

·临床研究与实践·

婴儿细胞色素 P450 氧化还原酶缺陷症 1 例
并文献复习

全文二维码

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【摘要】 目的 探讨细胞色素 P450 氧化还原酶缺陷症 (cytochrome P450 oxidoreductase deficiency, PORD) 的临床特征及诊疗策略。 **方法** 回顾性分析深圳市儿童医院骨科收治的 1 例 PORD 患儿临床资料,以“细胞色素 P450 氧化还原酶缺陷症”、“细胞色素 P450 氧化还原酶”、“*POR* 基因”为检索词,检索中国知网、万方医学网相关文献;以“cytochrome P450 oxidoreductase deficiency”、“PORD”、“cytochrome P450 oxidoreductase”、“*POR* gene”为检索词,检索 PubMed、Web of Science 数据库相关文献;检索时限为 2004 年 1 月至 2025 年 1 月;按照纳入与排除标准筛选后进行文献复习,对患儿性别、年龄、所在地区、临床特征、影像学特征及细胞色素 P450 氧化还原酶 (Cytochrome P450 oxidoreductase, *POR*) 基因突变类型进行总结分析。 **结果** 患儿女,7 个月 27 天,于 2023 年 12 月 7 日因“头颅畸形”就诊。典型临床表现包括前额突出、颅缝早闭、鼻梁低平、肘关节周围骨骼融合、阴蒂增大、阴唇部分融合及类固醇激素水平紊乱等。基因检测提示 p. G146fs * 111 和 p. R457H 复合杂合突变,其中 p. G146fs * 111 为首次发现的突变类型。患儿先后接受双侧下颌骨牵引成骨术及颅缝再造术。共纳入 50 篇符合要求文献,报道 169 例 PORD 患儿。其中男 68 例,女 101 例;主要临床症状包括:骨骼畸形 120 例 (120/169, 71.01%)、生殖器畸形 119 例 (119/169, 70.41%)、性激素异常或青春期延迟 134 例 (134/169, 79.29%)、肾上腺功能不全 110 例 (110/169, 65.09%);女性患儿中,有 39 例 (39/101, 38.61%) 存在卵巢囊肿。169 例 PORD 患儿中,携带 p. R457H 92 和 p. A287P50 突变类型者分别有 92 例 (92/169, 54.44%)、50 例 (50/169, 29.59%)。我国的 31 例患儿中,携带 p. R457H 基因者 22 例 (22/31, 70.97%)。 **结论** PORD 是一种罕见的常染色体隐性遗传病,其主要临床症状包括骨骼和生殖器官畸形、肾上腺皮质功能不全等,治疗需多学科协作。p. R457H 可能是我国乃至黄种人的热点突变类型。此外 p. G146fs * 111 为一新发突变,丰富了 *POR* 基因突变谱。

【关键词】 细胞色素 P450 氧化还原酶缺陷症; 诊断; 治疗; 婴儿**基金项目:** 深圳市儿童健康与疾病临床医学研究中心 (szcrc2024_006); 深圳市临床医学研究中心 (20220819113341005)

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Cytochrome P450 oxidoreductase deficiency in an infant: A case report and literature review

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【Abstract】 Objective To explore the clinical characteristics and management strategies of cytochrome P450 oxidoreductase deficiency (PORD). **Methods** The clinical data of one child with PORD admitted to the Department of Orthopedics, Shenzhen Children's Hospital, were retrospectively analyzed. Using the Chinese keywords “cytochrome P450 oxidoreductase deficiency,” “cytochrome P450 oxidoreductase,” and “*POR* gene,” relevant literature was retrieved from China National Knowledge Infrastructure (CNKI) and Wanfang databases. Using the English keywords “cytochrome P450 oxidoreductase deficiency,” “PORD,” “cytochrome P450 oxidoreductase,” and “*POR* gene,” relevant literature was searched in PubMed and Web of Science. The search period was from January 2004 to January 2025. After applying inclusion and exclusion criteria, a literature review was conducted, summarizing patient sex, age, geographic distribution, clinical manifestations, imaging find-

ings, and cytochrome P450 oxidoreductase (*POR*) gene mutation types. **Results** The patient was a 7-month-27-day-old girl who presented on December 7, 2023, with “cranial deformity.” Typical clinical features included frontal bossing, craniosynostosis, depressed nasal bridge, peri-articular elbow skeletal fusion, clitoromegaly, partial labial fusion, and disordered steroid hormone levels. Genetic testing identified compound heterozygous mutations p. G146fs * 111 and p. R457H, among which p. G146fs * 111 represents a newly discovered mutation. The patient underwent bilateral mandibular distraction osteogenesis followed by cranial suture reconstruction. A total of 50 eligible articles were retrieved, reporting 169 children with PORD: 68 males and 101 females. Major clinical manifestations included skeletal malformations in 120 cases (120/169, 71.01%), genital abnormalities in 119 cases (119/169, 70.41%), sex hormone abnormalities or delayed puberty in 134 cases (134/169, 79.29%), and adrenal insufficiency in 110 cases (110/169, 65.09%). Among female patients, ovarian cysts were observed in 39 cases (39/101, 38.61%). Across all reported patients, 92 carried the p. R457H mutation (92/169, 54.44%) and 50 carried p. A287P (50/169, 29.59%). Among the 31 reported patients in China, 22 (22/31, 70.97%) carried the p. R457H mutation. **Conclusions** PORD is a rare autosomal recessive disorder characterized primarily by skeletal and genital malformations and adrenal insufficiency, requiring multidisciplinary management. The p. R457H mutation may represent a hotspot mutation in Chinese and possibly East Asian populations. Additionally, p. G146fs * 111 is a newly identified mutation, expanding the mutation spectrum of the *POR* gene.

【Key words】 Cytochrome P450 Oxidoreductase Deficiency; Diagnosis; Therapy; Infant

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细胞色素 P450 氧化还原酶缺陷症 (cytochrome P450 oxidoreductase deficiency, PORD) 是一种罕见的常染色体隐性遗传病, 自 2004 年首次发现至今, 国内外仅报道 100 余例^[1-3]。细胞色素 P450 氧化还原酶 (cytochrome P450 oxidoreductase, *POR*) 由 680 个氨基酸组成, 其作用是将电子从烟酰胺腺嘌呤二核苷酸磷酸 (nicotinamide adenine dinucleotide phosphate, NADPH) 转移到 50 多种微粒体 P450 酶, 这些酶在类固醇和胆固醇生成以及药物代谢等过程中发挥重要作用^[4-6]。*POR* 基因突变后, 可导致部分 P450 酶活性降低甚至消失, 从而引起一系列临床症状 (如生殖器畸形、类固醇激素异常、男女性不孕不育以及类似 Antley-Bixler 综合征的骨骼畸形等), 且不同 *POR* 基因突变类型所致临床症状也有显著差异, 因此在临床中 PORD 很容易被漏诊和误诊^[7]。本研究回顾性分析深圳市儿童医院骨科收治的 1 例 PORD 患儿临床资料及诊疗过程, 并通过文献复习, 为临床上 PORD 的诊疗提供参考。

病例资料

一、本院患儿临床资料

患儿女, 7 个月 27 天, 2023 年 12 月 7 日因头颅

畸形于深圳市儿童医院就诊。患儿系 G1P1, 胎龄 38⁺₄ 周, 剖宫产娩出, 出生时体重 2 000 g, 否认出生窒息抢救史。生后即发现面部骨骼畸形、前额突出、眼距宽、鼻梁低等, 遂于出生医院行基因检测提示 *POR* 基因突变 (表 1), 其中 p. G146fs * 111 为既往未报道的突变类型。患儿于出生后 1 个月 22 天时因呼吸困难合并吞咽困难, 于当地医院行双侧下颌骨牵引成骨术, 至生后 6 个月 16 天时, 取出牵引装置, 患儿呼吸及吞咽情况明显改善。母亲孕期无特殊药物服用史, 无放射线接触史, 孕中期出现体毛旺盛、痤疮等男性化表现, 分娩后症状逐渐消失。父母均体健, 非近亲婚配, 否认遗传代谢病家族史。本研究已通过深圳市儿童医院伦理委员会审核批准 (202407602), 患儿家属同意并签署知情同意书。

入院体格检查: 身高 67.0 cm, 体重 6 600 g, 营养状态一般, 前囟稍隆起, 左冠状缝已闭合, 前额突出, 呈小短头畸形, 中面部发育畸形, 可见原手术瘢痕。双侧眼球突出, 眼距增宽, 鼻梁低平, 梨形鼻, 双耳廓无畸形, 右耳屏前副耳形成, 左耳中度听力障碍, 右耳轻度听力障碍。双侧肘关节呈约 90° 屈曲挛缩状态, 屈伸活动完全受限, 未触及肱桡关节, 桡骨近端与肱骨骨性融合, 双侧前臂呈旋前中立位, 前臂旋前活动范围约 30°, 无法旋后。双侧腕部

表 1 细胞色素 P450 氧化还原酶缺陷患儿家系 *POR* 基因检测结果

基因	转录本编号	染色体位置	核苷酸变化	氨基酸变化	临床意义	家系来源验证		
						父亲	母亲	患者
<i>POR</i>	NM_000941.2	chr7:75609725	c. 437delG	p. G146fs * 111	致病	无	杂合	杂合
<i>POR</i>	NM_000941.2	chr7:75614497	c. 1370G > A	p. R457H	致病	杂合	无	杂合

注 *POR*:细胞色素 P450 氧化还原酶

未见明显异常。双侧拇指指甲缺如,其余手指及手掌未见畸形,手指活动正常。双侧踇趾趾甲缺如,其余足趾未见明显畸形,足趾活动正常。脊柱及四肢其余部位未见明显异常。外生殖器畸形,表现为阴蒂增大合并阴唇部分融合。颈胸部、腹部及神经系统查体未见明显异常。

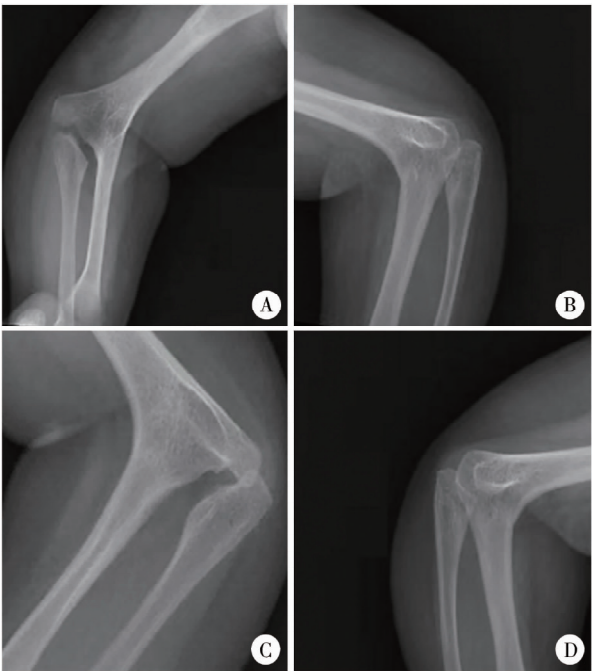
辅助检查:血清皮质醇:0.5 ug/dL(参考范围:0.5 ~ 16.6 ug/dL);睾酮:0.02 ng/dL(参考范围:0.03 ~ 0.48 ng/dL);促肾上腺皮质激素:92.56 pg/mL(参考范围:7.2 ~ 63.3 pg/mL);孕酮:9.6 ng/mL(参考范围:0.20 ~ 1.50 ng/mL);17-羟孕酮:4.3 ng/mL(参考范围:0.29 ~ 1.8 ng/mL);醛固酮、甲状腺功能检查三项、血、尿遗传代谢病筛查均未见异常。术前肝肾功能、生化及凝血功能检查无异常。颅脑 CT 提示:头颅形态失常,头颅指数(cephalic index, CI)约 100%,颌面部比例失常,双侧额骨部分缺失,左侧冠状缝已闭合,人字缝、侧冠状缝及颞顶缝未闭合。双侧肘关节 X 线检查提示:双侧肱骨远端与桡骨近端融合,双侧桡骨骨化中心未显示,双侧尺骨桡骨对合关系不佳(图 1、图 2)。

POR 基因检测结果:存在 c. 437delG (p. G146fs * 111) 和 c. 1370G > A (p. R457H) 复合杂合突变,分别遗传自母亲及父亲。经 Sanger 测序验证,父母为上述突变的杂合携带者且表型正常,符合常染色体隐性遗传模式(表 1、图 3)。

治疗及随访:患儿确诊重度颅缝早闭合并脑积水,予颅缝再造术,手术顺利,术后恢复良好,颅内压恢复至接近正常水平。

二、文献检索情况

检索中国知网、万方医学网、PubMed、Web of Science 数据库。检索关键词:细胞色素 P450 氧化还原酶缺陷症(cytochrome P450 oxidoreductase deficiency)、细胞色素 P450 氧化还原酶(cytochrome P450 oxidoreductase)、*POR* 基因(*POR* gene);检索时间范围为 2004 年 1 月至 2025 年 1 月。文献纳入标准:①临床研究类型文章;②研究对象中包含确诊为 PORD 患儿的文章。排除标准:①内容重复文



注 A:左侧肘关节正位片; B:左侧肘关节侧位片; C:右侧肘关节正位片; D:右侧肘关节侧位片

图 1 细胞色素 P450 氧化还原酶缺陷患儿双侧肘关节 X 线片
Fig. 1 Bilateral elbow radiographs of a child with cytochrome P450 oxidoreductase deficiency

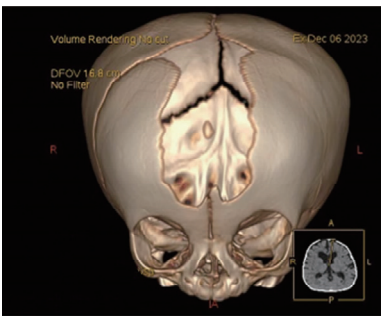


图 2 细胞色素 P450 氧化还原酶缺陷患儿颅脑 CT 三维成像图像

Fig. 2 Three-dimensional cranial CT images of a child with cytochrome P450 oxidoreductase deficiency

章;②缺少临床内容或临床数据不全的文章;③基础研究及综述等非临床研究文章。

共纳入文献 50 篇,排除重复病例后最终纳入 169 例 PORD 患儿(亚洲 80 例,其中中国 31 例),男女比例为 68 : 101;新生儿及儿童 124 例,占比 73.4%(124/169)。临床症状中,骨骼畸形 120 例(120/

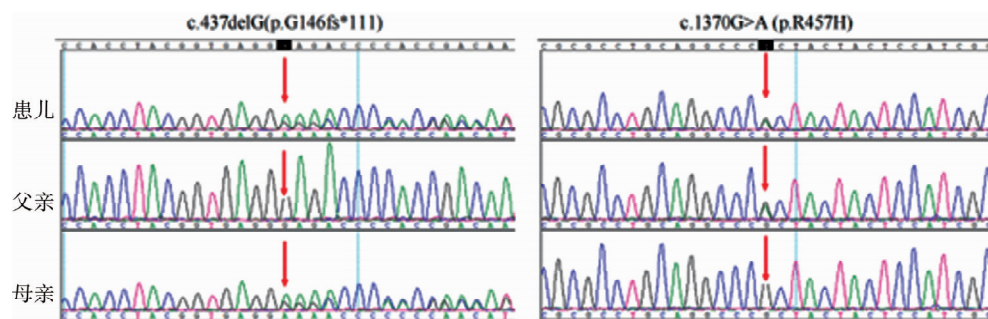


图3 细胞色素 P450 氧化还原酶缺陷患儿及其父母 *POR* 基因变义 Sanger 测序图

Fig. 3 Sanger sequencing results of *POR* gene variants in a child with cytochrome P450 oxidoreductase deficiency and her parents

169, 71.01%)、生殖器畸形 119 例 (119/169, 70.41%)、性激素异常或青春期延迟 134 例 (134/169, 79.29%)、肾上腺功能不全 110 例 (110/169, 65.09%); 另外, 在所有女性患儿中, 有 39 例 (39/101, 38.61%) 发生卵巢囊肿。在已知患儿的所有基因突变类型中, 携带 *p. R457H* 92 和 *p. A287P50* 突变类型的患儿分别为 92 例 (92/169, 54.44%) 和 50 例 (50/169, 29.59%)。中国的 31 例患儿中, 携带 *p. R457H* 基因者 22 例 (22/31, 70.97%)^[4-5,8-55]。

讨 论

Peterson 等^[3]在 1985 年报道了 1 例同时患有 21-羟化酶缺乏症 (21-hydroxylase deficiency, 21-OHD) 和 17 α -羟化酶缺乏症 (17 α -hydroxylase deficiency, 17-OHD) 的先天性肾上腺皮质增生症 (congenital adrenal hyperplasia, CAH) 病例, 但之后的研究发现, 这类病例中编码 21-羟化酶 (21-hydroxylase, CYP21A2) 和 17 α -羟化酶 (17 α -hydroxylase, CYP17A1) 的基因并未发生变异。直至 2004 年, Flück 等^[8]发现 *POR* 基因突变可引起 CYP21A2、CYP17A1 和 CYP19A1 等 P450 酶活性降低, 从而导致此类疾病的发生。目前已知 *POR* 可通过向细胞色素 P450 酶以及一些蛋白质和小分子供应电子, 在生物合成、胆固醇代谢、性激素代谢以及药物和毒素代谢中有重要作用。*POR* 基因突变致使 P450 酶活性降低, 且活性降低程度和 *POR* 基因突变类型相关, 因此 PORD 患者的临床症状也具有显著异质性^[1]。在我们收集的 169 例 PORD 患者中, 染色体性别中男女比例为 68 : 101, 大多数病例为儿童及新生儿。常见临床症状包括: 骨骼畸形 (120/169, 71.01%)、生殖器畸形 (119/169, 70.41%)、性激素异常或青春期延迟 (134/169, 79.29%) 和肾上腺功能不全 (110/169, 65.09%)。在女性患者中, 有 39

例 (39/101, 38.61%) 发生卵巢囊肿。我国共报道 31 例, 这些患者最初确诊年龄较其他国家患者稍偏大, 提示临床对该病的认知与关注度仍需提升。

大多数 PORD 患者存在不同程度类似 Antley-Bixler 综合征的骨骼畸形, 主要包括颅缝早闭、中面部发育不全、蜘蛛指、肘关节骨性融合和股骨弯曲等^[1,4,37]。以往研究发现, 骨骼畸形的严重程度和 *POR* 基因突变类型相关。Krone 等^[21]基于骨骼畸形部位和畸形严重程度建立评分机制, 量化不同 *POR* 基因突变类型的骨骼畸形严重程度, 发现轻中度畸形患者大多为 *POR* 基因错义突变的复合杂合子, 而几乎所有重度畸形患者 *POR* 基因都发生了比如移码突变、剪接突变等可引起主要功能缺陷的突变类型。以往一些研究普遍认为, 相较于其他 *POR* 基因突变类型, *R457H* 导致的骨骼畸形似乎更为严重^[16,31]。但 Dean 等^[1]的研究却发现 *R457H* 纯和子相较于 *R457H* 其他的组合类型以及 *A287P* 突变, 导致骨骼畸形的程度并不严重; 其次这些错义突变 (如 *C569Y*、*G539R*、*L577R* 和 *Y326D* 等) 所致的骨骼畸形也大多较轻。可见此领域仍存在争议, 可能需要更大规模的研究探索。针对 PORD 患者骨骼畸形的发生机制目前尚不明确, 可能和软骨细胞胆固醇合成酶, 如羊毛甾醇 14- α 脱甲基酶 (14 α -demethylase, CYP51A1) 和角鲨烯单氧化酶 (squalene monooxygenase, SQLE) 活性下降导致软骨细胞胆固醇合成受损, 引起细胞分化缺陷和细胞凋亡增加, 从而引起骨骼畸形^[37]。PORD 和安特利-比克斯勒综合征 (Antley-Bixler syndrome, ABS) 患者骨骼畸形症状十分相似, 但是由于治疗策略的差异, 需要临床医师准确鉴别, PORD 患者类固醇激素水平以及生殖器畸形在鉴别诊断中具有重要意义^[7]。

由于 PORD 患者 17,20-裂解酶 (17,20-desmolase, CYP17A1)、芳香化酶 (aromatase, CYP19A1) 及 21-羟化酶 (21-hydroxylase, CYP21A2) 等酶的活性缺

陷,引起睾酮、双氢睾酮的合成以及雄激素向雌激素的转化过程受损,从而导致患者出现不同程度的生殖器畸形^[4,31,44]。男性患儿胎儿期睾酮不足,出生后表现为男性化不足症状(如小阴茎、尿道下裂),部分患儿还会发生隐睾^[4]。女性患儿胎儿期,由于上述的 CYP17A1 功能受限,导致肾上腺产生并堆积大量 17-羟孕酮,激活“后门途径”后,生成活性更强的双氢睾酮^[31]。胎儿出生时出现阴蒂肥大、阴唇融合等外生殖器男性化特征,还会使母体孕期出现明显的男性化特征(如体毛增多、痤疮)。研究发现,相较于其他 *POR* 基因突变类型,当患儿发生 R457H 突变时,母体孕期男性化表现发生率最高^[1]。人类 *POR* 基因位于第 7 号染色体,全长 71753 bp,共包含 16 个外显子,其中 1 个为非翻译外显子,启动转录,位于上游 38.8kb 处。截至目前,累计报道约 200 余种 *POR* 基因突变和单核苷酸多态性,包括错义、无义、插入、缺失、重复、剪切位点突变及一个或多个外显子亚显微缺失等类型。本病例为 c.437delG(p. G146fs * 111)和 c.1370G > A(p. R457H)复合杂合突变,其中 *POR* 基因 c.437delG(p. G146fs * 111)突变类型既往未见报道,为新发突变,扩大了 *POR* 基因突变谱。

综上所述,PORD 是一种罕见的常染色体隐性遗传病。*POR* 基因变异谱复杂,导致 PORD 患者具有显著的表型差异性,其主要临床症状包括骨骼畸形、生殖器官畸形、肾上腺皮质功能不全等。治疗需要多学科协作(如制定个体化类固醇激素代替方案,必要时选择手术矫形骨骼和生殖器畸形等),已报道的 *POR* 基因突变类型中,p. R457H 可能是中国人乃至黄种人的热点突变类型;此外 c.437delG(p. G146fs * 111)为一新发突变,扩大了 *POR* 基因突变谱。临床医师需要提高对 PORD 的关注程度,争取早期确诊、规范治疗和改善预后。

利益冲突 所有作者声明不存在利益冲突

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