·综述·

遗传性弥漫性白质脑病合并轴索球样变研究进展

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【摘要】 遗传性弥漫性白质脑病合并轴索球样变是临床罕见的、进展性中枢神经系统遗传性白质变性病，临床以进行性认知功能障碍、性格改变、精神行为异常和运动障碍等为主要表现；影像学表现为非对称性、斑片状或弥漫性脑白质损害；特征性病理改变为弥漫性脑白质病变，伴显著轴索球样变性；集落刺激因子1受体（*CSF1R*）基因是目前确定的唯一致病基因。本文拟就遗传性弥漫性白质脑病合并轴索球样变的临床研究、分子遗传学和发病机制研究进展进行综述。

【关键词】 脑白质病，进行性多灶性； 弥漫性轴索损伤； 遗传性疾病，先天性； 巨噬细胞集落刺激因子； 综述

Research progress of hereditary diffuse leukoencephalopathy with spheroids

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【Abstract】 Hereditary diffuse leukoencephalopathy with spheroids (HDLS) is a rare and progressive disorder of hereditary white matter degeneration in the central nervous system (CNS). Clinically, the prominent manifestations are progressive cognitive impairment, personality change, mental and behavioral symptoms and movement disorders. Imaging is mainly characterized by asymmetric, patchy or diffuse white matter lesions. Distinctive neuropathology revealed diffuse white matter lesions with marked axonal degenerative spheroids. Colony stimulating factor 1 receptor (*CSF1R*) gene is currently the only pathogenic gene identified. This article reviews the research progress in clinical study, genetics and pathogenesis of the disease.

【Key words】 Leukoencephalopathy, progressive multifocal; Diffuse axonal injury; Genetic diseases, inborn; Macrophage colony-stimulating factor; Review

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遗传性弥漫性白质脑病合并轴索球样变（HDLS）是临床罕见的遗传性中枢神经系统白质变性病，临床表现多样，主要包括性格改变、精神行为异常、认知功能障碍、帕金森样症状和癫痫发作等。1984年，由Axelsson等[1]首次报告并命名。Rademakers等[2]于2011年通过全基因组相关性研究（GWAS）和全外显子组测序（WES），确定位于染色体5q32的集落刺激因子1受体（*CSF1R*）基因是遗传性弥漫性白质脑病合并轴索球样变的致病基因。已报道70余种致病性*CSF1R*基因突变[3-4]。2013年，Nicholson等[5]在色素性脑白质营养不良（POLD）家系中也发现*CSF1R*基因突变。基于两种疾病具有相似的临床表现和病理学特点，即临床和影像学均表现为以额叶功能障碍为主的精神症状和认知损害[6]；病理学表现为遗传性弥漫性白质脑病合并轴索球样变的患者存在与色素性脑白质营养不良相似的色素性巨噬细胞，色素性脑白质营养

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不良患者轴突扩张与遗传性弥漫性白质脑病合并轴索球样变相一致[5-6]，故目前将这两种疾病视为同一疾病谱，即成年发病的白质脑病合并轴索球样变和色素性胶质细胞（ALSP）[3,5-6]。目前，对其确切的发病机制尚不清楚。本文拟就遗传性弥漫性白质脑病合并轴索球样变的临床研究、分子遗传学研究和发病机制研究进展进行综述，以期提高临床对疾病的认识并促进疾病的深入研究。

一、临床研究进展

1.临床表现　遗传性弥漫性白质脑病合并轴索球样变临床表现多样且存在异质性，个体间亦存在显著差异，即使同一家系中携带同一突变的个体之间临床表现也明显不同，且存在疾病外显不全等特点，即部分患者出现早期影像学改变或携带*CSF1R*突变基因而无任何临床表现。发病年龄15～78岁，平均35～40岁；病程1～30年[7-8]。临床首发症状主要是显著的神经精神症状[3,5,9-11]，包括性格和行为改变（如易激惹、攻击行为、缺乏主动性、孤僻、淡漠）、精神症状（如焦虑、抑郁）、进行性认知功能障碍（如计算力、定向力、记忆力减退和执行功能障碍）；随后或同时出现运动障碍和步态障碍，包括非对称性帕金森综合征（如运动迟缓、姿势性震颤、肌强直）[12-13]、锥体束征、步态拖曳等；随着病情进展，逐渐出现皮质功能障碍，包括失用症（如失语、偏盲）[7,14]、癫痫发作[5,9]、共济失调[15]、构音障碍、吞咽困难等；最终丧失运动功能、缄默、长期卧床，死于各种并发症。其他少见症状与体征为痉挛性下肢瘫、四肢瘫或偏瘫[16-17]、肌阵挛[18-19]、严重头痛[20]、舌肌纤颤和萎缩[21]、急性脑卒中[22]、视神经萎缩[23]、眼睑痉挛和非对称性镜像运动表现[24]等。

2.影像学特点　遗传性弥漫性白质脑病合并轴索球样变典型MRI表现为早期双侧、非对称性、局限性T_2WI或FLAIR成像高信号（图1a）和T_1WI低信号，以额叶或额顶叶显著，累及深部脑白质和皮质下脑室周围白质纤维束[7,25-26]；亦可见皮质脊髓束受累，弥漫性脑萎缩和脑室扩大（图1b），伴胼胝体发育不良（图1c）和异常信号（通常认为是疾病早期影像学特征）[7,27-30]。随着病情进展，病灶逐渐融合呈片状，并呈对称性分布。一般不累及皮质下U型纤维、脑干和小脑皮质。研究显示，在*CSF1R*基因缺失性突变类型中，遗传性弥漫性白质脑病合并轴索球样变患者头部MRI脑白质病变严重性评分更高，且与病程呈负相关[26]。此外，亦有研究显示，部分遗传性弥漫性白质脑病合并轴索球样变患者头部CT可见多发点状钙化灶[7,28,31-32]，具有一定诊断价值，但与疾病进展无关[33]。扩散加权成像（DWI）呈小点状高信号，同时伴水分子扩散受限被认为是该病的特征性影像学表现[25]。磁敏感加权成像（SWI）无微出血灶，与遗传性脑小血管病可资鉴别。磁共振波谱（MRS）显示，N-乙酰天冬氨酸（NAA）峰值降低，胆碱（Cho）、乳酸（Lac）和肌醇（mI）峰值升高，且部分无症状性*CSF1R*基因携带者早期即可出现上述代谢改变[19,25,34]。

3.病理学特点　遗传性弥漫性白质脑病合并轴索球样变的尸体解剖学研究结果显示，大体标本可见脑组织广泛萎缩，弥漫性脑白质变性，呈黄褐色、海绵状或胶冻状，胼胝体变薄，皮质下U型纤维和小脑皮质多保留[3,19,27,35]；光学显微镜观察显示，轴索球样变伴色素性胶质细胞，以及弥漫性轴索变性、髓鞘缺失，是特征性病理改变[2-3,5]。组织学形态亦可见反应性胶质细胞增生以及少量富脂质的巨噬细胞和钙化灶[35-36]。免疫组织化学染色显示，轴索肿胀、球样变，髓鞘变薄或消失[36]。超微结构观察可见肿胀、球样变的轴索内含杂乱的神经纤维丝、线粒体和非特异性电子致密物，髓鞘不连续，呈碎片状或缺失[3,35]。

4.诊断　遗传性弥漫性白质脑病合并轴索球样变临床表现多样，且部分呈非典型，故临床极易误诊[18]。加之临床医师对该病的认识不足，其发病率远被低估。如果出现进行性认知功能下降、记忆力减退和人格障碍，结合可疑阳性家族史和典型脑白质改变，可以考虑遗传性弥漫性白质脑病合并轴索球样变，应注意与多种其他遗传性脑白质病变[37]或伴脑白质病变的遗传性脑小血管病[18]等相鉴别。2018年，Konno等[38]提出特异度较高（>96%）的诊断标准。其核心特征包括：（1）发病年龄≤60岁。（2）至少具备以下2种症状与体征，①认知功能障碍或精神症状。②锥体束征。③帕金森病。④癫痫发作。（3）常染色体显性遗传或散发。（4）头部CT和（或）MRI显示，①双侧脑白质病变。②胼胝体变薄。（5）排除导致脑白质病变的其他原因，①血管性痴呆（VaD），多发性硬化（MS）。②脑白质营养不良，如肾上腺脑白质营养不良（ALD）、Krabbe病、异染性脑白质营养不良（MLD）等。其排除依据包括：（1）发病年龄≤10岁。（2）除癫痫发作外，脑卒中样发作≥2次。（3）突出的周围神经病变。其支持依

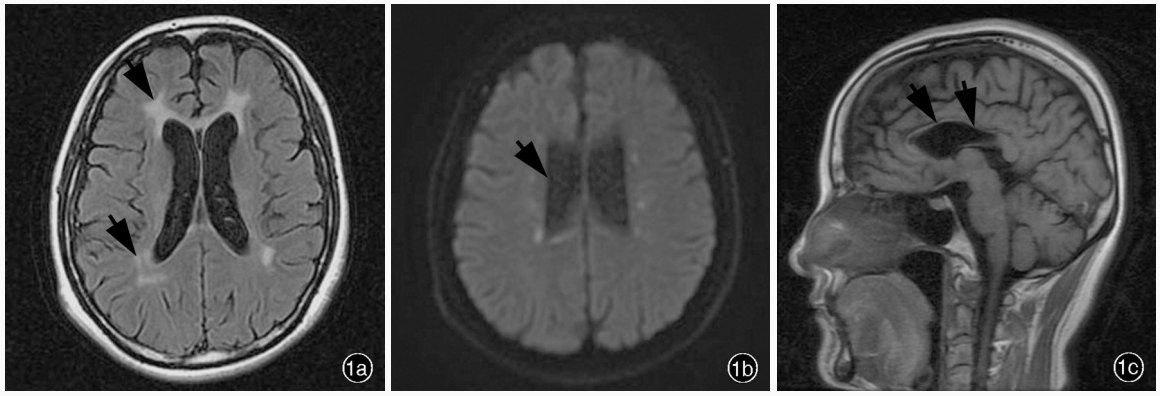

图1 遗传性弥漫性白质脑病合并轴索球样变患者头部MRI检查所见 1a 横断面FLAIR成像显示侧脑室周围高信号影（箭头所示） 1b 横断面DWI显示侧脑室扩大（箭头所示） 1c 矢状位T_1WI显示胼胝体发育不良（箭头所示）

Figure 1 Head MRI findings of HDLS patients Axial FLAIR image showed high-intensity signals in the periventricular white matter (arrows indicate, Panel 1a). Axial DWI showed periventricular enlargement (arrow indicates, Panel 1b). Sagittal T_1WI showed thinning of the corpus callosum (arrows indicate, Panel 1c).

据包括：(1)临床表现或认知功能评价提示额叶功能障碍。(2)病情进展迅速（发病5年内卧床）。(3)头部CT显示脑白质斑点状微小钙化灶。(4)与遗传性弥漫性白质脑病合并轴索球样变相符的病理改变。根据上述特征，分为确定的(definite)诊断，即满足核心特征(2)、(3)和(4)中①，且存在*CSF1R*基因突变；很可能的(probable)诊断，即满足核心特征(1)~(5)，但未行基因检测；可能的(possible)诊断，即满足核心特征(2)中①、(3)和(4)中①，但未行基因检测。

二、分子遗传学机制

*CSF1R*基因包含22个外显子，全长4006 bp，编码细胞表面膜蛋白CSF1R，该蛋白是包含972个氨基酸的多肽，是Ⅲ型受体酪氨酸激酶(RTK)，属于血小板源性生长因子受体(PDGFR)家族。此类受体具有相似的分子结构，包括高度糖基化的胞外配体结合结构域、螺旋跨膜结构域、近膜结构域以及胞内酪氨酸激酶结构域，其被一个插入结构域分为两部分[2,10,39]。酪氨酸激酶结构域高度保守，作为大多数细胞信号转导通路的关键调节因子，与多种疾病如肿瘤、糖尿病、炎症反应、严重骨骼疾病、动脉粥样硬化等相关[40-41]。通过与配体主要是集落刺激因子1(CSF1)相结合，形成受体同源二聚体，磷酸化胞质内酪氨酸残基，进而磷酸化下游分子靶点，激活一系列信号转导通路，主要调节巨噬细胞存活、增殖、分化和功能发挥[42-43]，尤其在中枢神经系统，CSF1R主要表达于小胶质细胞，对神经发生、神经连接和突触重塑等有重要调节作用，还参与其他多种生理功能，如胚胎发育调控、促进血管和淋巴细胞生成，调节心、肺、肾、胰、骨骼等器官发育[44-45]。亦有研究显示，CSF1R还可以与表达于皮肤和前脑的白细胞介素-34(IL-34)结合，发挥相似作用[43]。

遗传性弥漫性白质脑病合并轴索球样变呈常染色体显性遗传，亦可见散发病例报道[9,46-47]。迄今已报道70余种致病性*CSF1R*基因突变[4]，但尚无明确的表型-基因型关联性[48]。*CSF1R*基因突变主要为错义突变、无义突变、插入/缺失、移码突变，亦有剪切位点突变的报道[2-3,27]。绝大多数突变位于酪氨酸激酶结构域（外显子12~22），其中外显子17~20为突变高发区域[2-3]。研究显示，*CSF1R*基因突变可使酪氨酸激酶失活，但不影响受体同源二聚体形成，可能导致无信号转导功能的突变同源二聚体或野生型-突变型异源二聚体形成，从而影响下游靶点磷酸化，即显性负性机制(dominant-negative disease mechanism)[2]。亦有研究显示，与野生型相比，致病性*CSF1R*基因突变在全身各组织的表达水平和自身磷酸化程度均降低[28,41,49]。但位于不同结构域的*CSF1R*基因突变对自身和下游靶点磷酸化的影响不同：位于酪氨酸激酶结构域的致病性突变，其磷酸化信号完全丧失；而位于近膜区或激酶插入区的致病性突变，残留部分磷酸化信号[22,41]。突变的*CSF1R*基因仍表达于细胞膜表面，且不影响野生型*CSF1R*基因结合配体形成二聚体，以及后续功能发挥。Eichler等[50]报告1例*CSF1R*基因突变嵌合体遗传性弥漫性白质脑病合并轴索球样变患者，经异基因造血干细胞移植引入野生型*CSF1R*基因，病情

得到有效控制。上述研究表明，*CSF1R*基因突变可能导致酪氨酸激酶活性部分或完全丧失，从而影响下游靶点信号转导，即功能丧失性机制（loss of function mechanism）。而位于关键结构域的截短突变可能与无义突变介导的mRNA降解有关[28]。

*CSF1R*基因在中枢神经系统主要表达于小胶质细胞[51]，通过与配体结合，对小胶质细胞存活、增殖、分化和功能发挥以及对神经细胞稳态维持均具有调节作用[45,52]。脑组织正常发育过程中，小胶质细胞对突触功能的监测以及与中枢神经系统各种成分直接或间接相互作用，对神经功能的发挥和组织完整性的维持有显著影响[53-54]。近年来，小胶质细胞成为研究热点，其功能异常与多种疾病相关，包括神经变性病［如阿尔茨海默病（AD）、帕金森病（AD）、亨廷顿病（HD）、多发性硬化等］、创伤性病变［如颅脑创伤（TBI）、脊髓病变］、精神障碍（如精神分裂症）等[54-55]。*CSF1R*基因突变患者脑组织中可见小胶质细胞数目和形态改变，分布不均匀，且蛋白合成功能障碍，因此遗传性弥漫性白质脑病合并轴索球样变被认为是一种小胶质细胞病[51,56]，然而小胶质细胞异常如何引起疾病的作用机制尚待进一步阐明。

部分具有典型临床表现、影像学和病理学特征的遗传性弥漫性白质脑病合并轴索球样变患者未发现*CSF1R*基因或其他已知的遗传性脑白质病变相关基因突变[57]，表明该类脑白质病变具有高度遗传异质性，可能由于不同致病基因突变所致，但与趋向于相似的信号转导和代谢通路等机制有关，即可能由于基因突变或各种应激反应引起的小胶质细胞或巨噬细胞免疫应答或炎症反应的异常激活所致。有文献报道，具有典型遗传性弥漫性白质脑病合并轴索球样变临床表现但*CSF1R*基因突变阴性的患者，在条件受限的情况下，应结合临床考虑丙氨酰转移tRNA合成酶2（AARS2）相关脑白质病变的可能[58]。*AARS2*基因编码tRNA合成酶主要负责在线粒体翻译时转运丙氨酸，呈常染色体隐性遗传，与致死性婴幼儿心肌病[59]、进行性白质脑病伴卵巢功能衰竭[60]有关。尚待进一步研究*AARS2*基因相关疾病的表型谱，以提高与遗传性弥漫性白质脑病合并轴索球样变临床表现相似的疾病的鉴别诊断水平。其他疾病如多囊性脂膜性骨发育不良伴硬化性白质脑病（PLOSL）的致病基因*DAP12*和*TREM2*突变，也可以引起类似遗传性弥漫性白质脑病合并轴索球样变的临床和病理表现[57]。

三、治疗与展望

目前尚无针对遗传性弥漫性白质脑病合并轴索球样变的有效治疗方法，通常采取对症支持治疗。拟多巴胺类药或抗抑郁药对帕金森样症状、抑郁等精神症状的有效性尚未证实。随着疾病进展，患者性格、心理和运动功能显著改变，并影响生活质量，应监测患者行为改变并定期进行临床评估，同时辅以适当康复治疗，提高生活质量。有文献报道1例经异基因造血干细胞移植治疗的遗传性弥漫性白质脑病合并轴索球样变患者的病情得到有效控制和延缓[50]，但其长期疗效尚待进一步研究。*CSF1R*基因突变如何影响酪氨酸激酶相关信号转导通路、如何调控小胶质细胞或神经元功能，以及异常小胶质细胞在脑白质病变、轴索和髓鞘病变中扮演的角色，尚待进一步探究，这对于脑白质变性病或小胶质细胞病发病机制的研究具有重要意义，将为探索新的治疗方法提供更多依据。

利益冲突 无

参 考 文 献

[1] Axelsson R, Röyttä M, Sourander P, Akesson HO, Andersen O. Hereditary diffuse leucoencephalopathy with spheroids[J]. Acta Psychiatr Scand Suppl, 1984, 314:1-65.

[2] Rademakers R, Baker M, Nicholson AM, Rutherford NJ, Finch N, Soto-Ortolaza A, Lash J, Wider C, Wojtas A, DeJesus-Hernandez M, Adamson J, Kouri N, Sundal C, Shuster EA, Aasly J, MacKenzie J, Roeber S, Kretzschmar HA, Boeve BF, Knopman DS, Petersen RC, Cairns NJ, Ghetti B, Spina S, Garbern J, Tselis AC, Uitti R, Das P, Van Gerpen JA, Meschia JF, Levy S, Broderick DF, Graff-Radford N, Ross OA, Miller BB, Swerdlow RH, Dickson DW, Wszolek ZK. Mutations in the colony stimulating factor 1 receptor (CSF1R) gene cause hereditary diffuse leukoencephalopathy with spheroids[J]. Nat Genet, 2011, 44:200-205.

[3] Adams SJ, Kirk A, Auer RN. Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP): integrating the literature on hereditary diffuse leukoencephalopathy with spheroids (HDLS) and pigmentary orthochromatic leukodystrophy (POLD)[J]. J Clin Neurosci, 2018, 48:42-49.

[4] Konno T, Kasanuki K, Ikeuchi T, Dickson DW, Wszolek ZK. CSF1R-related leukoencephalopathy: a major player in primary microgliopathies[J]. Neurology, 2018.[Epub ahead of print]

[5] Nicholson AM, Baker MC, Finch NA, Rutherford NJ, Wider C, Graff-Radford NR, Nelson PT, Clark HB, Wszolek ZK, Dickson DW, Knopman DS, Rademakers R. CSF1R mutations link POLD and HDLS as a single disease entity[J]. Neurology, 2013, 80:1033-1040.

[6] Wider C, Van Gerpen JA, DeArmond S, Shuster EA, Dickson DW, Wszolek ZK. Leukoencephalopathy with spheroids (HDLS) and pigmentary leukodystrophy (POLD): a single entity[J]? Neurology, 2009, 72:1953-1959.

[7] Konno T, Yoshida K, Mizuno T, Kawarai T, Tada M, Nozaki H,

Ikeda SI, Nishizawa M, Onodera O, Wszolek ZK, Ikeuchi T. Clinical and genetic characterization of adult - onset leukoencephalopathy with axonal spheroids and pigmented glia associated with CSF1R mutation[J]. Eur J Neurol, 2017, 24:37-45.

[8] Sundal C, Baker M, Karrenbauer V, Gustavsen M, Bedri S, Glaser A, Myhr KM, Haugarvoll K, Zetterberg H, Harbo H, Kockum I, Hillert J, Wszolek Z, Rademakers R, Andersen O. Hereditary diffuse leukoencephalopathy with spheroids with phenotype of primary progressive multiple sclerosis[J]. Eur J Neurol, 2015, 22:328-333.

[9] Karle KN, Biskup S, Schüle R, Schweitzer KJ, Krüger R, Bauer P, Bender B, Nägele T, Schöls L. De novo mutations in hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS)[J]. Neurology, 2013, 81:2039-2044.

[10] Stabile C, Taglia I, Battisti C, Bianchi S, Federico A. Hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS): update on molecular genetics[J]. Neurol Sci, 2016, 37: 1565-1569.

[11] Baba Y, Ghetti B, Baker MC, Uitti RJ, Hutton ML, Yamaguchi K, Bird T, Lin W, DeLucia MW, Dickson DW, Wszolek ZK. Hereditary diffuse leukoencephalopathy with spheroids: clinical, pathologic and genetic studies of a new kindred[J]. Acta Neuropathol, 2006, 111:300-311.

[12] Lynch DS, Jaunmuktane Z, Sheerin UM, Phadke R, Brandner S, Milonas I, Dean A, Bajaj N, McNicholas N, Costello D, Cronin S, McGuigan C, Rossor M, Fox N, Murphy E, Chataway J, Houlden H. Hereditary leukoencephalopathy with axonal spheroids: a spectrum of phenotypes from CNS vasculitis to parkinsonism in an adult onset leukodystrophy series[J]. J Neurol Neurosurg Psychiatry, 2016, 87:512-519.

[13] Sundal C, Fujioka S, Van Gerpen JA, Wider C, Nicholson AM, Baker M, Shuster EA, Aasly J, Spina S, Ghetti B, Roeber S, Garbern J, Tselis A, Swerdlow RH, Miller BB, Borjesson - Hanson A, Uitti RJ, Ross OA, Stoessl AJ, Rademakers R, Josephs KA, Dickson DW, Broderick D, Wszolek ZK. Parkinsonian features in hereditary diffuse leukoencephalopathy with spheroids (HDLS) and CSF1R mutations[J]. Parkinsonism Relat Disord, 2013, 19:869-877.

[14] Lapalme-Remis S, Warman Chardon J, Bourque PR, Oboudiyat C. Diffuse leukoencephalopathy with spheroids presenting as primary progressive aphasia[J]. Neurology, 2016, 86:1464-1465.

[15] Keegan BM, Giannini C, Parisi JE, Lucchinetti CF, Boeve BF, Josephs KA. Sporadic adult - onset leukoencephalopathy with neuroaxonal spheroids mimicking cerebral MS[J]. Neurology, 2008, 70:1128-1133.

[16] Prieto - Morin C, Ayrignac X, Ellie E, Tournier - Lasserve E, Labauge P. CSF1R - related leukoencephalopathy mimicking primary progressive multiple sclerosis[J]. J Neurol, 2016, 263: 1864-1865.

[17] Kleinfeld K, Mobley B, Hedera P, Wegner A, Sriram S, Pawate S. Adult-onset leukoencephalopathy with neuroaxonal spheroids and pigmented glia: report of five cases and a new mutation[J]. J Neurol, 2013, 260:558-571.

[18] Sundal C, Lash J, Aasly J, Øygarden S, Roeber S, Kretzschman H, Garbern JY, Tselis A, Rademakers R, Dickson DW, Broderick D, Wszolek ZK. Hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS): a misdiagnosed disease entity[J]. J Neurol Sci, 2012, 314:130-137.

[19] Freeman SH, Hyman BT, Sims KB, Hedley - Whyte ET, Vossough A, Frosch MP, Schmahmann JD. Adult onset leukodystrophy with neuroaxonal spheroids: clinical, neuroimaging and neuropathologic observations[J]. Brain Pathol, 2009, 19:39-47.

[20] Granberg T, Hashim F, Andersen O, Sundal C, Karrenbauer VD. Hereditary diffuse leukoencephalopathy with spheroids: a volumetric and radiological comparison with multiple sclerosis patients and healthy controls[J]. Eur J Neurol, 2016, 23:817-822.

[21] Marotti JD, Tobias S, Fratkin JD, Powers JM, Rhodes CH. Adult onset leukodystrophy with neuroaxonal spheroids and pigmented glia: report of a family, historical perspective, and review of the literature[J]. Acta Neuropathol, 2004, 107:481-488.

[22] Konno T, Miura T, Harriott AM, Mezaki N, Edwards ES, Rademakers R, Ross OA, Meschia JF, Ikeuchi T, Wszolek ZK. Partial loss of function of colony-stimulating factor 1 receptor in a patient with white matter abnormalities[J]. Eur J Neurol, 2018, 25:875-881.

[23] Shu Y, Long L, Liao S, Yang J, Li J, Qiu W, Yang Y, Bao J, Wu A, Hu X, Lu Z. Involvement of the optic nerve in mutated CSF1R - induced hereditary diffuse leukoencephalopathy with axonal spheroids[J]. BMC Neurol, 2016, 16:171.

[24] Traschutz A, Hattingen E, Klockgether T, Paus S. Mirror movements and blepharoclonus as novel phenomena in hereditary diffuse leukoencephalopathy with spheroids[J]. Parkinsonism Relat Disord, 2018.[Epub ahead of print]

[25] Bender B, Klose U, Lindig T, Biskup S, Nagele T, Schols L, Karle KN. Imaging features in conventional MRI, spectroscopy and diffusion weighted images of hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS)[J]. J Neurol, 2014, 261:2351-2359.

[26] Sundal C, Van Gerpen JA, Nicholson AM, Wider C, Shuster EA, Aasly J, Spina S, Ghetti B, Roeber S, Garbern J, Borjesson-Hanson A, Tselis A, Swerdlow RH, Miller BB, Fujioka S, Heckman MG, Uitti RJ, Josephs KA, Baker M, Andersen O, Rademakers R, Dickson DW, Broderick D, Wszolek ZK. MRI characteristics and scoring in HDLS due to CSF1R gene mutations[J]. Neurology, 2012, 79:566-574.

[27] Kawakami I, Iseki E, Kasanuki K, Minegishi M, Sato K, Hino H, Shibuya K, Fujisawa K, Higashi S, Akiyama H, Furuta A, Takanashi M, Li Y, Hattori N, Mitsuyama Y, Arai H. A family with hereditary diffuse leukoencephalopathy with spheroids caused by a novel c.2442+2T>C mutation in the CSF1R gene[J]. J Neurol Sci, 2016, 367:349-355.

[28] Konno T, Tada M, Tada M, Koyama A, Nozaki H, Harigaya Y, Nishimiya J, Matsunaga A, Yoshikura N, Ishihara K, Arakawa M, Isami A, Okazaki K, Yokoo H, Itoh K, Yoneda M, Kawamura M, Inuzuka T, Takahashi H, Nishizawa M, Onodera O, Kakita A, Ikeuchi T. Haploinsufficiency of CSF - 1R and clinicopathologic characterization in patients with HDLS[J]. Neurology, 2014, 82:139-148.

[29] Kinoshita M, Kondo Y, Yoshida K, Fukushima K, Hoshi K, Ishizawa K, Araki N, Yazawa I, Washimi Y, Saitoh B, Kira J, Ikeda S. Corpus callosum atrophy in patients with hereditary diffuse leukoencephalopathy with neuroaxonal spheroids: an MRI-based study[J]. Intern Med, 2014, 53:21-27.

[30] Kondo Y, Kinoshita M, Fukushima K, Yoshida K, Ikeda S. Early involvement of the corpus callosum in a patient with hereditary diffuse leukoencephalopathy with spheroids carrying the de novo K793T mutation of CSF1R[J]. Intern Med, 2013, 52:503-506.

[31] Gore E, Manley A, Dees D, Appleby BS, Lerner AJ. A young-onset frontal dementia with dramatic calcifications due to a novel CSF1R[J]. Neurocase, 2016, 22:257-262.

[32] Konno T, Broderick DF, Mezaki N, Isami A, Kaneda D, Tashiro Y, Tokutake T, Keegan BM, Woodruff BK, Miura T, Nozaki H, Nishizawa M, Onodera O, Wszolek ZK, Ikeuchi T. Diagnostic value of brain calcifications in adult-onset leukoencephalopathy with axonal spheroids and pigmented glia[J]. AJNR Am J Neuroradiol, 2017, 38:77-83.

[33] Fujioka S, Broderick DF, Sundal C, Baker MC, Rademakers R, Wszolek ZK. An adult-onset leukoencephalopathy with axonal spheroids and pigmented glia accompanied by brain calcifications: a case report and a literature review of brain calcifications disorders[J]. J Neurol, 2013, 260:2665-2668.

[34] Abe T, Kawarai T, Fujita K, Sako W, Terasawa Y, Matsuda T, Sakai W, Tsukamoto-Miyashiro A, Matsui N, Izumi Y, Kaji R, Harada M. MR spectroscopy in patients with hereditary diffuse leukoencephalopathy with spheroids and asymptomatic carriers of colony-stimulating factor 1 receptor mutation[J]. Magn Reson Med Sci, 2017, 16:297-303.

[35] Riku Y, Ando T, Goto Y, Mano K, Iwasaki Y, Sobue G, Yoshida M. Early pathologic changes in hereditary diffuse leukoencephalopathy with spheroids[J]. J Neuropathol Exp Neurol, 2014, 73:1183-1190.

[36] Jin C, Washimi Y, Yoshida K, Hashizume Y, Yazawa I. Characterization of spheroids in hereditary diffuse leukoencephalopathy with axonal spheroids[J]. J Neurol Sci, 2015, 352:74-78.

[37] Tillema JM, Renaud DL. Leukoencephalopathies in adulthood[J]. Semin Neurol, 2012, 32:85-94.

[38] Konno T, Yoshida K, Mizuta I, Mizuno T, Kawarai T, Tada M, Nozaki H, Ikeda SI, Onodera O, Wszolek ZK, Ikeuchi T. Diagnostic criteria for adult-onset leukoencephalopathy with axonal spheroids and pigmented glia due to CSF1R mutation[J]. Eur J Neurol, 2018, 25:142-147.

[39] Lemmon MA, Schlessinger J. Cell signaling by receptor tyrosine kinases[J]. Cell, 2010, 141:1117-1134.

[40] He L, Hristova K. Physical-chemical principles underlying RTK activation, and their implications for human disease[J]. Biochim Biophys Acta, 2012, 1818:995-1005.

[41] Pridans C, Sauter KA, Baer K, Kissel H, Hume DA. CSF1R mutations in hereditary diffuse leukoencephalopathy with spheroids are loss of function[J]. Sci Rep, 2013, 3:3013.

[42] Nandi S, Gokhan S, Dai XM, Wei S, Enikolopov G, Lin H, Mehler MF, Stanley ER. The CSF-1 receptor ligands IL-34 and CSF-1 exhibit distinct developmental brain expression patterns and regulate neural progenitor cell maintenance and maturation[J]. Dev Biol, 2012, 367:100-113.

[43] Chitu V, Gokhan S, Nandi S, Mehler MF, Stanley ER. Emerging roles for CSF-1 receptor and its ligands in the nervous system[J]. Trends Neurosci, 2016, 39:378-393.

[44] Chitu V, Stanley ER. Regulation of embryonic and postnatal development by the CSF-1 receptor[J]. Curr Top Dev Biol, 2017, 123:229-275.

[45] Pixley FJ, Stanley ER. CSF-1 regulation of the wandering macrophage: complexity in action[J]. Trends Cell Biol, 2004, 14:628-638.

[46] Wu L, Liu J, Sha L, Wang X, Li J, Dong J, Jia J. Sporadic cases with novel mutations and pedigree in hereditary leukoencephalopathy with axonal spheroids[J]. J Alzheimers Dis, 2017, 56:893-898.

[47] Mateen FJ, Keegan BM, Krecke K, Parisi JE, Trenerry MR, Pittock SJ. Sporadic leucodystrophy with neuroaxonal spheroids. Persistence of DWI changes and neurocognitive profiles: a case study[J]. J Neurol Neurosurg Psychiatry, 2010, 81:619-622.

[48] Guerreiro R, Kara E, Le Ber I, Bras J, Rohrer JD, Taipa R, Lashley T, Dupuits C, Gurunlian N, Mochel F, Warren JD, Hannequin D, Sedel F, Depienne C, Camuzat A, Golfier V, Du Boisguéheneuc F, Schottlaender L, Fox NC, Beck J, Mead S, Rossor MN, Hardy J, Revesz T, Brice A, Houlden H. Genetic analysis of inherited leukodystrophies: genotype-phenotype correlations in the CSF1R gene[J]. JAMA Neurol, 2013, 70:875-882.

[49] Hiyoshi M, Hashimoto M, Yukihara M, Bhuyan F, Suzu S. M-CSF receptor mutations in hereditary diffuse leukoencephalopathy with spheroids impair not only kinase activity but also surface expression[J]. Biochem Biophys Res Commun, 2013, 440:589-593.

[50] Eichler FS, Li J, Guo Y, Caruso PA, Bjonnes AC, Pan J, Booker JK, Lane JM, Tare A, Vlasac I, Hakonarson H, Gusella JF, Zhang J, Keating BJ, Saxena R. CSF1R mosaicism in a family with hereditary diffuse leukoencephalopathy with spheroids[J]. Brain, 2016, 139:1666-1672.

[51] Tada M, Konno T, Tada M, Tezuka T, Miura T, Mezaki N, Okazaki K, Arakawa M, Itoh K, Yamamoto T, Yokoo H, Yoshikura N, Ishihara K, Horie M, Takebayashi H, Toyoshima Y, Naito M, Onodera O, Nishizawa M, Takahashi H, Ikeuchi T, Kakita A. Characteristic microglial features in patients with hereditary diffuse leukoencephalopathy with spheroids[J]. Ann Neurol, 2016, 80:554-565.

[52] Mouchemore KA, Pixley FJ. CSF-1 signaling in macrophages: pleiotrophy through phosphotyrosine-based signaling pathways[J]. Crit Rev Clin Lab Sci, 2012, 49:49-61.

[53] Graeber MB, Streit WJ. Microglia: biology and pathology[J]. Acta Neuropathol, 2010, 119:89-105.

[54] Li Q, Barres BA. Microglia and macrophages in brain homeostasis and disease[J]. Nat Rev Immunol, 2018, 18:225-242.

[55] Colonna M, Butovsky O. Microglia function in the central nervous system during health and neurodegeneration[J]. Annu Rev Immunol, 2017, 35:441-468.

[56] Erblich B, Zhu L, Etgen AM, Dobrenis K, Pollard JW. Absence of colony stimulation factor-1 receptor results in loss of microglia, disrupted brain development and olfactory deficits[J]. PLoS One, 2011, 6:E26317.

[57] Fernández-Vega I, Pérez de Heredia-Goñi K, Santos-Juanes J, Goñi Imizcoz M, Zaldumbide L, Zarranz JJ, Ferrer I. Sporadic adult-onset leucodystrophy with axonal spheroids and pigmented glia with no mutations in the known targeted genes[J]. Histopathology, 2016, 68:308-312.

[58] Lynch DS, Zhang WJ, Lakshmanan R, Kinsella JA, Uzun GA, Karbay M, Tüfekçioglu Z, Hanagasi H, Burke G, Foulds N, Hammans SR, Bhattacharjee A, Wilson H, Adams M, Walker M, Nicoll JA, Chataway J, Fox N, Davagnanam I, Phadke R, Houlden H. Analysis of mutations in AARS2 in a series of CSF1R-negative patients with adult-onset leukoencephalopathy with axonal spheroids and pigmented glia[J]. JAMA Neurol, 2016, 73:1433-1439.

[59] Götz A, Tyynismaa H, Euro L, Ellonen P, Hyötyläinen T, Ojala T, Hämäläinen RH, Tommiska J, Raivio T, Oresic M, Karikoski R, Tammela O, Simola KO, Paetau A, Tyni T, Suomalainen A. Exome sequencing identifies mitochondrial alanyl-tRNA synthetase mutations in infantile mitochondrial cardiomyopathy[J]. Am J Hum Genet, 2011, 88:635-642.

[60] Dallabona C, Diodato D, Kevelam SH, Haack TB, Wong LJ, Salomons GS, Baruffini E, Melchionda L, Mariotti C, Strom TM, Meitinger T, Prokisch H, Chapman K, Colley A, Rocha H, Ounap K, Schiffmann R, Salsano E, Savoiardo M, Hamilton EM, Abbink TE, Wolf NI, Ferrero I, Lamperti C, Zeviani M,

Vanderver A, Ghezzi D, van der Knaap MS. Novel (ovario) leukodystrophy related to AARS2 mutations [J]. Neurology, 2014, 82:2063-2071.

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·临床医学图像·

椎管内（髓内及硬脊膜下）脂肪瘤

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Intraspinal (intramedullary and subdural) lipoma

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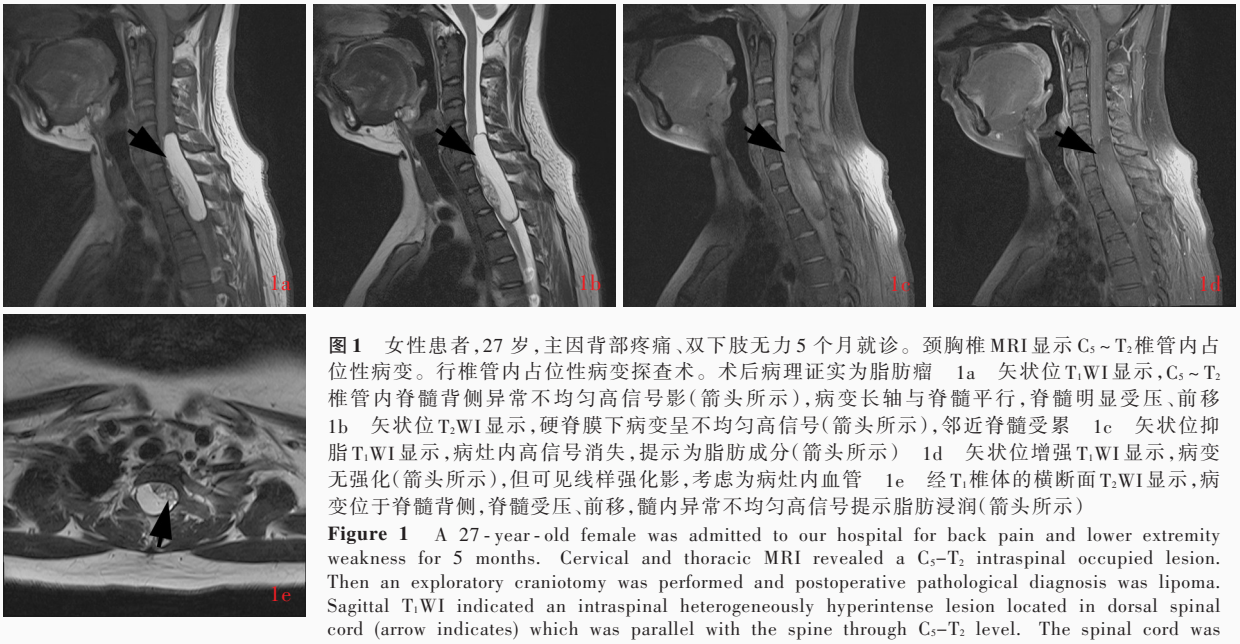

图1 女性患者，27岁，主因背部疼痛、双下肢无力5个月就诊。颈胸椎MRI显示C_5～T_2椎管内占位性病变。行椎管内占位性病变探查术。术后病理证实为脂肪瘤 1a 矢状位T_1WI显示，C_5～T_2椎管内脊髓背侧异常不均匀高信号影（箭头所示），病变长轴与脊髓平行，脊髓明显受压、前移 1b 矢状位T_2WI显示，硬脊膜下病变呈不均匀高信号（箭头所示），邻近脊髓受累 1c 矢状位抑脂T_1WI显示，病灶内高信号消失，提示为脂肪成分（箭头所示） 1d 矢状位增强T_1WI显示，病变无强化（箭头所示），但可见线样强化影，考虑为病灶内血管 1e 经T_1椎体的横断面T_2WI显示，病变位于脊髓背侧，脊髓受压、前移，髓内异常不均匀高信号提示脂肪浸润（箭头所示）

Figure 1 A 27-year-old female was admitted to our hospital for back pain and lower extremity weakness for 5 months. Cervical and thoracic MRI revealed a C_5–T_2 intraspinal occupied lesion. Then an exploratory craniotomy was performed and postoperative pathological diagnosis was lipoma. Sagittal T_1WI indicated an intraspinal heterogeneously hyperintense lesion located in dorsal spinal cord (arrow indicates) which was parallel with the spine through C_5–T_2 level. The spinal cord was compressed severely to the anterior part of spinal canal (Panel 1a). Sagittal T_2WI showed a subdural heterogeneously hyperintense lesion (arrow indicates) with involvement of the adjacent spinal cord (Panel 1b). Sagittal T_1WI with fat suppression showed the hyperintense signal within the lesion disappeared, indicating fatty content (arrow indicates, Panel 1c). Enhanced sagittal T_1WI with fat suppression showed no enhancement of the lesion (arrow indicates), but several linear enhancements which indicated vessels within the lesion (Panel 1d). Axial T_2WI on T_1 level showed the lesion was located in the dorsal spinal cord and spine cord was compressed forward obviously. The abnormal heterogeneously hyperintense signal revealed fatty infiltration (arrow indicates, Panel 1e).

椎管内（髓内及硬脊膜下）脂肪瘤与胚胎期原始脑膜残留和异常脂肪分化相关，若脂肪组织内陷于椎管，扰乱神经沟正常闭合，可合并脊柱裂、脊髓脊膜膨出、脊髓拴系、皮下脂肪瘤和皮毛窦等症状。脂肪瘤可发生于髓内，也可起源于脊膜下方且向外生长形成硬脊膜下脂肪瘤，通常位于脊髓背侧近中线处，累及数个椎体节段。发生于颈胸段椎管者多不伴硬脊膜囊缺损和皮肤异常；发生于腰骶段椎管者多伴硬脊膜缺损，可位于髓内、硬脊膜下和硬脊膜外，常合并脊髓膨出、脊髓脊膜膨出等发育畸形，以及皮下脂肪瘤和皮毛窦等。CT可见特征性极低密度影（脂肪成分CT值-80～-10 HU），边界清晰，可伴钙化，强化后低密度区不增强。硬脊膜下病灶与脊髓长轴平行，邻近硬脊膜下隙增宽，脊髓受压变形、移位。MRI呈短T_1（图1a）、长T_2（图1b）改变，瘤体两侧侧缘呈高和低信号带状影，系化学位移效应所致；抑脂序列可见病灶内高信号脂肪区域被抑制，呈极低或无信号（图1c），具有一定特征性；增强扫描病变无强化，病灶较大时可包绕邻近血管和神经成分，即血管穿过病变，呈线样强化（图1d），亦为特征性改变。病灶向髓内浸润性生长，可见短T_1、长T_2信号的脂肪成分，强度不均匀（图1e）。椎管内病变呈高信号、抑脂序列呈低信号、无强化征象是诊断椎管内脂肪瘤的重要影像学依据，应注意与同样含脂肪成分的皮样囊肿、畸胎瘤相鉴别。T_1WI呈高信号时还应与亚急性期出血性病变、黑色素瘤、肠源性囊肿、表皮样囊肿相鉴别。

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