

• 病例报告 •

PANK2 突变致非典型泛酸激酶相关神经变性 1 例并文献复习

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A case of atypical pantothenate kinase-associated neurodegenerative disease caused by PANK2 mutation and literature review

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泛酸激酶相关神经变性(pantothenate kinase-associated neurodegeneration, PKAN)是一种罕见的常染色体隐性遗传病,由位于染色体20p13上的泛酸激酶2(pantothenate kinase2, PANK2)基因突变引起,导致铁在大脑基底节区域异常沉积,引发锥体外系症状、言语障碍、精神症状、认知功能减退和视网膜色素变性等。本文报道1例成年发病的非典型PKAN患者,该患者以精神障碍为首发症状,后出现肌张力障碍、构音障碍、步态异常、肢体震颤等临床表现。神经影像学表现为典型“虎眼征”。通过全外显子基因测序,发现该患者PANK2NM_1386393.1:c.1172T>A (p.Ile391Asn)/c.1039G>C (p.Asp347His)

杂合突变。此外,结合以往的文献报道,综述了PKAN的发病机制、遗传特征、临床表现、影像学特点以及治疗策略。

1 病例资料

患者,男,31岁,6年前逐渐出现性格改变和睡眠障碍,至苏州市广济医院就诊,诊断为“抑郁症”。后逐渐出现口齿欠清、反应迟钝,仍未予重视。近2年来,患者言语不清进行性加重,反应迟钝伴记忆力减退,出现行走不稳伴频繁跌倒,偶有双上肢不自主抖动,影响日常生活及活动,遂于2024年6月至南京医科大学附属苏州市立医院就诊。该患者无相关家族史,父母非近亲结婚。体格检查:神志清,精神一般,言语欠清,查体合作,记忆力、计算力稍减退,视力正常,双侧瞳孔等大等圆,直径3.0 mm,对光反射灵敏,眼球运动可,角膜未见K-F环,无面舌瘫。颈项强直,四肢肌力正常,肌张力增高,双上肢可见不自主运动,宽基步态,明显共济运动障碍,双

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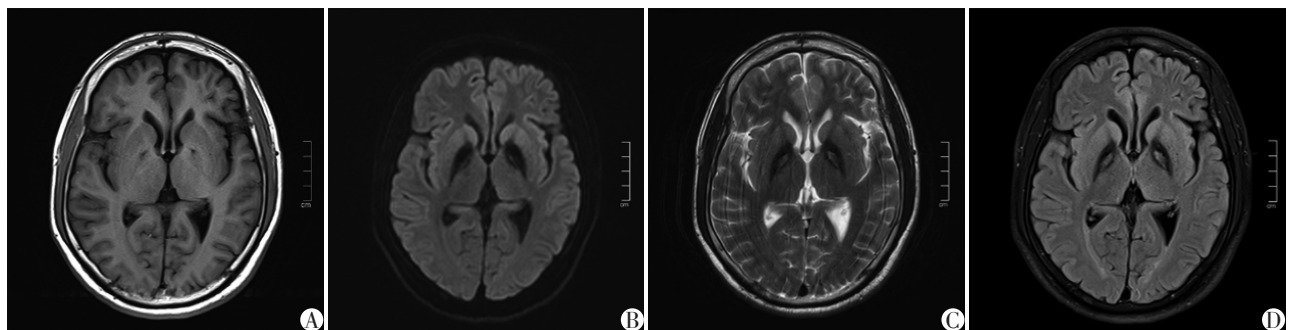
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下肢腱反射亢进, 双侧病理征阴性。实验室检查: ①血尿粪常规、凝血、生化全套、心肌酶谱、血清铁、血铜蓝蛋白、免疫系列、体液免疫、甲状腺功能等均未见明显异常; 脑脊液常规、生化、病原学未见异常。②心脏彩超示室间隔膜部瘤, 腹部超声正常。头颅MRI: 两侧苍白球对称性短T2异常信号, 其前侧内可见长T2信号, 呈典型“虎眼征”(图1)。③汉密尔顿抑郁量表(Hamilton depression scale, HAMD)评分为15分; 简易精神状态评价量表(mini-mental state examination, MMSE)评分为24分/30分。④基因检测: 全外显子基因测序示患者PANK2基因存在

c.1172T>A(p.Ile391Asn)和c.1039G>C(p.Asp347His)复合杂合突变(图2)。入院后予苯海索、巴氯芬等改善肌张力障碍, 奥氮平控制精神症状, 舍曲林抗抑郁, 营养神经等治疗, 患者症状有所改善。

2 讨论

PKAN是脑组织铁沉积性神经变性疾病(neurodegeneration with brain iron accumulation, NBIA)的主要亚型, 又称NBIA I型, 约占50%^[1]。其发病率目前没有准确数据报道, 但多数研究认为在1~3/1 000 000^[2]。该病最早由Hallervorden和Spatz

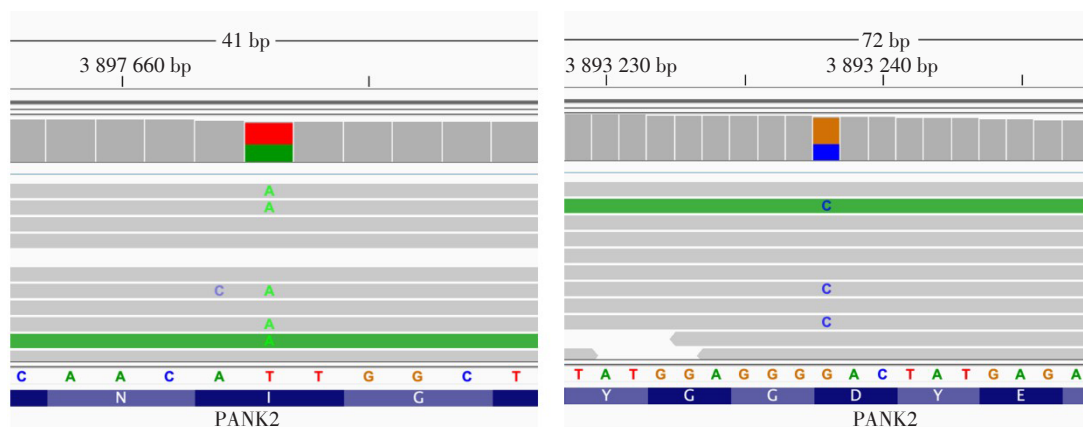


The patient's cranial MRI scanning T1W1(A) showed bilateral pallidum slightly high signal and its anteromedial symmetric low signal, DWI(B), T2W2(C), Flair(D) showed bilateral pallidum low signal and its anteromedial symmetric high signal, which was typical of the "eye of the tiger" sign.

图1 患者头颅MRI呈典型“虎眼征”

Figure 1 The typical "eye of the tiger" sign on the patient's cranial MRI

Gene	Chromosomal location	Mutation information	Zygosity	Inheritance pattern
PANK2	chr20: 3897663	NM-001386393.1: c.1172T>A(p.Ile391Asn)	Heterozygous	AR
PANK2	chr20: 3893228	NM-001386393.1: c.1039G>C(p.Asp347His)	Heterozygous	AR



Whole-exon gene sequencing test of the patient showed missense mutations in c.1172 T>A(chr20.3897663) and c.1 039 G>C in the PANK2 gene (chr20.3893238).

图2 患者全外显子基因测序结果

Figure 2 The result of the patient's whole-exon gene sequencing

于1922年提出,并命名为Hallervorden-Spatz综合征或苍白球黑质红核色素变性,后因伦理争议逐渐被弃用。随着分子遗传学的发展,NBIA谱系已明确了15种致病基因,划分为14种疾病亚型,现采用“突变蛋白相关性神经变性病”命名。PKAN由20p12.3~p13染色体上的PANK2基因突变所致,故命名为泛酸激酶相关性神经变性病^[3]。

PKAN临床表现多样,异质性强,研究发现发病年龄与病情进展相关,起病越晚,生存期可能越长^[4]。根据发病年龄和临床特点,分为早发经典型PKAN和晚发非典型PKAN^[5]。经典型PKAN平均发病年龄3~6岁,临床表现相对一致,以肌张力障碍、步态异常等锥体外系症状为主,常伴锥体束症状、认知障碍及视网膜色素变性,病情进展相对较快且非匀速线性,明显的恶化期和较长的稳定期交替出现,绝大多数患者于发病后10~15年内丧失行走能力。非典型PKAN发病年龄跨度较大,儿童晚期至成年均可发病,以言语障碍和精神症状为特点,可以是首发或唯一临床表现,震颤和帕金森综合征具有特异性,运动损害相对较轻,多无视网膜病变,病情进展缓慢,发病后15~40年内丧失行走能力,有报道称中国患者多为此型^[6]。极少数患者起病早但病程进展慢或起病晚而进展快,有些学者将其归类为“中间型”^[7]。一项关于亚洲人和白种人PKAN患者临床表型的研究认为其临床表现具有种族差异性,亚洲患者以构音障碍和肌张力障碍常见,认知障碍较少,而白种人临床表现更复杂,锥体束征、精神症状及震颤麻痹更常见^[8]。有报道称非典型PKAN患者中,伴PANK2基因突变者常伴精神症状和言语障碍,而无突变者常无此表现^[9]。本例患者成年起病,以精神症状为首发,主要表现为构音困难、肌张力障碍、姿势异常等,基因检测证实PANK2突变,符合非典型PKAN诊断。

本例患者头颅MRI-T2加权像显示苍白球周边低信号围绕着前内侧高信号,呈典型“虎眼征”。高信号是由于组织水肿和胶质细胞增生所致,低信号则反映此处有铁沉积。尽管铁沉积于苍白球和黑质是明确的病理表现,但其为病因还是后果,目前尚无定论。部分研究认为脂质代谢的改变和/或线粒体以及溶酶体缺陷促使了疾病发生和进展,进而导致铁沉积^[10]。既往多项研究发现疾病早期阶段头颅MR可无“虎眼征”^[11],学者们认为该疾病临床特征早于影像学改变。然而,有研究者发现部分确诊为PKAN的患者,其兄弟姐妹虽无任何临床表现,

但头颅MR可见典型“虎眼征”。Baumeister等^[12]曾报道1例伴PANK2基因突变的经典型PKAN患者,其“虎眼征”在病程中消失了,表明疾病影像学改变与疾病临床症状、病情变化并不一致。既往研究认为PANK2基因突变与“虎眼征”之间存在高度相关性^[13],伴PANK2基因突变者均可见“虎眼征”,阴性患者仅见苍白球低信号。然而目前研究证实这一观点并不绝对,“虎眼征”并非PKAN特异表现,在其他疾病也可见到,且有少部分伴基因突变的PKAN患者始终未见“虎眼征”,也有患者存在“虎眼征”但不伴PANK2基因突变^[14-15]。然而这些都是极罕见的情况,“虎眼征”仍是诊断PKAN必不可少的影像学依据。

本例患者全外显子基因检测显示为PANK2基因复合杂合变异,位于第5外显子1172位碱基T被A替换(T1172A),导致第391位氨基酸由异亮氨酸变为天冬酰胺,位于第3外显子1039位碱基G被C替换(G1039C),导致第347位的天冬氨酸变为了组氨酸。患者所携带的c.1172T>A(p.Ile391Asn)变异为PANK2基因编码区错义变异,目前已在多例神经退行性病变患者中报道,且与本患者临床特征及影像学特征一致,证明此为致病相关变异。另外,与该变异同一氨基酸位置的其他错义变异p.Ile391Thr,也在相关病例中被报道。患者所携带的c.1039G>C(p.Asp347His)变异为错义变异。该变异在大规模人群频率数据库gnomAD中有2例杂合子报道,未见纯合子报道,但目前尚未有文献报道其致病性。PKAN为常染色体隐性遗传,致病基因PANK2位于染色体20p13,主要表达于线粒体,是泛酸生物合成辅酶A(coenzyme A, CoA)过程中的关键调节酶,CoA在能量代谢、脂肪酸代谢、神经递质和谷胱甘肽代谢等多种重要代谢途径中起着核心作用。当PANK2基因突变时,将导致CoA合成受阻、半胱氨酸及其中间产物积聚,这些底物易于在铁离子催化下快速发生氧化,产生自由基并使脂质过氧化等,而对细胞产生毒性作用引起神经元变性坏死^[16]。现已报道100多种PANK2基因突变,具有遗传异质性,包括碱基缺失、重复、插入、无义和错义突变等,以无义和错义突变为主,可以是纯合、杂合或复合杂合突变^[17]。在中国,由于近亲结婚者较少,携带纯合基因突变患者的比例较其他国家明显低。PANK2基因的7个外显子均已检测到变异发生,但其分布是不均匀的,亚洲人集中在第3、4号外显子,而欧洲人突变热点在第6外显子^[8]。这表明PANK2基

因突变存在群体特异性,因此基因型与表型间关系更加复杂。多项研究发现早发经典型PKAN患者都伴有PANK2基因突变,多为无义突变;而晚发非典型PKAN患者只有35%有此突变,且多为错义突变。这可能与无义突变造成蛋白质过早截断而活性完全丧失,错义突变造成氨基酸替代而蛋白活性部分保留相关^[18]。

目前尚无有效方法阻止PKAN病情进展,公认的治疗标准仍侧重于对症治疗,以改善肌张力、缓解症状、减少铁沉积和缓解疾病进程为目标^[19-20]。肌张力障碍患者可能会因病情恶化而严重致残,常采用肌注肉毒素,口服抗胆碱能、巴氯芬、苯二氮卓类药物和其他抗痉挛药物联合治疗。左旋多巴治疗震颤麻痹疗效有限,且易诱发异动症和加重精神症状,通常不推荐使用。舞蹈症状可用喹硫平、奥氮平等控制。精神症状则可用苯二氮卓类药物和选择性5-羟色胺再摄取抑制剂(selective serotonin reuptake inhibitor, SSRI)改善。维生素B5通过提高CoA水平和逆转线粒体功能障碍而用于治疗PKAN患者,可能会改善非典型PKAN患者的步态、言语和思维清晰度,但对于多数经典型PKAN患者治疗效果有限。研究发现使用硼甲酸酯作为替代磷酸泛酸盐来治疗PKAN是安全的,但并未改善患者的日常活动能力^[21]。铁螯合剂如去铁酮可以穿过血脑屏障,降低患者苍白球铁含量^[22],并且安全无不良反应,但不同研究结果存在差异,仍需更多研究来论证。采用脑深部电刺激(deep brain stimulation, DBS)手术治疗,短时间内患者的肌张力障碍就能得到明显改善。但由于该疾病是渐进性的,术后易复发或进展恶化,该方法目前尚存在争议。然而对于药物治疗难以控制症状的患者,仍建议早期行手术治疗^[23]。多种针对该疾病的新疗法已处于研发阶段^[24],期待未来能通过基因治疗或PANK激活剂从根本上控制患者症状、延缓疾病进程和改善预后。

根据发病年龄、临床症状及辅助检查,本病例均符合非典型PKAN诊断。经巴氯芬、苯海索、奥氮平、舍曲林等对症治疗后,患者临床症状有所改善,后续仍需持续随访观察。PKAN具有显著临床异质性和遗传异质性,本研究患者以精神障碍为首发症状,且携带的c.1039G>C(p.Asp347His)变异目前还未有文献报道过,为PKAN的基因型-表型相关性研究提供了新的临床证据。

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所有作者声明无利益冲突。

Conflict of Interests:

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白玉洁进行了文献研究和撰写文章,俞孝天和马博敦协助整合诊疗资料,冯红选负责课题选立,侯晓夏负责文章修改和润色,胡睿瑶参与患者整个诊疗过程,桂千和朱伟制定治疗方案,程庆璋审核稿件,协调沟通及对外联络。

Author's Contributions:

BAI Yujie did literature research and wrote the article. YU Xiaotian and MA Bodun helped integrate diagnosis and treatment materials. FENG Hongxuan was responsible for topic selection. HOU Xiaoxia revised and polished the article. HU Ruiyao participated in the patient's diagnosis and treatment. GUI Qian and ZHU Wei formulated the treatment plan. CHENG Qingzhang reviewed the manuscript and handled coordination and liaison.

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