脐血干细胞移植治疗CINCA综合征及文献复习

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【摘要】 **目的** 研究脐血干细胞移植(umbilical cord blood transplantation,UCBT)治疗慢性婴儿神经-皮肤-关节(chronic infantile neurological cutaneous articular,CINCA)综合征的可行性及疗效。**方法** 回顾性分析1例于2018年11月在复旦大学附属儿科医院接受UCBT治疗的CINCA综合征患儿的临床特点、诊疗经过及预后,并进行相关文献复习。**结果** 患儿男,出生后即反复出现红色斑丘疹,36月龄起出现反复发热,伴随肺部感染、关节炎和全心增大。全外显子测序提示*NLRP3*基因存在c.913G>A(p.D305N)杂合突变,诊断该43月龄患儿为CINCA综合征。患儿于50月龄接受非亲缘HLA 7/10相合UCBT,移植时患儿体重17.3 kg。脐血输注总有核细胞数8.84×10^7/kg,$CD34^+$细胞数2.38×10^5/kg。预处理采用清髓方案。单用他克莫司预防移植物抗宿主病(graft versus host disease,GVHD)。患儿发生Ⅰ度急性GVHD,经治疗后好转。移植后+28天嵌合率检测提示为完全供者嵌合,随访嵌合状态稳定。造血重建:中性粒细胞植入时间+27天,血小板植入时间+31天。免疫重建:移植后+90天,$CD19^+$B淋巴细胞>200/μL,患儿脱离丙种球蛋白替代治疗;移植后+180天患儿$CD4^+$T淋巴细胞>200/μL。随访患儿,无发热、皮疹等症状,基因突变位点已修复,心超检查提示全心增大较前好转,关节B超正常。截至2020年8月31日,患儿无病生存28个月。**结论** 该患儿为国内首例采用UCBT治愈的儿童CINCA病例,UCBT是我国CINCA患儿可选择的治疗方案。

【关键词】 慢性婴儿神经-皮肤-关节(CINCA)综合征; *NLRP3*基因突变; 脐血干细胞移植(UCBT)
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Umbilical cord blood stem cell transplantation for CINCA syndrome and literature review

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【**Abstract**】 **Objective** To investigate the feasibility and efficacy of umbilical cord blood stem cell transplantation (UCBT) in the treatment of chronic infantile neurological cutaneous articular (CINCA) syndrome. **Methods** Clinical features, diagnosis and treatment process and prognosis of a patient with CINCA syndrome who received UCBT in Children's Hospital, Fudan University in Nov 2018 was retrospectively analyzed. **Results** A male child had repeated red maculopapular rashes after birth, and he occurred recurrent fever accompanied with pulmonary infection, arthritis and whole heart enlargement from the age of 36 months. Whole exome sequencing revealed that the *NLRP3* gene had a heterozygous mutation of c.913G>A (p.D305N). Combined with the clinical characteristics and genetic sequencing results, the 43-month-old child was diagnosed with CINCA syndrome. The patient received unrelated HLA 7/10-matched UCBT at the age of 50 months. The patient's weight was 17.3 kg at the time of transplantation. The dose of total nucleated cells of cord blood transfusion was 8.84×10^7/kg, and the dose of $CD34^+$ cells was $2.38\times$

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10^5/kg.The patient received myeloablative conditioning regimen. Tacrolimus was used for the prevention of graft versus host disease (GVHD).The patient had developed grade Ⅰ acute GVHD and gradually improved aftertreatment. The patient achieved complete donor chimerismat day 28 after transplantation. Hematopoietic reconstruction: the neutrophil and platelet engraftment were 27 and 31 days, respectively. Immunefunction reconstruction: at day 90 after transplantation, the count of $CD19^+$B lymphocytes was higher than 200/μL.Then the patient was discontinuation of intravenous immunoglobulin replacement. The count of $CD4^+$T lymphocytes was higher than 200/μL at day 180 after transplantation.The patient had no fever, rash and other symptoms.The genetic mutation site had been repaired.Echocardiography showed that the whole heart enlargement was better than before, and the joint B-ultrasound was normal.The patient had a disease-free survival of 28 months after UCBT by Aug 31, 2020. **Conclusion** This is the first pediatric case of CINCA cured by UCBT.UCBT is an alternative treatment for children with CINCA in China.

【Key words】 chronic infantile neurological cutaneous articular (CINCA) syndrome; *NLRP3* gene mutation; umbilical cord blood transplantation (UCBT)

慢性婴儿-神经-皮肤关节(chronic infantile neurological cutaneous articular,CINCA)综合征是一种十分罕见的系统性自身炎症性疾病,是冷吡啉相关周期性综合征(cryopyrin-associated periodic syndromes,CAPS)的一种。CAPS综合征是*NLRP3*基因错义突变导致的一种单基因遗传病[1],包括家族性寒冷型自身炎症综合征(familial cold autoinflammatory syndrome, FCAS)、Muckle-Wells综合征(MWS)和CINCA综合征。这些综合征虽然被描述为不同的临床实体,但均有发热、荨麻疹样皮疹和不同程度关节受累等相似临床表现[2]。这3种疾病的严重程度逐渐递增:FCAS病情最轻,MWS居中,CINCA最为危重。如诊断和治疗不及时,常导致重要脏器受累、淀粉样变性而早期死亡。国外CINCA综合征的主要治疗方式是IL-1拮抗剂,但患者易耐药且副作用大,且国内尚未有IL-1β拮抗药物上市。该疾病是一种终生性疾病,无法治愈,后期可有不可逆的中枢神经系统损害,预后极差[2-3],目前国内采用激素、免疫抑制剂等治疗,但患儿须终生用药,药物相关副作用大,预后不佳。我们在国内首次报道1例CINCA综合征患儿通过非亲缘脐血干细胞移植(umbilical cord blood transplantation,UCBT)成功治疗的病例,提示UCBT可能是我国CINCA患儿可选择的治疗方案。

资料和方法

临床资料 收集复旦大学附属儿科医院于2018年11月诊断的1例CINCA综合征病例。该患儿为男性,43月龄,因"反复发热、皮疹7月"就诊。入院时颜面可见大片红色斑丘疹,伴发热、肺部感染,其余查体未见明显异常。本研究通过复旦大学儿科医院伦理委员会审批通过(2017-159号-01)。

全外显子测序 基于Sanger测序法,完善患儿家系全外显子测序,结果显示*NLRP3*基因存在3号外显子c.913G>A(p.D305N)杂合变异,其父母均未检测出该变异。

移植方案 采用清髓方案进行预处理。他克莫司单药预防移植物抗宿主病(graft versus host disease,GVHD)。前列地尔和熊去氧胆酸预防肝静脉闭塞病(hepatic veno-occlusive disease,VOD)。排除移植禁忌后,患儿于2018年11月接受非亲缘HLA7/10相合UCBT。

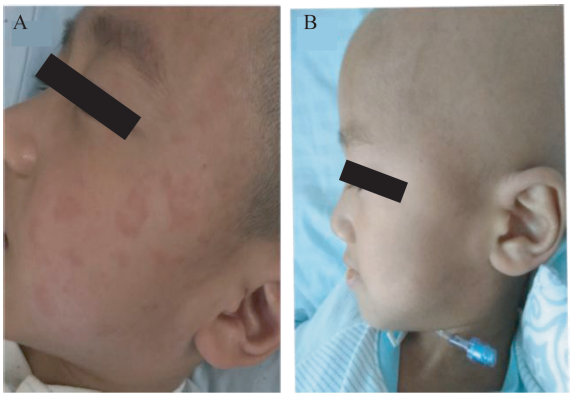
植活标准 中性粒细胞植活定义为连续3天中性粒细胞计数>0.5×10^9/L,血小板植活定义为连续7天血小板计数>20×10^9/L并脱离血小板输注。中性粒细胞植活后,通过短串联重复序列-聚合酶链反应技术进行移植后嵌合率检测:植入率≥95%为完全嵌合状态,5%~94%为混合嵌合状态,<5%为植入失败。

随访 自确诊之日起,截至2020年8月31日,随访时间28个月。随访内容:移植后患儿临床症状(发热、皮疹情况等),移植后血常规、肝肾功能、免疫功能、基因突变位点、心超、关节B超、眼底及听力检查。

结　　果

临床特点　患儿，男性，43月龄时因“反复发热、皮疹7月”首次入院。患儿出生后即反复出现红色大片斑丘疹，未予特殊处理可自行消退，36月龄起出现反复发热，红色风团样皮疹伴痒感，肺部感染，全心增大，关节炎，予美林、激素、抗生素治疗后症状可缓解，但极易反复，皮疹发作逐渐频繁。患儿为足月顺产，出生体重3 400 g，父母体健，无类似疾病家族史。患儿移植前后皮疹表现如图1所示。

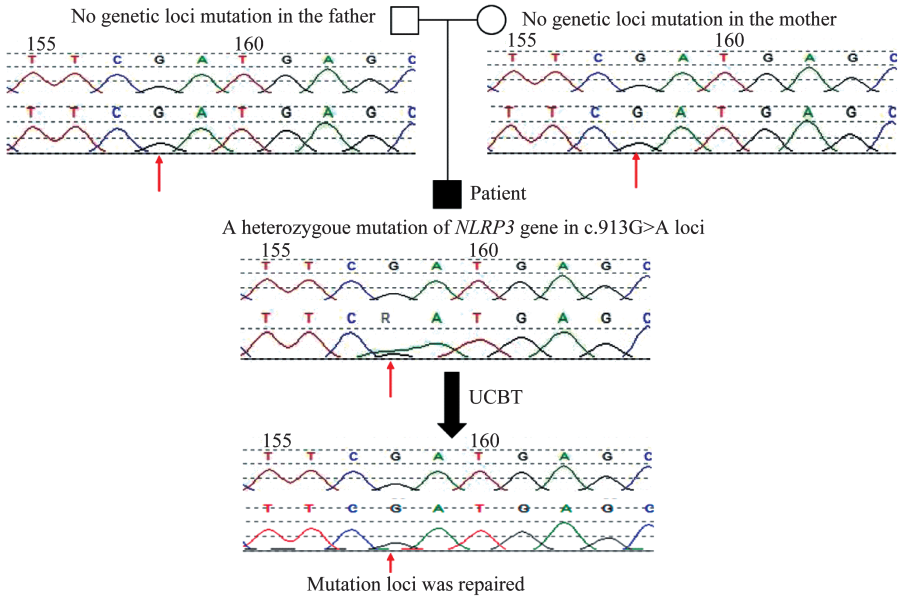
入院后完善检查：血常规提示白细胞（white blood cell，WBC）（7.6～22.4）×10^9/L，中性粒细胞百分比62.5%～75.3%，血红蛋白93～109 g/L，血小板（245～465）×10^9/L，嗜酸性粒细胞（0.11～2.01）×10^9/L，C反应蛋白（C reactive protein，CRP）8～70 mg/L，红细胞沉降率（erythrocyte sedimentation rate，ESR）23～49 mm/h。免疫球蛋白、尿常规、肝肾功能、脑脊液检查均正常，自身抗体均阴性。关节B超提示：双踝关节少量积液伴滑膜增厚，双侧骶髂关节内探及血流信号；心超提示：全心增大，卵圆孔未闭，二、三尖瓣轻度反流，心功能正常；眼底检查提示：视盘边界糊，视乳头水肿，视力未见明显异常；脑干诱发电位提示双耳听力正常；家系全外显子测序结果显示*NLRP3*基因存在3号外显子c.913G＞A（p.D305N）杂合变异，即913位碱基由鸟氨酸（G）突变为腺嘌呤（A），相应的305位氨基酸由天冬氨酸（D）变为天冬酰胺（N）。其父母均未检测出该变异，该患儿出现的*D305N*突变为新突变（图2）。主要临床及实验室特征总结见表1。



A: There were large red maculopapular rashes with some blisters in the center on the face before UCBT; B: The rash subsided after transplantation.

图1　1例CINCA综合征患儿UCBT治疗前后面部皮疹情况比较

Fig 1　Comparison of facial rashes in a patient with CINCA syndrome before and after UCBT



Sanger sequencing showed that the child had a heterozygous mutation of c.913G＞A, which was not detected in his parents; the mutation was repaired after UCBT.

图2　CINCA综合征患儿UCBT治疗前家系测序和UCBT治疗后患儿基因位点复查结果

Fig 2　Sequencing of the family of the CINCA syndrome patient before UCBT and the reexamination results of gene loci of the child after UCBT

表1 患儿移植前后主要临床表现和辅助检查

Tab 1 Main clinical features and auxiliary examinations before and after UCBT of the CINCA syndrome

Clinical features and auxiliary examinations	Before UCBT	After UCBT	Reference range
Age (mo)	36-44	>51	-
Fever	Recurring	None	-
Rash	Recurring	None	-
WBC ($\times10^9$/L)	7.6-22.4↑	3.4-8.9	4-10
CRP (mg/L)	8-70↑	<8	<8
ESR (mm/h)	23-49↑	6-18	0-21
Eosinophils ($\times10^9$/L)	0.11-2.01↑	0.1-0.28	0.06-0.3
IgE (kU/L)	195.2-447.12↑	34.31-48.03	<100
Joint B-ultrasound	Bilateral sacroiliac joint exploration and blood flow signals, a small amount of bilateral ankle joint effusion with thickened synovial membrane	Normal	-
Echocardiography	whole heart enlargement;	Normal	-
Fundus examination	Blurred optic disc boundary, papilledema	Normal	-
NLRP3 gene	c.913G>A (p.D305N)	No mutation	-

移植方案 患儿配得HLA高分辨7/10相合非亲缘脐血,移植时体重17.3 kg,脐血输注总有核细胞数8.84×10^7/kg,CD34+细胞数2.38×10^5/kg。预处理采用清髓方案,具体用药:利妥昔单抗200 mg/m^2+氟达拉宾175 mg/m^2+白消安13.2 mg/kg+环磷酰胺100 mg/kg。GVHD预防单用他克莫司口服,维持血药浓度5~10 ng/mL。预防VOD采用前列地尔和熊去氧胆酸,两药联用至移植后+30天。

移植相关并发症 患儿移植后+8天开始出现皮疹、发热,考虑为Ⅰ度急性GVHD(aGVHD),经短期予甲基强的松(1 mg/kg)、美罗培南及退热等对症治疗后好转,移植后+15天甲基强的松逐渐减停。患儿发生Ⅰ度黏膜炎,未予特殊处理,自行好转。未发生VOD、出血性膀胱炎、肝肾功能损害、重症肺炎等并发症。

植入及重建 移植后+28天提示为完全供者嵌合,随访嵌合状态稳定。移植后+27天中性粒细胞植入,+31天血小板植入。免疫重建(图3):移植后+90天CD19+B淋巴细胞>200/μL,患儿脱离丙种球蛋白替代治疗;移植后+180天患儿CD4+T淋巴细胞>200/μL。

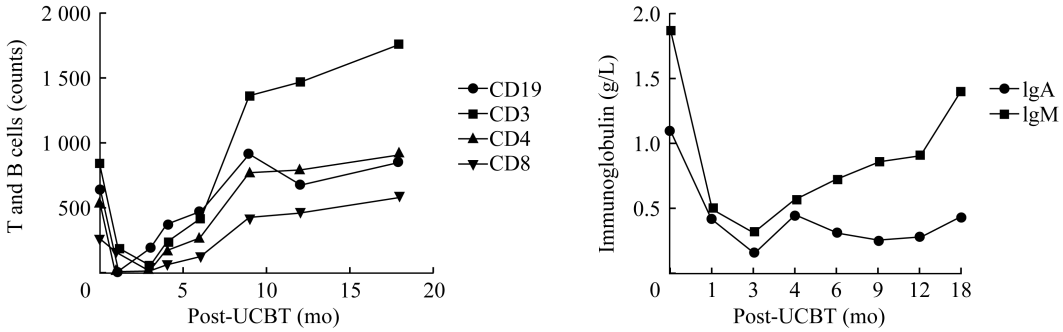


图3 CINCA综合征患儿移植后免疫功能重建

Fig 3 Immune reconstruction of the CINCA syndrome patient after UCBT

随访 移植后+30天复查*NLRP3*基因位点未检测到变异(图2)。移植后+42天患儿出院,截至2020年8月31日,随访时间28个月。患儿现已停药,无反复发热、皮疹等表现,移植后皮损明显好转,定期监测血常规、肝肾功能、巨细胞病毒等,患儿已恢复正常造血与免疫功能,突变基因位点被修复。随访心超、关节B超均正常。随访眼底检查及听力检测均正常。

讨　论

CINCA临床表现以新生儿期皮疹、反复发热伴关节症状和慢性无菌性脑膜炎三联征为主要特征，其中神经系统症状出现较晚，年幼儿多无慢性无菌性脑膜炎的表现。在年长儿中，头痛为慢性脑膜炎的突出表现，部分患者因神经受损可出现听力和视力减退。关节和骨骼改变是CINCA的另一典型表现，早期表现为关节积液、关节炎症，后期可因骨骺结构破坏而产生额面隆起、鞍状鼻等特殊面容。CINCA是CAPS最严重的一种类型，无法自愈，预后差。本例患者自婴幼儿期反复发热伴皮肤表现，尽管尚无神经系统表现，但患者年龄尚小，且有关节受累证据，符合CINCA综合征的临床特点。

*NLRP3*基因与CAPS发病关系的认识始于MWS和FCAS，大规模位置克隆研究发现MWS和FCAS患者的*NLRP3*基因存在多个错义突变[4]。2002年，国际上首次在CINCA患者中也发现*NLRP3*基因的错义突变，提示*NLRP3*也为CAPS的致病基因，并将CINCA也并入了CAPS家族中[5-6]。目前已经有约230种*NLRP3*基因突变登记在Infever数据库中。*NLRP3*基因（也称为*CIAS1*基因）位于1号染色体长臂44区，共有9个外显子，其中3号外显子最大，为突变的高发部位。CAPS家族的3种综合征已证实均是由*NLRP3*基因突变引起的[1,7-8]，*NLRP3*突变为一种功能获得性突变，可导致下游炎症反应异常激活，IL-1β等炎症因子过度释放。本例患者的杂合突变也是如此。正如Shinar等[9]在遗传性周期热的基因诊断指南中指出，对临床表现疑似CAPS的病例可首先对*NLRP3*基因3号外显子进行序列比对分析来进行疾病筛查。CINCA的致病基因*NLRP3*基因编码Cryopyrin蛋白，该蛋白含有pyrin功能域、核酸结合域和亮氨酸富集结构域，是核苷酸蛋白质寡聚化样受体家族的一种，参与形成炎性小体。炎性小体的活化需要两条独立的信号通路（1和2）共同作用[10]，正常情况下可进一步激活下游炎症反应，保护机体免受内外环境威胁和维持内环境稳态。不适当的活化可影响炎性小体的功能，进而导致过度炎症反应。体外实验证实CAPS中*NLRP3*基因突变为一种功能获得性突变，可致cryopyrin炎性小体活性增高，促炎因子释放增加，进一步触发下游级联炎性反应[11]。突变的Cryopyrin缺少信号2介导的蛋白折叠机制，患者外周血淋巴细胞显示IL-1β、IL-18等炎症细胞因子大量释放[12]。伴有*NLRP3*突变的基因编辑小鼠可产生与人类CAPS相似的表型和炎症因子释放[13-14]。以上研究均表明，CAPS发病可能涉及*NLRP3*基因突变导致下游IL-1β、IL-18等炎症因子释放及过度的炎症反应。

许多内源性细胞因子受体拮抗剂可阻断细胞因子与相对应受体的结合[15]。Anakinra是最先被研究的一种重组型IL-1受体拮抗剂，临床试验结果证实其可减轻3种类型CAPS的临床表现和降低炎症细胞因子水平[16-19]。此外，IL-1受体重组蛋白Rilonacept[20]和IL-1β单克隆抗体Canakinumab[21]相继于2008年和2009年被美国FDA批准用于CAPS的治疗。虽然IL-1β受体抑制剂对CAPS治疗效果确切，但药物的有效性和安全性尚存争议，长期临床实践表明患者易产生耐药，需要加大剂量或调整方案[22]，且长期服用免疫抑制剂的患儿易感染，需早期服用抗生素预防[23]，少数患者还有眩晕等严重并发症。

针对靶向IL-1受体的小分子抑制剂显示出一定疗效[24]，但国内尚无该药上市及相关临床试验，国内关于此病的报道较少，目前无造血干细胞治疗先例。张俊梅等[25]于2019年报道了10例CINCA综合征病例，一线治疗采用糖皮质激素和免疫抑制剂，疗效不佳者加用生物制剂，10例患儿中有2例加用托珠单抗，2例加用卡那单抗，2例加用托法替布治疗。8例患儿病情好转，但需长期用药维持，生活质量欠佳，家庭经济负担重。本例患儿首先采用以糖皮质激素为基础的传统抗炎治疗，发热、皮疹有所好转，但激素减量后，发热、皮疹反复且加重，激素剂量始终大于1 mg/kg，激素相关副作用（如向心性肥胖、高血压、骨质疏松、高眼压）均有出现，家属拒绝加用其他免疫抑制剂。

异基因造血干细胞移植（allogeneic hematopoietic stem celltransplantation，allo-HSCT）是治愈免疫缺陷病及自身炎症性疾病的有效手段，UCB作为异基因移植物来源的一种，具有检索简单、获取快捷、HLA相合度要求稍低、对供体无风险等优点[26]。既往我院采用UCBT治疗自身炎症性疾病，如极早发型炎症性肠病（very earlyonset infl

ammatory bowel disease,VEO-IBD),患儿移植后基因修复,临床症状持续缓解[27]。本研究中UCBT移植后,患儿逐渐恢复正常造血与免疫功能,突变基因位点被修复。随访过程中,患儿皮损明显好转,无反复发热、皮疹等表现,心超、关节B超无异常,现已停药,生活质量良好,表明allo-HSCT是治愈CINCA综合征的有效手段。

该患儿为国内首例采用UCBT治愈的儿童CINCA病例,对于UCBT治疗该病的长期疗效还需要长期随访和扩大病例数。但在国内尚无IL-1受体抑制剂的情况下,UCBT是CINCA患儿可选择的治疗方案。

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（上接第325页）

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