

· 论著 ·

LIG4综合征临床特点一例报告及文献复习

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【摘要】目的 分析LIG4综合征的临床特点、免疫学、遗传学特点。**方法** 分析一例LIG4综合征病例的临床资料,对患儿及其父母进行二代高通量基因测序,结合国内外文献总结该病的临床特点。**结果** 该患儿临床以生长发育迟缓、阴茎短小入院,有小头畸形、生长迟缓、发育迟滞、鸟样面容、细胞免疫缺陷、骨骼畸形、小阴茎、睾丸缺如的特点,垂体MRI提示垂体柄阻断综合征,生长因子、性激素、甲状腺激素缺乏,基因结果显示LIG4基因存在第2外显子c.1406G>A和c.1882delC复合杂合变异,且c.1882delC既往未见报告。结合复习国内外报告的64例临床、免疫学及基因变异位点。**结论** LIG4综合征临床存在特殊表型及体征,部分患儿可能存在垂体柄阻断,通过对本例病例临床特征及相关文献复习,进一步扩展了LIG4综合征的临床表型及基因谱。

【关键词】 LIG4综合征; 垂体柄阻断综合征; LIG4基因

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Clinical Features and Literature Review of One Case of LIG4 Syndrome

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Abstract: Objective To analyze the clinical, immunological and genetic characteristics of LIG4 syndrome. **Methods** The clinical data of one case of LIG4 syndrome were analyzed, the second generation of high-throughput gene sequencing was performed on the child and his parents, and the clinical characteristics of LIG4 syndrome were summarized by combining with domestic and foreign literatures. **Results** The patient was clinically admitted with growth retardation and penile shortness, with microcephaly, growth retardation, developmental retardation, bird-like visage, cellular immune deficiency, skeletal deformity, micropenis and testicular absence. Pituitary MRI indicated pituitary stem blocking syndrome, growth factor, sex hormone and thyroid hormone deficiency. Gene results showed that LIG4 gene had A complex heterozygous mutation of the second exon c.1406G>A and c.1882delC, and c.1882delC had not been reported in the past. 64 cases of clinical, immunological and genetic variation were reviewed. **Conclusion** LIG4 syndrome has special clinical phenotype and signs, and some children may have pituitary stalk occlusion. By reviewing the clinical characteristics of this case and related literature, the clinical phenotype and gene profile of LIG4 syndrome are further expanded.

Keywords: LIG4 Syndrome; Pituitary Stalk Blocking Syndrome; LIG4 Gene

DNA连接酶IV(Ligase IV 4, LIG4, OMIM#601837) 位于染色体 13.q33-34, 编码911个多肽氨基酸^[1]。DNA连接酶IV(LIG4)综合征(OMIM#606593)该病是由于LIG4 基因突变导致XRCC4/LIG4复合体参与DNA断链末端的比对和缺口填补过程受阻,使DNA损伤修复障碍引起的。临床以小头畸形、异常面部特征、对电离辐射敏感和联合免疫缺陷为特征的异常罕见的常染色体隐性遗传病^[2]。以“LIG4 综合征”为主题词检索中国知网、万方数据库、中国生物医学文献数据库、PubMed数据库中检索,检索到相关文献68篇,共 LIG4 综合征病例63 例(44例非中国人^[3-22], 19例中国人^[23-29]),具有广泛的临床特征。同时伴垂体柄阻断综合征的病例未见报告,本文分析1例以小阴茎就诊的连接酶4综合征的患儿,分析其临床特点、实验室和基因检测结果,并总结相关文献,提高临床医师对该病的认识。

1 资料与方法

患儿,男,10月25天,以“生长发育迟缓、阴茎短小10月”于2020年6月就诊于郑州大学附属儿童医院内分泌遗传代谢科。患儿为G2P1,有宫内发育停滞病史,多次保胎治疗,足月顺产,出生后体重1.8kg,身长40cm,头围29cm,3月体重2.2kg,身长45cm,头围32cm,6月体重2.5kg,身长50cm,头围33cm,9月体重2.9kg,身长52cm,头围34cm,现体重:2.9Kg(<3rd),身长:52.5cm,平素食欲差,现进奶量约360mL/天。4月会竖头,现可独坐,不会独站。患儿父母非近亲结婚,否认家族性、遗传性病史。母孕第一胎因宫内发育停滞自然流

产。体格检查:体重:2.9Kg(<-4SD),身长:52.5cm(<-4SD),BMI 10.5kg/m²,头围约34.5cm。精神反应欠佳,营养不良,全身皮肤苍白,弹性正常,皮下脂肪菲薄约0.2cm,颅缝重叠,前囟已闭,眼窝无凹陷,口唇稍苍白,悬雍垂缺如,鄂弓低平,心肺腹查体无异常,外阴呈男性外观,尿道外口正常,双侧阴囊未触及睾丸,阴茎短小,阴茎约0.8cm×0.4cm,GAD:2.0cm,脊柱无畸形,右手拇指多指畸形,左手拇指侧弯,双足第2、3足趾并趾,活动无受限,四肢末梢暖,四肢肌张力正常。实验室检查:血常规+CRP:白细胞 $3.07 \times 10^9/L \downarrow$,中性粒细胞计数 $1.93 \times 10^9/L \downarrow$,淋巴细胞计数 $0.74 \times 10^9/L \downarrow$,红细胞 $3.25 \times 10^{12}/L \downarrow$,血红蛋白99g/L $\downarrow$,血小板 $153 \times 10^9/L$;淋巴细胞亚群:T淋巴细胞(CD3+)66%,T8淋巴细胞(CD3+CD8+)11%,T4淋巴细胞(CD3+CD4+)48%,NK细胞(CD16+56+)19%,CD4/CD84.52 $\uparrow$,B细胞(CD19+)14%;免疫球蛋白:IgM 0.41g/L,IgG 0.21g/L $\downarrow$,IgA 0.93g/L,补体C4 0.37g/L,补体C31.06g/L,提示免疫功能低;8点促肾上腺皮质激素17.560pg/mL,皮质醇4.24 μ g/dL $\downarrow$;甲轴三项:促甲状腺激素3.47mIU/L 游离三碘甲状腺原氨酸4.26pmol/L $\downarrow$,游离甲状腺素6.52pmol/L $\downarrow$;胰岛素样生长因子:6ng/mL $\downarrow$;基础性轴:卵泡刺激素<0.100mIU/mL,黄体生成素<0.100mIU/mL,睾酮<0.025ng/mL,雌二醇<5.00pg/mL,垂体泌乳25.84ng/mL;LHRH激发后30分卵泡刺激素<0.100mIU/mL,黄体生成素<0.100mIU/mL;60分卵泡刺激素<0.100mIU/mL,黄体生成素<0.100mIU/mL;90分卵泡刺激素<0.100mIU/mL,黄体生成素

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<0.100mIU/mL; HCG激发后睾酮<0.025ng/mL↓; 人抑制素B: 22.40pg/mL↓; 抗苗勒管激素5ng/mL↓; 染色体: 46XY, CNV未见明显异常。睾丸超声: 双侧浅表部位未见典型睾丸声像图; 胸腹部立位片: 左侧12肋缺如、右侧1肋较短小, 提示先天发育异常; 心脏彩超: 卵圆孔未闭三尖瓣少量反流; 盆腔MRI: 未见典型睾丸征象; 头颅MRI: (1)脑白质发育符合8月龄儿, (2)双侧脑沟、脑回略宽大; 垂体MRI: (1)考虑垂体柄阻断综合征, (2)小脑扁桃体下缘变尖, 约达枕骨大孔水平线下2mm。临床诊断: (1)垂体柄阻断综合征, (2)重度营养不良, (3)多指[趾]和并指[趾]畸形, (4)足月小样低体重儿, (5)先天性肋骨缺如(十二肋), (6)46,XY性发育异常(双侧隐睾、小阴茎), (7)免疫功能缺陷根据患儿极度生长迟缓、喂养困难、小头畸形、发育落后、营养不良、小阴茎、睾丸缺如、免疫功能缺陷、多发畸形, 多种垂体激素缺乏、垂体柄阻断, 需行全外显子基因检测。本研究经医院医学伦理委员会批准, 先证者监护人签署知情同意书。二代高通量基因测序:采集患儿(及父母)静脉血2mL, 由我院儿研所进行检

测, 检测结果根据美国医学遗传学和基因组学学院/分子病理学协会(ACMG/AMP)的变异分类指南对统计出的变异结果进行致病性分类。对判断为致病、可能致病及临床意义未明的患者,采用相同变异位点的 Sanger 测序法对患者及父母进行检测。

2 结果

测序结果显示患儿LIG4基因存在第2外显子c.1406G>A和c.1882delC复合杂合变异, 其中c.1406G>A(p.Gly469Glu)为错义变异, 源于母亲, 为HGMD数据库有该位点的相关报告, Clinvar数据库对该位点致病性分析报告为致病变异。c.1882delC(p.Arg628Glyfs*7)为移码突变, 源于父亲, 经检索千人基因组、ESP6500及dbSNP数据库基因变异数据库和相关文献为未报告的新发变异, 其在人群中的变异率极低, 所在区域氨基酸序列高度保守, 为蛋白质的重要组成部分, 临床符合LIG4综合征特点, 根据ACMG指南, 该变异判定为致病性变异。

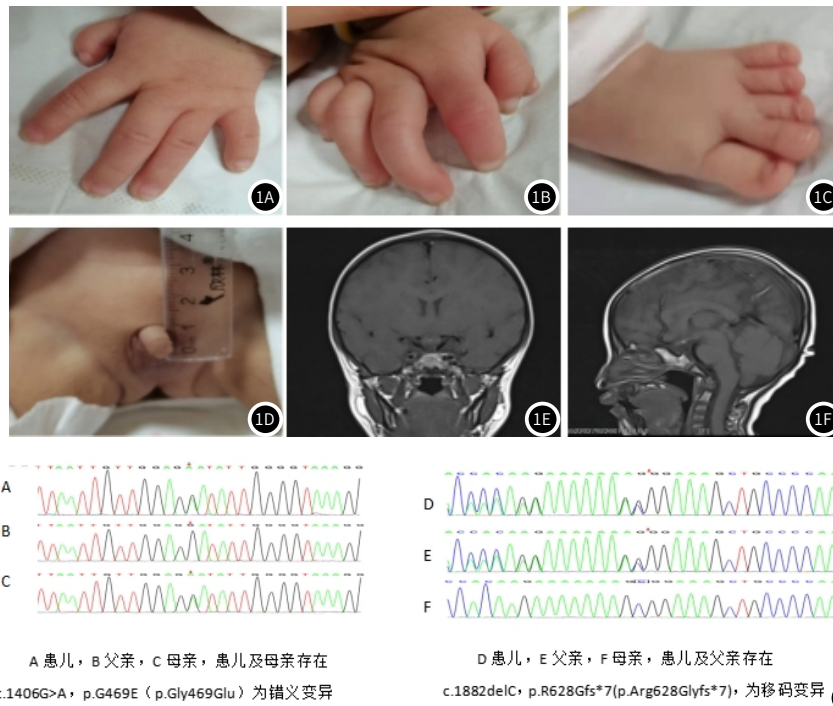


图1A-1F 为患儿体征及垂体MRI。图2 为患儿及父母基因突变谱。

3 讨论

DNA-连接酶IV缺陷病(DNA ligase IV deficiency, LIG4 deficiency)是一种罕见的常染色体隐性遗传疾病, 该病是由于LIG4 基因变异导致XRCC4/LIG4复合体参与DNA断链末端的比对和缺口填补过程受阻, 使DNA损伤修复障碍引起的, 完全缺乏LIG4功能会导致神经元发育受损而导致晚期胚胎死亡^[30-31]。患儿临床表现为辐射敏感、小头畸形、特殊面容、生长发育迟缓、联合免疫缺陷、自身免疫性疾病和肿瘤等。Altmann T在1999年^[5]首次报告。目前全球报告63例, 具有广泛的临床特征。国外报告28例中26例中存在小头畸形, 4例患者的面部特征异常, 被描述为“鸟状”或“塞克尔综合征状”(喙状鼻子, 面部中部突出, 前额萎缩和小颌), 13例患者双侧内眦皱褶和鼻子改变^[4, 6], 8例存在骨骼畸形^[2, 4, 6]。中国报告19例^[23-24, 26-29], 患儿中平均发病年龄在7.4月, 诊断年龄为21.1月, 出生大部分足月小样儿(17/19), 主要以小头畸形(18/19)、生长迟缓(18/19)、特殊面容(10/19)、发育落后(9/19)及免疫缺陷(19/19)为临床特征, 2例存在肿瘤, 一例为白癥, 未见骨骼畸形报告。本例患儿存在小头畸形, 严重矮小, 营养不良, 鸟样面容, 体液免疫缺陷, 感染, 骨骼畸形, 与既往报告一致。本例目前无肿瘤发生, 可能与年龄小有关, 需定期随

访, 减少电离辐射, 警惕肿瘤的发生。

该患儿无睾丸, 阴茎短小, 查垂体核磁提示垂体柄阻断综合征, 存在腺垂体功能减退, 给予补充甲状腺激素及氢化可的松后功能明显好转。行HCG激发后提示睾丸无功能, 睾丸彩超及盆腔核磁未找到睾丸存在, 再既往报告中有1例胎儿存在无睾丸情况^[32], 3例患者存在性腺功能减退, 表现为原发性闭经或未能通过青春期^[4, 6, 14], 且患儿存在极度矮小, 故垂体柄阻断综合征可能为LIG4综合征的又一临床特征。可能LIG4基因突变影响脑垂体的发育, 使睾丸或卵巢在胚胎时期发育异常, 不能形成功能正常的性腺。

LIG4综合征的临床表型与LIG4基因变异的类型相关^[2], 在动物实验中, DNA连接酶IV 的活性完全丧失导致广泛的神经元凋亡, 导致胚胎不能存活^[33], 由此推测其临床严重程度与DNA连接酶IV 的活性相关。小鼠模型(LIG4Y288C)中出现生长迟缓和免疫缺陷^[34, 35], 而LIG4R278H的小鼠模型中主要表现为白血病、细胞放射敏感性增加和发育迟缓, 但没有明显的免疫缺陷^[5-6, 36], 这提示不同基因型可能与临床表型存在一定关系。LIG4综合征是由LIG4基因纯合或复合杂合突变引起的, 迄今LIG4基因共发现39致病突变, 22个错义突变, 14缺失突变, 插入突变2个, 1个调控区突变。国外报告85%的基因型是p.R814X/p.和K424Rfs×20; 面部畸形

在p.R814X/p.K424Rfs×20(7/7)基因型较p.R278/p.K424Rfs*20(0/9)更为常见; p.R814X/p.K424Rfs×20的患者主要缺乏IgG, 患者p.R278/p.K424Rfs×20主要以有IgA和IgM水平下降, 伴轻度畸形, p.R278/p.K424Rfs×20最早出现消化道症状, 如选择性IgA缺乏症患者一样。文献报告LIG4基因C.833G>T(R278L)及C.2440C>T(R814X)突变生长发育正常或轻度受限, 甚至可以无免疫缺陷。中国既往报告的19例中, 18例存在LIG4基因R278L变异, 故与Jiang等报告的中国儿童热点突变LIG4基因R278L一致, 但均有生长发育受限, 反复感染病史, 与国外报告不一致; R278L突变位于ATP结合位点附近。我们预测其功能机制可能与之前报告的相同位置的R278H突变类似, 连接酶与XRCC4之间的相互作用不受影响, 但酶-腺苷酸复合物的形成严重受损, 导致连接酶活性剩余约10%也可能, 通过改变氢键来影响DNA连接酶IV的蛋白质结构^[19], 故基因型和表型之间存在一定联系, 加深我们对本病的理解。但一项报告显示同胞兄妹中, 相同的LIG4基因复合杂合突变本例患儿LIG4基表现不同临床表型, 故同一基因型又存在广泛的临床表现。本例患儿为复合杂合变异, 其中c.1882delC(p.Arg628Glyfs×7)为移码突变, 为未报告的新变异。

本病一旦确诊应尽早定期给予免疫球蛋白改善免疫缺陷, 应用抗生素及抗病毒药物预防反复感染。该患儿存在免疫缺陷, 长期定期应用免疫球蛋白, 未预防应用抗生素。骨髓移植改善免疫功能的根治方法, 骨髓移植对神经系统、生长发育落后的改善不明显, 且移植后继发各种感染导致死亡。故本病要早期诊断, 如存在小头畸形、生长发育迟缓、特殊面容、反复感染的患儿, 应及早完善免疫功能, 如存在免疫缺陷, 高度怀疑本病, 进一步行基因检测明确诊断, 一旦确诊本病, 及早干预, 避免发生反复感染, 改善预后。本病生长发育明显落后, 但由于有肿瘤易感性, 故生长激素应用有待商榷。

总之, LIG4综合征是一种罕见的遗传代谢病, 存在特殊体征及免疫缺陷, 可通过全外显子检测确诊本病。垂体柄阻断综合征可能为本病的有一临床特征。

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