·罕见病专栏·

中年女性，进行性走路困难35年余——*POLR3A*基因复合杂合突变致HLD7

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【摘要】本文报告1例*POLR3A*基因突变致髓鞘形成不良的脑白质营养不良7型（hypomyelinating leukodystrophy type 7，HLD7）病例。患者为53岁女性，表现为进行性加重的痉挛性步态和构音障碍，并伴部分感觉功能受累，幼儿时期有运动里程碑发育延迟和牙齿发育异常。MRI提示有脑白质病变和小脑萎缩。基因检测提示患者*POLR3A*基因存在复合杂合变异c.928T>A（p.W310R）和c.3295C>T（p.R1099C），该变异位点既往未见报告。本病以对症支持治疗为主。本文通过对该病例的报告及文献回顾，期望提高对HLD7及POLR3-HLD疾病谱系的认识，并为临床诊治提供参考。

【关键词】POLR3A 髓鞘形成不良的脑白质营养不良7型 步态异常 运动发育迟滞 牙齿发育异常 基因突变

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One middle-aged female with progressive walking difficulties for more than 35 years—— a case of HLD7 due to compound heterozygous mutation of *POLR3A* gene. *LI Ling, ZHU Zeyu, CAO Li, TIAN Wotu. Department of Neurology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital,* shanghai 200233, China. Tel: 021-24056187.

【Abstract】This study reported the clinical data of a case of hypomyelinating leukodystrophy type 7 (HLD7) caused by novel mutations in the *POLR3A* gene. The patient was a 53-year-old female with adult-onset progressive spastic gait, dysarthria and partial sensory dysfunction, in combination with delayed motor milestones and abnormal tooth development. MRI showed white matter abnormalities and cerebellar atrophy. Genetic testing identified compound heterozygous mutations c.928T>A(p.W310R)and c.3295C>T(p.R1099C)in *POLR3A* in the patient, which were not previously reported. The main therapy is symptomatic treatment. We aim to improve the awareness and clinical diagnosis of HLD7 and POLR3-HLD spectrum among physicians by case report and literature review.

【Key words】POLR3A Hypomyelinating leukodystrophy type 7 Gait abnormality Motor retardation Hypodontia Genetic mutation

1 病例资料

患者，女，53岁，因“进行性走路困难35年余”就诊，18岁时出现姿势不协调，走路时肩部摆动，左右转弯不能一次完成，跑步速度减慢。26岁分娩后逐渐出现走路不稳，双下肢无力，鞋子磨损以双侧鞋底前侧较明显，症状进行性加重。曾多家医院就诊，走路不稳症状未见明显好转。42岁起，不能独立上下楼梯，需人搀扶。44~46岁期间出现平地行走困难，需人搀扶，同时伴有尿急、尿失禁、尿频（1次/2 h），并出现情绪不稳定，夜间腿部疼痛导致睡眠较差。46岁起，行动需依赖轮椅。53岁起出现明显的入睡困难和早醒，伴有吐词欠清，但反应速度和记忆力尚可。患者目前推助行器可走几步，平躺时平移下肢可，向上移动不能。患者自述4岁学会走路，牙齿发育晚于同龄儿，牙齿稀疏（图1A）。家族史：否认父母近亲婚配和阳性家族史（图1B）。

体格检查：（2014年5月）一般检查及心、胸、腹部查体未见异常，神清对答可，吐词欠清，脑神经查体阴性，双下肢肌张力增高，双上肢肌力5级；左下肢：髂腰肌4，股二头肌3，股四头肌5^-，胫骨前肌4，腓肠肌4^+，右下肢：髂腰肌4，股二头肌3，股四头肌5^-，胫骨前肌4，腓肠肌4^+；双下肢内收

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5级，双下肢外展4⁻级。指鼻试验正常，跟膝胫试验略差，行走呈痉挛步态需搀扶，浅感觉检查未见异常，图形觉、位置觉差，双踝音叉振动觉减退。双上肢腱反射(+)，双下肢膝反射(+++)，踝反射(++++)。髌阵挛(−)，双侧踝阵挛持续(+)，双侧病理征(+)。2021年4月随访，神清，吐词欠清，语速尚可，反应速度、记忆力尚可。下肢肌肉萎缩，双上肢肌力稍下降，平躺时平移下肢可，向上移动不能。跟-膝-胫试验不能配合。

辅助检查：患者分别于46岁和51岁时行头MRI，脑室周围对称性白质异常，胼胝体变薄，小脑萎缩，顶叶欠饱满；胸颈髓MRI示胸髓变细(图1C)。

该患者外周血样本行全外显子测序结果提示*POLR3A*(RNA polymerase III subunit A)基因存在双杂合变异(c.928T>A和c.3295C>T)。家系共分离结果显示双杂合变异分别来自父亲(c.928T>A)和母亲(c.3295C>T)，故患者为*POLR3A*复合杂合突变，符合常染色体隐性遗传规律(图1D)。

本例患者成年期起病，以痉挛性步态和构音障碍为主要临床特点，呈进行性加重，并伴部分感觉功能受累，有运动里程碑发育延迟和牙齿发育异常，影像学提示脑白质病变和小脑萎缩等表现。结合临床表型、辅助检查结果与基因检测结果，诊断为髓鞘形成不良的脑白质营养不良7型

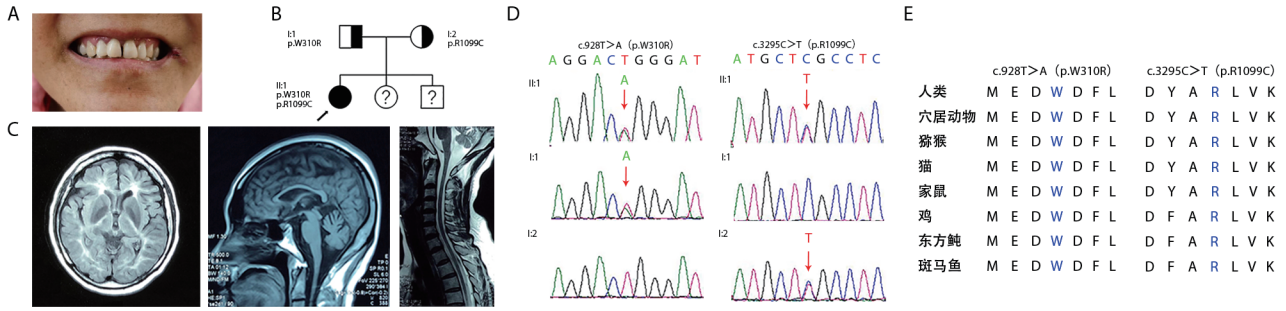

图1　HLD7患者家系图、头颅影像学及基因一代测序结果　图1A示先证者牙齿照片。图1B家系图：先证者(II:1)；父亲(I:1)、母亲(I:2)和其他家庭成员均无相似临床症状。图1C先证者头颅MRI显示脑室周围对称性白质异常，胼胝体变薄，小脑萎缩，顶叶欠饱满；脊髓MRI示胸髓变细。图1D先证者(II:1)存在*POLR3A*基因复合杂合突变，分别来自父亲c.928T>A(p.W310R)和母亲c.3295C>T(p.R1099C)。图1E 7号外显子编码的氨基酸W310和25号外显子编码的氨基酸R1099在不同物种之间呈高度保守。

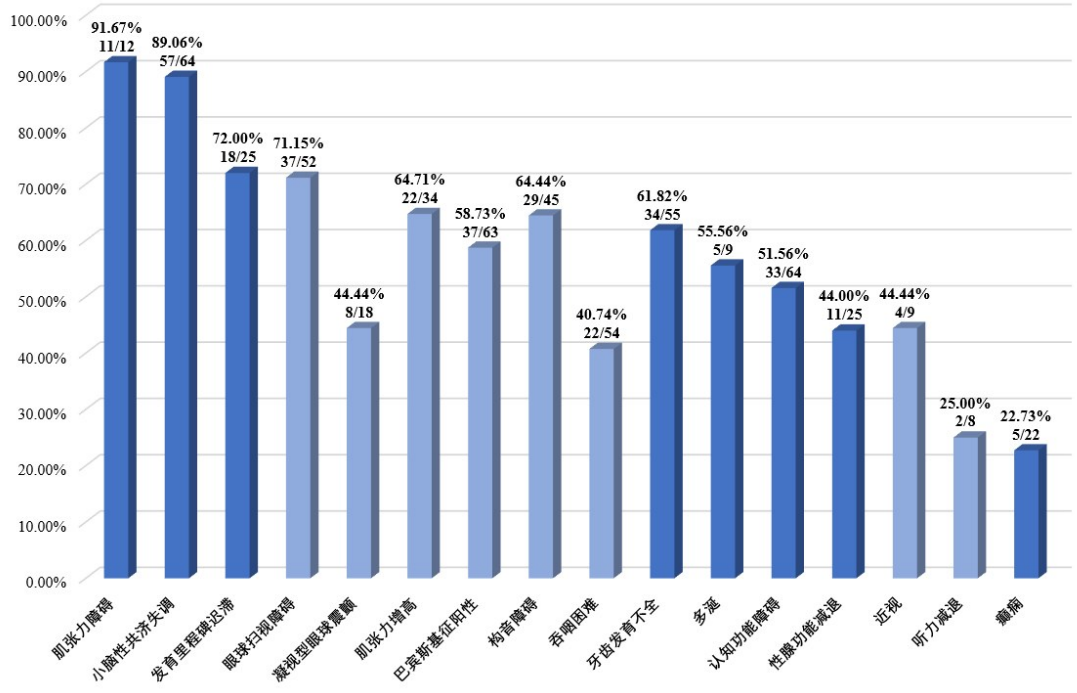

图2　已报告的共计91例*POLR3A*基因突变患者临床特征频率分布柱状图

(hypomyelinating leukodystrophy type 7, HLD7)。

2 讨论

髓鞘形成不良性疾病(hypomyelinating disorders, HMD)是一组以髓鞘形成障碍为特征的遗传性疾病,遗传方式包括X连锁、常染色体显性和常染色体隐性遗传,此外还可能由染色体畸变导致,如18q缺失综合征等。头颅MRI的典型特征为白质持续T_2高信号,可有轻度T_1低、等或高信号[1]。临床表现为在新生儿期或婴儿期出现眼球震颤和发育迟缓,也可能出现肌张力减退、痉挛、锥体外系体征、共济失调或癫痫发作等表现[2]。

HMD于1885年被首次报告,最初命名为PMD(pelizaeus-merzbacher disease)[3]。目前,已发现27种HMD[2, 4-8]。在日本0~19岁群体中HMD的患病率为0.78/10万[9]。其中POLR3相关髓鞘形成不良的脑白质营养不良(Pol III-related hypomyelinating leukodystrophy, POLR3-HLD)最初于2003年被报告[10];随后,在印度、荷兰、加拿大、美国、罗马、日本、中国等也陆续被报道;临床表型谱主要包括运动功能障碍、牙齿发育异常、内分泌功能障碍、近视为主的眼科异常等[2, 11-13]。发病年龄从18个月到17岁不等,多为11~13岁[14-15]。根据主要临床特征可分为以下综合征:4H综合征(hypomyelination, hypodontia, hypogonadotropic hypogonadism):髓鞘脱失、牙齿稀疏和促性腺激素分泌不足;ADDH(ataxia, delayed dentition, and hypomyelination):共济失调、萌牙延迟和髓鞘发育不良;TACH综合征(tremor-ataxia with central hypomyelination):震颤-共济失调伴中枢神经系统髓鞘形成不良;LO综合征(leukodystrophy with oligodontia):脑白质病伴少牙症;HCAHC综合征(hypomyelination with cerebellar atrophy and hypoplasia of the corpus callosum):髓鞘形成不良伴小脑萎缩和胼胝体发育不良[16-18]。POLR3-HLD的致病基因包括*POLR3A*(HLD7型)、*POLR3B*(HLD8型)、*POLR1C*(HLD11型)和*POLR3K*(HLD21型)[19-24]。研究发现,与*POLR3B*突变患者相比,*POLR3A*突变患者起病略晚,但起病后进展迅速,预期寿命更短[12, 25]。而*POLR3K*患者多有严重的消化功能障碍[20]。而大多数*POLR1C*突变患者具有典型POLR3-HLD表现[19, 21],部分病例还存在颅面发育异常,即Treacher Collins综合征(鸟面综合征),其预后较差[26-28]。其中,*POLR3A*基因相关的POLR3-HLD被归类为HLD7。本文对全球已报告的91例HLD7患者进行文献复习,总结其临床特点见图2:其中肌张力障碍最为常见(91.67%),此外还包括小脑性共济失调(89.06%)、发育里程碑迟滞(72.00%)、眼球扫视障碍(71.15%)、眼球震颤(44.44%)、肌张力增高(64.71%)、Babinski征阳性(58.73%)、构音障碍(64.44%)、吞咽困难(40.74%)、牙齿发育不全(61.82%)、多涎(55.56%)、认知功能障碍(51.56%)、低促性腺素性功能减退症(44.00%)、近视(44.44%)、听力障碍(25.00%)和癫痫(22.73%)。

由于几乎所有HLD患者脑白质存在轻度T_2高信号,因而头颅MRI检查对于提示HLD的临床诊断非常重要[29]。4H综合征或POLR3-HLD的MRI特点为视辐射、内囊后肢及丘脑前外侧部分锥体束的T_2低信号,小脑白质轻度T_2高信号,齿状核相对低信号;小脑萎缩常于10岁以内出现,这在其他HMD中较为罕见[29-30]。MRI上,*POLR3B*突变患者的小脑异常更显著,而*POLR3A*突变患者则以白质损害为主[12, 31]。然而,也有研究发现部分*POLR3A*突变患者可没有白质受累或胼胝体变薄、小脑萎缩和脑干萎缩的证据;相反,可能出现纹状体和红核受累。这表明POLR3-HLD的表型谱仍在进一步扩展[32-33]。

*POLR3A*基因共有31个外显子,全球范围已报告了60多个致病性突变,包括错义突变、无义突变、剪接位点突变、插入突变、缺失突变和大片段插入/缺失突变[2]。其中以错义突变最为常见[12, 17, 31-32, 34]。*POLR3A*基因内含子区域突变,可能导致遗传性痉挛性共济失调表型[35-36]。迄今,尚未发现明确的*POLR3A*热点突变[37]。在来自荷兰、加拿大、美国的105名4H综合征患者中,大多数法裔加拿大患者以杂合或纯合形式携带*POLR3A*的c.2015G>A突变(7/10),可能与奠基者效应有关;其余欧洲患者多具有*POLR3B*突变(53/62),其中51例患者具有*POLR3B*的c.1568T>A杂合突变;地中海人群患者多携带*POLR3A*突变[12]。本研究所报告的*POLR3A*基因复合杂合变异c.928T>A(p.W310R)和c.3295C>T(p.R1099C)为错义突变,根据MutationTaster (http://www.mutationtaster.org/)预测结果,c.928T>A和c.3295C>T均为致病性,在1000 Genomes数据库中未发现该突变。W310和R1099在不同物种之间呈高度保守(图1E)。根据ACMG评估和分级指南,这两个变异被评为致病(1PS+1PM+2PP)。

*POLR3A*基因位于10q22.3,其与*POLR3B*和*POLR1C*共同编码RNA聚合酶III复合物(RNA polymerase III, Pol III)的亚基,Pol III是合成非编码小RNA(如5SrRNA和tRNA)过程中的必需酶,这些非编码小RNA进一步参与mRNA翻译过程[24, 38]。目前,致病性*POLR3A*突变导致疾病发生的机制尚未明确。一项研究应用CRISPR-Cas9技术将*POLR3A* c.2554A>G (p.M852V)引入人类不同的细胞系内,并评估其

对Pol III发生、入核、DNA结合、转录和翻译水平的影响，显示在所有细胞模型中，参与神经系统翻译调节的BC200 RNA (BCYRN1)均全程受累；此外，在少突胶质细胞中BC200基因敲除所引起的转录组和蛋白组学变化远大于单纯*POLR3A*基因敲除；编码髓鞘碱性蛋白的MBP基因mRNA水平在*POLR3A*突变细胞中显著降低[39]。因此，BC200 RNA作为*POLR3A*突变的下游效应分子，在少突胶质细胞分子生物学改变和POLR3-HLD进展中扮演重要角色[39]。

本病尚无有效治疗方法，以对症治疗和多学科合作为主，建议由包括儿科神经学家、临床遗传学家、物理治疗师、职业治疗师、言语和语言病理学家、神经心理学家、康复医师、牙医、内分泌学家、眼科医生、耳鼻喉专家和初级保健医师在内的多学科团队提供个性化护理。需要避免服用容易导致窒息的食物，也要避免D2受体阻滞剂类药物（例如氟哌啶醇或利培酮等精神安定药，甲氧氯普胺等抗恶心药物），后者可进一步加剧锥体外系症状[16]。随着高通量测序技术的发展及分子生物学研究的不断深入，POLR3-HLD的表型谱与发病机制有望被进一步揭示。

3 点评

本文报告1例由*POLR3A*基因复合杂合突变导致的HLD7的罕见病例，并对HMD及POLR3-HLD进行文献回顾与总结。临床实践中，对于慢性起病、进行性加重的痉挛步态，伴牙齿发育异常和运动里程碑发育迟滞，MRI提示有脑白质和小脑异常者，应首先考虑进行HLD相关基因筛查。在临床表型上，尤要注意与痉挛性截瘫相鉴别；进一步结合影像学发现，则需与其他先天性或获得性白质脑病相鉴别，尤其是各种脑白质营养不良等。基因检测可为疾病分型和确诊提供重要帮助。

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