑似存在tau蛋白病理改变或*MAPT*基因突变患者。在一项病因学动物实验中,采用tau蛋白抗体以阻断tau蛋白聚集,结果显示,该抗体具有减少蛋白聚集、改善动物行为学之功效[92]。目前尚处于实验室阶段的研究还包括针对*C9Orf72*基因突变患者的反义寡核苷酸治疗[93],以及增加*GRN*基因突变患者血清GRN水平[94]。

行为异常型额颞叶痴呆患者的非药物治疗与药物治疗同样重要。非药物治疗方案主要来自医师的临床经验,包括一系列结构性活动、功能训练等。家庭教育,舒缓、规律的睡眠作息表,社会工作者介入,运动和语言治疗等均可以改善患者及其家属的生活质量[72]。其中照料者干预是有效途径,但尚无用于行为异常型额颞叶痴呆治疗的文献报道,

表1 行为异常型额颞叶痴呆药物治疗临床试验[73-91]

Table 1. Clinical trials on pharmacological treatments for bvFTD[73-91]

Medication	Dose	Subject	Study design	Combined study outcome	Side effect
Trazodone	Up to 300 mg/d	bvFTD	Double blind crossover RCT	Improved behavior	Fatigue, dizziness, hypotension
Fluvoxamine	50–150 mg/d	bvFTD, SD	Open label	Improved stereotypy	Appetite loss
Paroxetine	Up to 40 mg/d	bvFTD	Open label, open label RCT, double blind crossover RCT	No definite behavioral benefit	Well tolerated
Fluoxetine	20 mg/d	bvFTD	Open label	Improved mood, compulsions and eating disorders	Well tolerated
Sertraline	50–125 mg/d	bvFTD	Open label CT, open label	Improved stereotypy	Well tolerated
Citalopram	40 mg/d	bvFTD	Open label	Improved behavior	Well tolerated
Donepezil	Up to 10 mg/d	bvFTD	Open label, discontinuation of treatment	No benefit	Worse behavioral symptoms
Galantamine	Up to 24 mg/d	bvFTD, PPA	Open label to double blind RCT	No benefit	Mild gastrointestinal symptoms
Rivastigmine	Up to 9 mg/d	bvFTD	Open label CT	Improved behavior	Well tolerated
Quetiapine	Up to 150 mg/d	bvFTD, PNFA, SD	Double blind crossover RCT	No definite benefit	Somnolence
Olanzapine	Up to 10 mg/d	bvFTD	Open label	Improved agitation and anxiety	Somnolence, mild gastrointestinal symptoms
Methylphenidate	40 mg once	bvFTD	Double blind crossover CT	Improved decision making within a few hours	Non-significant blood pressure increase
Dextroamphetamine	20 mg/d	bvFTD, PNFA, SD	Double blind crossover RCT	Improved behavior	Well tolerated
Memantine	Up to 20 mg/d	bvFTD, PNFA, SD	Open label, double blind RCT	No benefit	Well tolerated
Oxytocin	Intranasal oxytocin (24, 48, or 72 IU, 2 times/d)	bvFTD, SD	Double blind RCT	No benefit	Well tolerated

bvFTD, behavioral variant frontotemporal dementia, 行为异常型额颞叶痴呆; SD, semantic dementia, 语义性痴呆; PPA, primary progressive aphasia, 原发性进行性失语; PNFA, progressive non-fluent aphasia, 进行性非流利性失语; RCT, randomized controlled trial, 随机对照试验; CT, controlled trial, 对照试验

多学科干预可以延缓行为异常型额颞叶痴呆的病情进展。

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