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出生缺陷　罕见病

·专题报道·

尿素循环障碍患儿慢性期治疗和管理

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［摘　要］ 尿素循环障碍（UCD）是一组致死、致残率较高的遗传代谢病，需要长期饮食和药物治疗及管理。除希特林蛋白缺乏症和行肝移植治疗的患儿，其他慢性期患儿均需要终身低蛋白饮食，保证其相应年龄的安全蛋白质摄入量以及充足的碳水和脂肪的供能比，必要时补充必需氨基酸及无蛋白奶粉；药物治疗主要包括氮清除剂（苯甲酸钠、苯丁酸钠、苯丁酸甘油酯）、尿素循环激活/底物补充剂（*N*-氨基甲酰谷氨酸、精氨酸、瓜氨酸）等。规范饮食及药物治疗后未达预期效果、出现严重进展性肝病或出现反复发作的患儿建议行肝移植。基因疗法、干细胞疗法和酶替代疗法等新技术可能是UCD患儿治疗的新选择。UCD患儿需要定期检测血氨、肝功能和血氨基酸等生化指标，并评估体格生长、智力发育和营养摄入情况，及时调整治疗方案。

［关键词］ 尿素循环障碍；遗传性代谢缺陷；儿童；慢性期；健康管理；鸟氨酸氨甲酰基转移酶；鸟氨酸转氨甲酰酶；综述
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Treatment and management for children with urea cycle disorder in chronic stage

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［**Abstract**］ Urea cycle disorder (UCD) is a group of inherited metabolic diseases with high disability or fatality rate, which need long-term drug treatment and diet management. Except those with Citrin deficiency or liver transplantation, all pediatric patients require lifelong low protein diet with safe levels of protein intake and adequate energy and lipids supply for their corresponding age; supplementing essential amino acids and protein-free

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milk are also needed if necessary. The drugs for long-term use include nitrogen scavengers (sodium benzoate, sodium phenylbutyrate, glycerol phenylbutyrate), urea cycle activation/substrate supplementation agents (*N*-carbamylglutamate, arginine, citrulline), etc. Liver transplantation is recommended for pediatric patients not responding to standard diet and drug treatment, and those with severe progressive liver disease and/or recurrent metabolic decompensations. Gene therapy, stem cell therapy, enzyme therapy and other novel technologies may offer options for treatment in UCD patients. The regular biochemical assessments like blood ammonia, liver function and plasma amino acid profile are needed, and physical growth, intellectual development, nutritional intake should be also evaluated for adjusting treatment in time.

[**Key words**] Urea cycle disorder; Inborn error of metabolism; Children; Chronic phase; Health management; Ornithine carbamyl transferase; Ornithine transcarbamylase; Review

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[**缩略语**] 尿素循环障碍(urea cycle disorder,UCD);鸟氨酸氨甲酰基转移酶(ornithine carbamoyl transferase,OCT,OTC);信使RNA(messenger RNA,mRNA)

UCD是由于尿素循环代谢过程中酶或转运体缺陷引起氨解毒或精氨酸合成障碍,导致以血氨升高为特征的一组遗传代谢病,致残、致死率较高[1-2]。UCD分为近端、远端及转运体障碍三类,至少有10种亚型[2-3],需要终身治疗及管理。通过限制蛋白质摄入及药物治疗,将患儿血氨控制在理想范围,维持稳定的代谢环境,避免高氨危象和并发症的发生,进而保证患儿正常生长发育[1-2, 4-5]。但UCD患儿长期治疗和管理涉及不断变化的生长和发育需求、疾病严重程度变化及其固有代谢复杂性、环境因素和家庭对疾病管理及认知差异等,因此较为困难,具有一定的挑战性[2, 6-8]。本文主要针对UCD患儿慢性期治疗及管理进行介绍,以期为临床工作者在实践诊治中提供参考。

1 饮食管理

UCD慢性期治疗的核心目标是尽量减少尿素循环的氮负荷,除希特林蛋白缺乏症和行肝移植治疗患儿外,低蛋白饮食是饮食管理的关键,须终身坚持[9-10]。蛋白质耐受量与UCD相关酶残存活性,患儿性别、年龄、生长发育速度,代谢稳定性等有关,须定期进行膳食评估和个体化饮食管理,保证安全的蛋白质摄入量及充足的碳水和脂肪供能比,以满足患儿正常生长及代谢需求[9]。与年龄较大的儿童比较,婴儿早期的快速生长增加了蛋白质耐受性,代谢控制可能更容易实现[2, 11]。然而,过度限制蛋白质摄入会影响氨基酸失衡,还可能导致内源性蛋白质分解代谢亢进,引起血氨升高,影响患儿智能和体格发育[9, 12]。

UCD患儿应尽可能食用天然蛋白质以确保充分摄入必需氨基酸,有利于生长发育。各年龄段患儿每日蛋白质安全摄入推荐量:小于2月龄患儿为1.8 $g\cdot kg^{-1}\cdot d^{-1}$,2~5月龄患儿为1.5 $g\cdot kg^{-1}\cdot d^{-1}$,6月龄~1.5岁患儿为1.1 $g\cdot kg^{-1}\cdot d^{-1}$,大于1.5岁患儿为0.9 $g\cdot kg^{-1}\cdot d^{-1}$[2]。对于天然蛋白质耐受差的患儿可选择低蛋白质食品,同时提供同龄健康儿童推荐的每日热卡摄取量,若蛋白质摄入不足可由含必需氨基酸的特殊配方营养粉补充,若热卡摄取量不足可用无蛋白营养粉补充。对于食欲缺乏和/或拒食,反复呕吐、反流、干呕等而无法吸吮或吞咽的患儿进行管饲喂养,其中需要长期管饲和/或连续过夜喂养的患儿可行胃造口术灌食,以确保足够的蛋白质和能量摄入[2, 9]。每日蛋白质及必需氨基酸按3~4次平均分配于正餐中及睡前加餐(可减少夜间分解代谢),以提高蛋白质利用率,维持血氨水平稳定[2, 9]。

补充必需氨基酸非常重要,一般需要占总蛋白质摄入量的20%~30%,对于天然蛋白质耐受极

差的患儿补充必需氨基酸可增加到总蛋白质摄入量的50%,随餐服用必需氨基酸的特殊配方营养粉可提供高质量的氮源和产生更少的“废氮”[2, 11, 13]。服用苯丁酸钠会降低体内支链氨基酸水平,建议使用支链氨基酸补充剂或增加必需氨基酸中支链氨基酸的比例。定期监测血氨基酸的变化,当血支链氨基酸水平较低时,应及时调整UCD患儿膳食中天然优质蛋白质的比例和量,优化血氨基酸水平有利于患儿正常生长和增加蛋白质耐受性[1, 14]。

长期低蛋白饮食可导致患儿必需微量元素、维生素和脂肪酸缺乏的风险,对儿童成长产生不利影响[15-16]。应额外补充维生素及矿物质等微量元素,尤其是铁、钙、锌、铜和维生素B_{12}等,还需在膳食中注意增加如核桃油、菜籽油或葵花籽油等富含多不饱和脂肪酸的油脂类食物,或单独补充二十二碳六烯酸或花生四烯酸,以弥补必需脂肪酸的不足[2, 9]。此外,低蛋白饮食的UCD患儿通常会因为能量过量摄入,具有脂肪积累的风险[17-18]。

2 药物治疗

UCD的药物治疗主要包括氮清除剂(苯甲酸钠、苯丁酸钠、苯丁酸甘油酯),尿素循环激活/底物补充剂(*N*-氨基甲酰谷氨酸、精氨酸、瓜氨酸)和其他辅助药物(乳果糖、左卡尼汀)[2]。

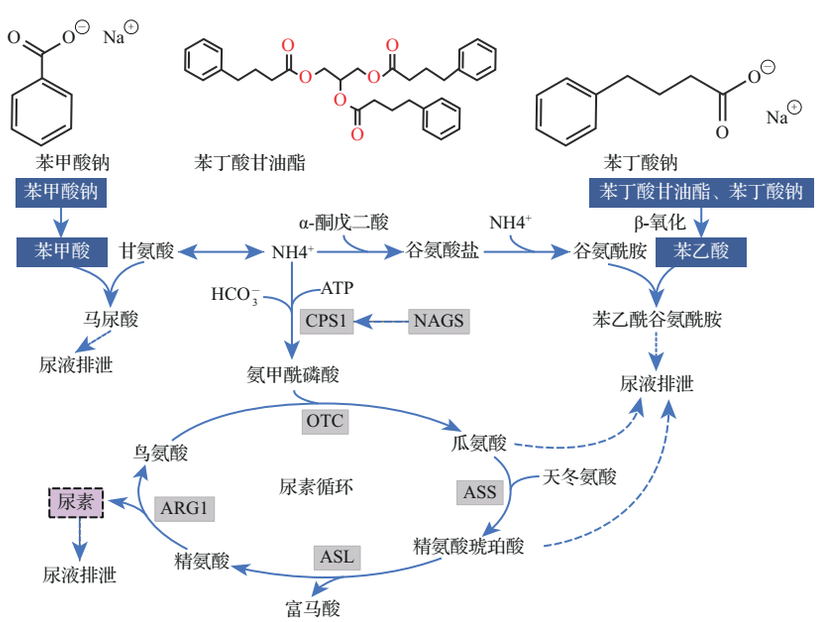
2.1 氮清除剂

氮清除剂可以清除28%~59%的“废氮”,增加UCD患儿的蛋白质摄入,并改善患儿的智力和生长发育,是UCD治疗的核心药物[2, 19-20]。氮清除剂主要绕过尿素循环途径发挥降氨作用[21-22],见图1。UCD患儿单独或联合使用氮清除剂,每日最大剂量不超过12 g[2, 9]。不同氮清除剂对氮的清除效率存在差异,苯甲酸钠通过与甘氨酸结合生成马尿酸能消除一单位氮;苯丁酸钠经β-氧化为苯乙酸,后者与谷氨酰胺结合生成苯乙酰谷氨酰胺,可消除两单位氮;而苯丁酸甘油酯是苯丁酸的前药,由三分子苯丁酸和一分子甘油酯化形成,苯丁酸甘油酯主要通过胰脂肪酶水解后生成苯丁酸,苯丁酸经β-氧化为苯乙酸发挥作用,因此能与三分子谷氨酰胺结合,理论上消除氮的效率更高[21-22]。

苯甲酸钠是一种常见的食品防腐剂,尽管苯甲酸钠常规用于UCD临床治疗,但目前国内尚无相关制剂上市[23]。苯甲酸钠推荐口服剂量为100~250 mg·kg^{-1}·d^{-1},分3~4次,餐时服用[1-2, 24]。

苯丁酸钠推荐口服剂量:当患儿体重低于20 kg时为100~250 mg·kg^{-1}·d^{-1},当体重不低于20 kg时则为2.0~5.5 g·m^{-2}·d^{-1},均需要分3~4次,餐时服用[1, 24]。由于每克苯丁酸钠含125 mg钠,可能存在钠潴留风险[21, 24]。苯丁酸钠还会抑制支链α-酮酸脱氢酶复合物E1α亚基磷酸化,提高复合物活性从而加速支链氨基酸分解代谢,引起支链氨基酸缺乏症,用药期间须定期监测血支链氨基酸水平,必要时额外补充支链氨基酸[25]。

苯丁酸甘油酯无色无味、不含钠和糖、用药体积小,尤其适用于儿童患者。苯丁酸甘油酯推



氮清除剂生成的苯甲酸或苯乙酸可绕过尿素循环分别与甘氨酸或谷氨酰胺结合,生成马尿酸或苯乙酰谷氨酰胺,并从尿液排泄,发挥降氨作用. NH_4^+:铵离子;HCO_3^-:碳酸氢根离子;ATP:腺苷三磷酸;NAGS:*N*-乙酰谷氨酸合成酶;CPS:氨基甲酰磷酸合成酶;OTC:鸟氨酸氨甲酰基转移酶;ASS:精氨基琥珀酸合成酶;ASL:精氨基琥珀酸裂解酶;ARG:精氨酸酶.

图1 氮清除剂作用机制示意图

Figure 1 The mechanism of nitrogen scavengers

荐口服剂量为4.5~11.2 mL·m^{-2}·d^{-1}，分3~4次，餐时服用[1, 24]。既往使用苯丁酸钠的UCD患儿首次使用苯丁酸甘油酯的剂量需通过“苯丁酸甘油酯日剂量(mL)=苯丁酸钠颗粒总日剂量(g)×0.86”公式换算获得[26]。由于苯丁酸甘油酯需经小肠中胰脂肪酶水解成苯丁酸，口服苯丁酸甘油酯产生苯丁酸的速度相比苯丁酸钠慢约75%，因此服用苯丁酸甘油酯的UCD患儿血氨控制更平稳[27-29]。苯丁酸甘油酯能长期平稳控制血氨水平，减少高氨危象发生率，提高患儿的蛋白质摄入量，改善患儿生长发育和认知功能[30-32]。

2.2 尿素循环激活/底物补充剂

N-氨基甲酰谷氨酸是*N*-乙酰谷氨酸类似物，能激活氨甲酰磷酸合成酶1，是*N*-乙酰谷氨酸合成酶缺乏症长期治疗的一线药物，推荐口服剂量为10~100 mg·kg^{-1}·d^{-1}，分3~4次服用[1-2, 24]。

精氨酸和瓜氨酸作为尿素循环底物补充剂，促进尿素循环，常与氮清除剂联合使用[33-34]。精氨酸可用于除精氨酸酶1缺乏症外的UCD患儿，推荐口服剂量为100~250 mg·kg^{-1}·d^{-1}，每日最大剂量不超过6 g[1-2]。服用期间须定期监测血精氨酸，空腹血精氨酸应维持于70~120 μmol/L[2]。瓜氨酸可用于精氨基琥珀酸合成酶缺乏症、精氨基琥珀酸裂解酶缺乏症和希特林蛋白缺乏症外的UCD患儿。推荐口服剂量为100~250 mg·kg^{-1}·d^{-1}，每日最大剂量不超过6 g[1, 24]。

对于近端UCD患儿，使用瓜氨酸能结合天冬氨酸生成精氨酰琥珀酸，相比精氨酸治疗多消除一个氮原子，排氮疗效稍优于*L*-精氨酸，可替代精氨酸，两者无需同时使用[9, 11, 24]。UCD患儿睡前补充的瓜氨酸和/或精氨酸用量应占其每日用量约25%，以便优化夜间的尿素循环[2, 15]。

2.3 其他辅助药物

乳果糖是人工合成的不可吸收双糖，经结肠细菌分解代谢后酸化结肠环境，从而阻断氨的吸收，其通便作用也能加速氨的排泄。一般可在患儿便秘时使用，每日口服剂量为5~10 mL[35]。

低蛋白饮食可引起肉碱缺乏，使用左卡尼汀可用于防治继发性肉碱缺乏[24, 36]，推荐口服剂量为50~100 mg·kg^{-1}·d^{-1}。

3 肝移植

肝移植是治愈UCD的方法，患儿术后能正常饮食，不需要服用降氨药物，生活质量有所提高，其生长发育会有一定程度的改善[2, 9]。对于规范饮食及药物治疗后未达预期、严重进展性肝病或出现反复发作的高氨血症患儿应考虑肝移植[1-2]。但是，肝移植不能逆转已发生的神经系统损害，故应在患儿出现严重神经系统损害前且代谢稳定时行肝移植手术[9, 37]。

肝移植手术需要移植科和遗传代谢科等多科室的密切合作，并应在有能力处理高氨血症的医疗机构进行，以应对肝移植术前禁食、全身麻醉、术中出血、术后感染等因素可能诱发的UCD急性发作[2, 38]。UCD患儿肝移植围手术期管理旨在防止内源性分解代谢，避免血氨升高[39-40]。围手术期患儿应纠正高氨血症，血氨目标浓度为低于80 μmol/L，根据需要维持性给予降氨药物[40-41]；尽量安排UCD患儿当日第一台手术，术前需要静脉输注10%葡萄糖，必要时注射脂肪乳以补充能量的需要[9, 41]；选择合适的麻醉剂有助于手术期间的血氨控制，如OTC缺乏症患儿可使用咪达唑仑、*S*-氯胺酮和芬太尼麻醉，保证足够麻醉深度及疼痛控制，血氨水平保持在正常范围内，且神经状态稳定[38-39]；术前、术间和术后应密切监测患儿临床症状及血氨水平的变化，术后直至患儿代谢稳定后方可停止静脉葡萄糖输注[9, 41]；术后还应定期开展多科室随访以全面评估患儿康复情况，并根据相关指标变化调整治疗方案[41-42]。

4 研究中的新方法

mRNA疗法：将尿素循环相关酶的mRNA配制成脂质纳米粒或非病毒性双纳米粒递送系统，将mRNA靶向递送至缺陷细胞并瞬时表达所需的蛋白质以缓解疾病。OTC缺乏症的mRNA疗法(ARCT-810)现处于Ⅱ期临床试验阶段，其他UCD亚型仅处于动物研究阶段[43-46]。

昂伐卡基(DTX301)疗法：将优化的*OTC*基因包装于腺相关病毒载体8中，单次外周静脉输注给药后，能提供持久的肝脏基因表达，其治疗OTC缺乏症已进入Ⅲ期临床试验阶段(NCT05345171)[47]。

肝源间充质干细胞疗法：异源成人肝脏经胶原酶消化后获得的祖细胞即间充质干细胞(具备优先分化为肝细胞的状态)，经过处理和重构后可静脉注射。该干细胞疗法在UCD患者中的安

全性已在Ⅰ/Ⅱ期临床试验中得到验证,目前正在欧洲开展重复注射和最优剂量治疗UCD患者的Ⅱ期临床试验[48]。

酶替代疗法:聚乙二醇精氨酸酶是一种聚乙二醇化的钴取代重组人精氨酸酶1,能有效降低精氨酸酶1缺乏症患者血精氨酸水平[49],2023年1月已完成精氨酸酶1缺乏症的Ⅲ期临床试验[50]。

肠道菌疗法:由大肠杆菌*Nissle1917*改造的工程益生菌(SYNB1020)能将氨转化为*L*-精氨酸,目前已完成健康受试者的Ⅰ期临床试验[51]。

其他新疗法:胰高血糖素受体抑制剂能降低OTC缺陷小鼠谷氨酰胺酶的表达,有利于氨的消耗,减少高氨血症发生,该疗法目前处于OTC缺乏症动物研究阶段[52]。

5 监测及特殊管理

UCD患儿需要终身监测和随访,随访频率应根据患儿的年龄、生长情况、疾病严重程度、代谢稳定性以及饮食和药物治疗的依从性进行调整,至少每1~3月随访1次[2]。监测的内容包括:患儿血氨、肝功能和血氨基酸等生化指标,维持血氨低于80 μmol/L,血谷氨酰胺低于1000 μmol/L,必需氨基酸和支链氨基酸在正常范围内,其中精氨酸酶1缺乏症患者的血精氨酸水平应控制在200 μmol/L以下[1-2];患儿的身高、体重、头围等体格生长情况,了解其膳食构成,尤其关注患儿的蛋白质摄入量,并了解其营养补充剂和药物服用的情况以及有无皮炎等营养素缺乏症状;患儿智力发育情况,建议每1~2年行头颅核磁共振成像或磁共振波谱检查,以便发现神经系统的细微变化,及时调整治疗方案[1, 9]。

此外,在UCD患儿的长期管理中,应避免使用可致血氨升高的药物,如皮质类固醇、丙戊酸和大环内酯类抗菌药物等[9]。疫苗接种与UCD患儿代谢无关,UCD患儿若临床状况良好、无接种禁忌证且代谢稳定,应正常预防接种[1, 9, 53]。感染、发热、呕吐等疾病易引发UCD急性发作,故该疾病期间应注意血氨监测和能量补充[1],呕吐患儿应警惕使用任何止吐药,避免掩盖高氨血症迹象而诱发其他神经系统症状[2, 54],体温高于38 ℃的患儿应及时给予退热药[9, 54]。需要择期手术时应在患儿病情稳定且无任何并发症时进行,并在术前、术中、术后加强监测和管理[1, 9]。

6 结 语

UCD患儿的长期管理应满足患儿稳定代谢和生长发育的需求。除长期低蛋白饮食管理外,还需补充必需营养物,并联合降氨药物稳定代谢,以改善神经认知功能和保障患儿的正常生长发育。定期随访和评估患儿生长、营养和疾病状态,及时个体化调整患儿治疗管理方案。成功的UCD患儿长期管理离不开多学科专业医疗人员、家庭和社会的支持和共同努力。

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