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· 中西医结合临床案例 ·

1例父源性3-甲基巴豆酰辅酶A羧化酶缺乏症的家系分析及护理体会

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摘要: 本文报道1例经新生儿疾病筛查检出的3-甲基巴豆酰辅酶A羧化酶缺乏症(3-MCCD)患儿。患儿因新生儿筛查提示3-羟基异戊酰基肉碱(C5OH)轻度升高被召回,经高通量测序确诊为MCCCI基因c.980C>G父源性杂合突变,其父亲为该位点纯合突变。患儿无明显临床症状,予饮食调控、应激防护及代谢监测,同时构建“患儿—父亲—家庭”三级家系护理管理模式,开展喂养指导、症状预警与居家健康宣教。随访结果显示,患儿生长发育正常、代谢指标稳定,父亲未见代谢失代偿表现,家属照护能力提升。本案提示,新生儿筛查中C5OH轻度升高需重视父源性基因溯源与家系共筛。

关键词: 3-甲基巴豆酰辅酶A羧化酶缺乏症; 父源性; 新生儿疾病筛查; 家系健康管理

Pedigree Analysis and Nursing Experience of a Case of Paternally Derived 3-Methylcrotonyl-CoA Carboxylase Deficiency

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ABSTRACT: This paper reports a case of 3-methylcrotonyl-CoA carboxylase deficiency (3-MCCD) detected through newborn disease screening. The infant was recalled due to a mildly elevated 3-hydroxyisovaleryl carnitine (C5OH) level indicated by newborn screening, and was subsequently confirmed by high-throughput sequencing to carry a paternally derived heterozygous c.980C>G mutation in the MCCCI gene, with the father identified as a homozygous carrier at the same locus. The infant presented with no obvious clinical symptoms and received dietary regulation, stress protection, and metabolic monitoring. Meanwhile, a three-tier family nursing management model of "child - father - family" was established to provide feeding guidance, symptom warning, and home-based health education. Follow-up results showed that the infant achieved normal growth and development with stable metabolic indicators, the father exhibited no signs of metabolic decompensation, and the family's caregiving capacity was significantly improved. This case suggests that mild elevation of C5OH in newborn screening warrants attention to paternal ge-

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netic tracing and pedigree co-screening.

KEY WORDS: 3-methylcrotonyl-CoA carboxylase deficiency; paternal origin; newborn disease screening; pedigree health management

3-甲基巴豆酰辅酶A羧化酶缺乏症(3-Methylcrotonyl-CoA carboxylase deficiency, 3-MCCD)是一种亮氨酸代谢异常的常染色体隐性遗传病,因MCCCI或MCCC2基因突变导致羧化酶活性缺陷,进而引起体内代谢物蓄积及继发性肉碱缺乏^[1]。新生儿串联质谱筛查有助于该病的早期检出,但临床既往对父源性变异重视不足,相关报道较少^[2-3]。本文回顾1例经新生儿疾病筛查发现的父源性MCCCI致病基因携带者及其家系,结合串联质谱(Tandem mass spectrometry, MS/MS)及基因检测结果,总结家系一体化护理管理经验,为父系溯源及同类病例的护理干预提供参考。

1 临床资料

1.1 一般资料

男婴,1个月12天,G₁P₁,37⁺3周顺产,出生体重2900 g,纯母乳喂养,出生时无窒息、黄疸。父母体健,非近亲婚配,无家族遗传病史。出生72 h规范采集足跟血行新生儿遗传代谢病筛查^[4],结果示3-羟基异戊酰肉碱(C5OH):0.89 μmol/L(参考范围:0.06~0.55 μmol/L,下同),随即启动筛查阳性召回流程,复查并完善血液生化指标检测及尿液气相色谱-质谱(Gas chromatography mass spectrometry, GC/MS)分析^[5-6]。

1.2 辅助检查

1.2.1 实验室检查

男婴血常规、肝肾功能、血氨、pH值、电解质、

乳酸及血糖结果均在正常范围内;尿液GC/MS检测示3-羟基异戊酸(3-hydroxyisovaleric acid, 3-HIVA):2.83 μmol/L(参考范围:0.00~6.10 μmol/L),3-甲基巴豆酰甘氨酸(3-methylcrotonylglycine, 3-MCG):0.06 μmol/L(参考范围:0.00~1.05 μmol/L),未见典型有机酸代谢病改变。患儿父母完善串联质谱(MS/MS)检查:母亲C5OH:0.47 μmol/L,血浆游离肉碱(free serum carnitine, C0):17.28 μmol/L(参考范围:8.5~50 μmol/L,以下同);父亲C5OH:29.77 μmol/L, C0:3.64 μmol/L。

1.2.2 基因检测

经知情告知后,母亲拒绝基因检测。采集新生儿及其父亲外周血,参考GRCh37/hg19基因版本,根据美国医学遗传学和基因组学学会(American College of Medical Genetics and Genomics, ACMG)分类标准进行变异致病性分析^[7]。

1.3 诊断与鉴别诊断

1.3.1 诊断

基因分析结果显示,男婴MCCCI基因第10外显子存在c.980C>G(p. Ser327Ter)致病性单杂合突变,父亲MCCCI基因存在c.980C>G(p. Ser327Ter)致病性纯合突变。综合代谢表型与基因结果,诊断新生儿为MCCCI基因c.980C>G(p. Ser327Ter)杂合变异,其父亲为MCCCI基因c.980C>G(p. Ser327Ter)纯合无义变异,详见表1。

表1 家系成员检测结果

检测对象	检测时间	生化表型(μmol/L,参考值)		尿气相质谱	基因结果
		C5OH(0.06~0.55)	C0(8.5~50)	3-HIVA、3-MCG	MCCCI
男婴	3天	0.89	17.36	正常	c.980C>G/p. Ser327Ter杂合
	28天	0.72	20.02	未检测	
父亲	36岁	29.77	3.64	未检测	c.980C>G/p. Ser327Ter纯合
母亲	25岁	0.47	17.28	未检测	未检测

1.3.2 鉴别诊断

需与C5OH升高相关遗传代谢病鉴别:①多种羧化酶缺乏症:包括生物素酶缺乏症(biotinidase deficiency, BTDD, OMIM:609019)、全羧化酶合成酶缺乏症(holocarboxylase synthetase deficiency, HLCS, OMIM:253270)^[8-10]。BTDD由

生物素酶基因(biotinidase gene, BTDD)突变引起生物素酶活性下降,导致人体吸收、利用生物素障碍;HLCS表现为皮肤、神经、呼吸及免疫等多系统非特异性损害,生化和分子检测有助于鉴别诊断。②β-酮硫解酶缺乏症:β-酮硫解酶缺乏症(β-ketothiolase deficiency, BKD, OMIM 203750)又

称线粒体乙酰乙酸辅酶 A 裂解酶缺乏症,由 *ACAT1* 基因变异所致,血液中 C5OH 和 C5:1 水平升高,可引发代谢性酸中毒^[11-12],基因测序有助于鉴别诊断。③3-羟基-3-甲基戊二酰辅酶 A 裂解酶缺乏症:3-羟基-3-甲基戊二酰辅酶 A 裂解酶缺乏症 (3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency, HMGCLD, OMIM 246450) 由 *HMGCL* 基因变异导致,以急性代谢紊乱及神经系统损害为主要表现^[13],基因测序有助于鉴别诊断。

1.4 治疗

患儿为无症状父源性杂合变异,无代谢失代偿表现,采取非药物健康管理:①饮食管理:哺乳期按需哺乳,避免长时间饥饿,辅食采用低亮氨酸均衡饮食;②应激防控:避免感染、饥饿、剧烈运动等诱因,教会家属识别呕吐、嗜睡及肌张力异常等代谢危象先兆;③定期监测:按年龄规律复查串联质谱、血氨、乳酸、肝肾功能及尿有机酸;④家系筛查与遗传咨询:完善家系评估,告知常染色体隐性遗传模式,提供再生育及产前筛查指导。随访至 2023 年 10 月,患儿生长发育与同龄儿童无异,未出现代谢异常。

2 护理

2.1 护理评估

2.1.1 个体评估

①男婴:1 个月 12 天, *MCCCI* 基因杂合变异,

无临床症状;C5OH 轻度升高,存在饥饿、感染及高蛋白饮食诱发代谢危象及生长发育滞后的风险。②父亲:36 岁, *MCCCI* 纯合突变,确诊 3-甲基巴豆酰辅酶 A 羧化酶缺乏症 (3-MCCD); C5OH 29.77 $\mu\text{mol/L}$ (显著升高),血浆游离肉碱 (C0) 3.64 $\mu\text{mol/L}$ (继发性肉碱缺乏),存在急性代谢失代偿风险。

2.1.2 家庭评估

家属对 3-MCCD 疾病认知不足,存在“无症状即无风险”的认知误区;缺乏喂养管理、症状识别及应急处置能力;因疾病遗传风险产生焦虑情绪。

2.2 护理诊断

患儿:①有代谢危象的危险:与基因变异致代谢物潜在堆积有关;②有生长发育迟缓的风险:与饮食管控不当、代谢功能异常潜在影响有关。父亲:①有急性代谢失代偿的危险:与纯合基因突变、继发性肉碱缺乏有关;②健康管理执行无效:与疾病认知缺失、缺乏防控意识有关。家庭:①健康素养不足:与疾病专业信息获取不足有关;②照护技能不足:缺乏饮食管理、危象识别及居家健康指导能力;③焦虑:与疾病遗传风险、长期照护负担有关。

2.3 护理计划

遵循“个体化、分龄段、连续性、家系化”原则,构建“患儿—父亲—家庭”三级护理体系,核心目标及措施详见表 2。

表 2 核心目标及措施

护理对象	核心目标	关键措施框架
患儿	保障生长发育正常,降低代谢危象风险	定期随访监测,饮食与感染防控,家属应急培训
父亲	纠正肉碱缺乏,避免代谢失代偿	定期代谢指标监测,规律生活方式指导
家庭	提升照护能力,缓解焦虑	疾病科普与照护技能培训,心理支持

2.4 护理措施

2.4.1 患儿健康指导

①饮食管理:纯母乳喂养期间按需哺乳,日间喂养间隔 ≤ 4 h,夜间 ≤ 6 h;辅食优先选择低亮氨酸食物(米粉、蔬菜泥及水果泥),少量分次添加优质蛋白,每日蛋白摄入量控制在 1.5~2.0 g/(kg·d)。②风险防控:按时接种疫苗,避免前往人群密集场所,指导家属识别早期异常症状(呕吐、嗜睡、拒奶及肌张力低下),出现不适及时就医。③监测建议:建议每 3~6 个月行串联质谱 (MS/MS) 检测 (C5OH、C0) 及体格发育评估,每年行血生化、尿液气相色谱-质谱 (GC/MS) 检测^[2]。

2.4.2 父亲健康指导

①生活方式干预:三餐规律,可适当加餐,禁食时间不超过 12 h;减少肥肉、动物内脏及高蛋白豆制品等摄入;避免剧烈运动与过度劳累,感冒、腹泻等感染时及时治疗。②代谢监测:每 3~6 个月复查 C5OH、C0、血生化及乳酸;遵医嘱口服左卡尼汀,动态调整剂量^[14]。③症状识别:指导识别代谢异常症状(头晕、乏力、恶心及意识模糊),出现症状时立即补充碳水化合物并及时就医^[15]。

2.5 护理评价

①代谢指标稳定:患儿 C5OH 由初筛 0.89 $\mu\text{mol/L}$ 降至 0.65~0.80 $\mu\text{mol/L}$ 并长期平稳;游

离肉碱(C0)维持在 $18 \sim 22 \mu\text{mol/L}$;血氨、乳酸及尿有机酸全程正常。②生长发育正常:随访至5岁3个月,身高、体重及头围均位于P50~P75,智力、运动、语言发育与同龄儿相仿。③无并发症发生:无抽搐、皮疹、肌张力异常及代谢危象发作。④家庭照护能力提升:家属可独立完成饮食管理、症状识别与应急处理,焦虑情绪明显缓解。

3 结果和随访

3.1 治疗结果

患儿确诊为父源性 *MCCCI* 基因杂合变异,经长期门诊随访健康管理,无临床症状,无器官功能损害,生长发育正常。

3.2 随访

随访方式:以门诊定期随访为主,电话随访为辅。随访内容:①体格发育、神经心理发育评估;②串联质谱(C5OH、C0)、血氨、乳酸及肝肾功能监测;③饮食、感染、应激及症状监测;④父亲代谢指标与健康状况评估。随访结果(2023年10月24日):①患儿体格、智力及运动发育均正常,已正常入托;②C5OH轻度波动但长期稳定,无代谢异常;③无神经系统损伤、皮疹及代谢危象发作;④父亲经规范护理管理暂未发生代谢失代偿,无临床症状;⑤家属掌握疾病知识,完成遗传咨询,明确再生育风险。

4 讨论

3-甲基巴豆酰辅酶A羧化酶缺乏症(3-MCCD)是一种由 *MCCCI* (3q25-q27) 或 *MCCC2* (5q12-q13) 基因突变导致的常染色体隐性遗传代谢病,其特征为血液中C4DC+C5OH升高以及尿液中3-甲基巴豆酰甘氨酸(3-MCG)排泄增加;同时堆积的3-羟基异戊酰辅酶A(3-Hydroxyisovaleryl Coenzyme A, 3-HIV-CoA)与左旋肉碱结合,导致继发性肉碱缺乏^[16]。中国新生儿筛查专家组于2018年在全国32家筛查中心搜集到7819662例筛查结果,共诊断125例3-MCCD,统计患病率为 $1/62557$ ^[17]。

4-3-MCCD临床表型异质性强,基因型与生化表型无法预测病情进展^[18-20],同一家系不同成员的临床表现可从无症状到癫痫、心肌病、智力落后不等,无症状携带者仍存在应激励发代谢危象的风险^[21-23]。因此,必须落实长期随访、饮食管控、感染与饥饿应激防控,将健康管理关口前移。

在护理健康管理层面,本病例采用家系统筹、预防为主的全程干预策略,对父源性3-MCCD携带者

与家系患者开展分层护理。通过优化喂养方案、加强应激因素防控、定期代谢指标随访及应急技能培训,维持患儿代谢稳态,保障生长发育;对父亲开展肉碱监测、饮食运动指导及健康预警教育,减少急性代谢失衡发生。本案例报道以期临床护理实践及同类病例的健康管理提供参考与借鉴。

患者知情同意:病例报告公开得到患者或家属的知情同意。

利益冲突声明:作者声明本文无利益冲突。

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