四川大学学报（医学版） 2024，55（3）：756－761
J Sichuan Univ（Med Sci） doi: 10.12182/20240560606

在线全文

*ELF4*基因缺陷的类白塞病样综合征2例报告*

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【摘要】 患儿1，男，13岁，因“反复口腔溃疡3年，腹痛8个月，肛周溃疡10 d”入院；患儿2，男，3岁，因“反复腹痛、腹泻、发热3月余”入院，两患儿经基因检测发现X连锁的*ELF4*缺陷（“deficiency in *ELF4*, X-linked”, DEX），确诊为*ELF4*基因缺陷的类白塞病样综合征。患儿1先后予以甲泼尼龙静脉冲击，泼尼龙、美沙拉嗪口服对症治疗。患儿2先后予糖皮质激素联合肠内营养，巯嘌呤口服等治疗。后2例患儿症状缓解出院。

【关键词】 *ELF4*基因 免疫失调性疾病 白塞病 克罗恩病

Two Cases of Behcet's Disease-Like Syndrome with Gene Deficiency in *ELF4*

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【**Abstract**】 The patient 1, a 13-year-old boy, was admitted due to "recurrent oral ulcers for 3 years, abdominal pain for 8 months, and perianal ulcers for 10 days"; The patient 2, a 3-year-old boy, was admitted due to "recurrent abdominal pain, diarrhea, and fever for over 3 months". Genetic testing of both patients revealed "deficiency in *ELF4*, X-linked" (DEX), and the patients were diagnosed with Behcet's disease-like syndrome due to deficiency in *ELF4*, accordingly. The patient 1 was successively given intravenous methylprednisolone pulses and oral prednisone and mesalazine for symptomatic treatment. The patient 2 was successively treated with corticosteroids combined with enteral nutrition, as well as oral mercaptopurine. Subsequently, both patients showed improvements in symptoms and were discharged.

【**Key words**】 *ELF4* gene Diseases of immune dysregulation Behecet's disease Crohn's disease

原发性免疫缺陷病（primary immunodeficiency diseases, PID）近年被逐渐更新概念为“人类免疫出生错误（human inborn errors of immunity, IEI）”。IEI目前分为10组类型，包括：①联合免疫缺陷；②具有综合征特征的联合免疫缺陷；③主要以抗体缺乏为主类型；④免疫失调疾病（diseases of immune dysregulation, DID）；⑤吞噬细胞先天性缺陷；⑥固有免疫和先天免疫缺陷；⑦自身炎性疾病；⑧补体缺乏；⑨骨髓衰竭；⑩表型模拟IEI类型（phenocopies of inborn errors of immunity）。X连锁的*ELF4*缺陷（"deficiency in *ELF4*, X-linked", DEX）是近年才发现的一种单基因自身炎症失调性疾病[1]，被归类为IEI中的DID组[2]。*ELF4*突变体因无法有效驱动抗炎及抗病毒基因表达而致病[3]。包括本文2例患儿在内，截至目前全球共报道11例DEX病例[1,3-4]。本文回顾性分析我院2例DEX患儿的诊疗经过，以供临床医生借鉴参考。

1 病例资料

1.1 患儿1病史和查体

患儿1，男，13岁，因“口腔反复溃疡3年，腹痛8个月，肛周溃疡10 d”于2015年4月入院，入院前3年患儿无明显诱因出现反复口腔溃疡，每年1～2次，局部喷雾后可缓解。入院前1年口腔溃疡加重，每年发作6次。入院前8个月患儿再次出现左侧颊黏膜1.5 cm×1 cm口腔溃疡，伴阵发性脐周疼痛，伴头晕和反复低热，无咳嗽、呕吐、腹泻、黏液血便等症状。于当地医院就诊（具体诊疗情况不详），患儿腹痛较前暂缓解。后患儿口腔溃疡及腹痛反复发作。多次就诊于四川大学华西口腔医院，口服及局部用药后溃疡稍有愈合。入院前10 d，患儿无明显诱因出现肛周疼痛。就诊于四川大学华西医院，见口腔左侧咽腭弓及肛周溃疡。因患儿仍有吞咽疼痛及阵发性脐周隐痛，为求进一步治疗收入我科。

患儿系G_2P_2，家中顺产，出生体质量3 500 g，否认出生窒息、抢救史。患儿奶奶有肺结核病史。患儿父母及患儿哥哥均体健。

* 四川省自然科学基金面上项目（No. 2024NSFSC0633）和中央高校基本科研业务费专项资金（No. SCU2022F4080）资助

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出版日期：2024-05-20

入院查体: 体温37 ℃, 脉搏92 min^{-1}, 呼吸22 min^{-1}, 血压103/57 mmHg(1 mmHg= 0.133 kPa), 体质量31 kg(< 第3百分位), 慢性病容, 神志清楚, 表情自如, 营养欠佳。左咽腭弓见一2.5 cm×0.6 cm溃疡, 上覆浓苔。肛门见一0.5 cm×0.5 cm溃疡, 上覆白色分泌物。全腹触诊柔软, 脐周压痛、无反跳痛。肝脾肋下未触及。余心肺、泌尿及神经系统查体未见异常。

1.2　患儿1实验室检查

入院后完善血常规、C反应蛋白、血沉、肝肾功、大小便常规、体液免疫、细胞免疫、自身抗体全套、中性粒细胞胞浆抗体、针刺试验、病原学及结核相关检查、肿瘤全套、腹部增强CT均未见明显异常。结肠镜检结果详见图1, 余阳性检查详见表1。

1.3　患儿1诊疗经过

入院后考虑诊断“1.克罗恩病？2.白塞病？3.肠结核待排”。先后予头孢他啶、甲硝唑抗感染, 康复新对症, 静脉营养支持治疗。完成系列临床排筛后高度疑诊“克罗恩病”。虽实验室检查未发现结核感染证据, 但考虑患儿来自结核高发区且患儿奶奶有肺结核病史, 此基础上结合我国2015年前儿童克罗恩病诊疗指南, 决定先予诊断性抗结核治疗, 若无效则按克罗恩病方案治疗。口腔溃疡愈合后嘱患儿出院口服抗结核药物。

诊断性抗结核治疗2月余后, 患儿复查再次入院。抗结核治疗期间患儿口腔溃疡再发, 肛周溃疡伴脓液, 脐周隐痛及低热反复发作。复查肠镜: 病变较前显著好转, 回结肠无明显异常。复查肠道黏膜病理详见表1。完善全基因组外送检查, 治疗上停用抗结核药物, 先后予头孢他啶、甲硝唑抗感染, 甲泼尼龙冲击治疗3 d后改强的松口服, 加用美沙拉嗪对症。后患儿临床症状缓解出院。因2015年DEX尚属未知疾病, 未从其基因报告中获得有价值的实质性发现。

1.4　患儿1预后

随着基因分析数据更新, 我们在2022年的回顾性分析中发现, 该患儿基因结果高度符合DEX。再次联系患

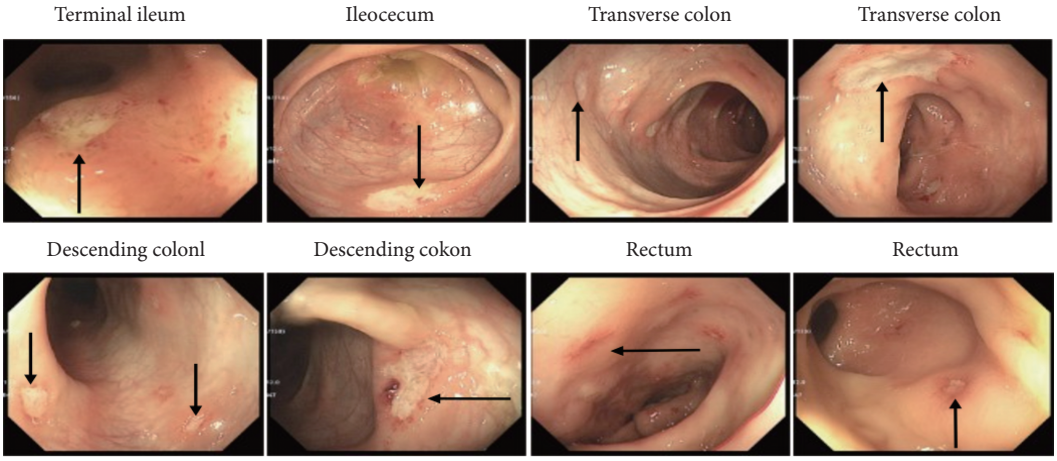

图 1　患儿1病情最严重时肠镜检查

Fig 1　Enteroscopic images of the patient 1 during the most severe phase of his illness

There was an irregular-shaped ulcer measuring approximately 1 cm×2 cm in the terminal ileum, with a thin layer of moss on the ulcer base and moderate congestion and edema in the surrounding mucosa. An irregular ulcer measuring approximately 2 cm×2 cm is visible near the ileocecal valve in the ileocecal region, with a thin layer moss on the ulcer base and congestion and edema in the surrounding mucosa.

表 1　患儿1阳性辅助检查总结

Table 1　Summary of auxiliary examinations with positive results in patient 1

Examination item	First hospitalization (2015.04)	Second hospitalization (2015.07)
Inflammatory markers	Fecal calprotectin 636 μg/g; Inflammatory factors IL-1β 8.34 pg/mL (< 5 pg/mL), IL-8 12.37 pg/mL (< 62 pg/mL), IL-2R 520.87 U/mL (223-710 U/mL), IL-6 14.89 pg/mL (< 5.9 pg/mL), and TNF-α 10.33 pg/mL (< 8.1 pg/mL)	Fecal calprotectin 1 047 μg/g; Inflammatory factors IL-1β 11.46 pg/mL (< 5 pg/mL), IL-8 26.60 pg/mL (< 62 pg/mL), IL-2R 486.52 U/mL (223-710 U/mL), IL-6 38.89 pg/mL (< 5.9 pg/mL), and TNF-α 17.34 pg/mL (< 8.1 pg/mL)
Pathological biopsy	Oral and epiglottic mucosal biopsy showed inflammatory ulcer and lymphoproliferative lesion with necrosis. Intestinal mucosal biopsy revealed focal erosion in the terminal ileum with severe active inflammation and active ulcer formation in the ileocecal region with granulation tissue hyperplasia. The above changes were suspected to be signs of Crohn's disease.	Intestinal mucosal biopsy showed mild chronic inflammation was observed in the mucosa of the ileocecal, transverse, and descending colons. Slight chronic inflammation was present in the rectal mucosa with lymphoid tissue hyperplasia. No granulomatous inflammation or vascular lesions were identified in any of the lesions.

IL: interleukin; IL-2R: interleukin-2 receptor; TNF-α: tumor necrosis factor-α.

儿并进行基因全外显子测序及重分析。结果显示,患儿位于X染色体的*ELF4*基因p.R234X (c.700C>T)突变[5]。截至2022年,患儿已上大学,疾病未再有严重复发。

1.5 患儿2病史和查体

患儿2,男,3岁,因“反复腹痛、腹泻、发热3月余”于2022年8月入院。入院前3个月,患儿饮用池塘水开始出现阵发性腹痛,部位及性质不能描述,程度不剧,伴解稀便2~3次/d,无明显黏液脓血,无发热,未予特殊处理。入院前2个月,患儿仍诉腹痛,解黄绿色稀便数次每天,伴发热,最高40 ℃。外院予头孢曲松抗感染、地塞米松抗炎治疗后患儿体温正常,但腹痛、腹泻未缓解。此后患儿反复腹痛、腹泻。入院前10 d,患儿进食炸鸡后再次发热(37.5 ℃),伴腹痛、腹泻,于我院感染科就诊。完善血常规+CRP示:白细胞15.1×10^9 L^{-1},C反应蛋白87 mg/L。考虑“感染性腹泻”,先后予头孢地尼、美罗培南抗感染,益生菌调节肠道菌群,蒙脱石散止泻,硫酸锌、麦滋林修复肠道黏膜及补液治疗后患儿仍反复发热,且大便见可疑假膜。感染科疑诊抗生素相关性肠炎,予万古霉素口服治疗后患儿病情仍无缓解。为进一步治疗收入我科。

患儿系G_2P_2,出生体质量3 050 g,否认出生窒息、抢救史。患儿1岁时患“肛周脓肿”。患儿父母及患儿姐姐体健。

入院查体:体温36.5 ℃,脉搏96 min^{-1},呼吸25 min^{-1},体质量13.5 kg(<第10百分位),神志清、反应可,慢性病容,全身未见皮疹,浅表淋巴结未扪及肿大。舌尖及口腔黏膜可见数枚溃疡。余心、肺、腹部、泌尿及神经系统查体未见异常。

1.6 患儿2实验室检查

血常规:白细胞18.6×10^9 L^{-1},红细胞3.74×10^{12} L^{-1},血红蛋白97 g/L,血小板276×10^9 L^{-1},中性粒细胞百分比75.1%。肝肾功能、细胞免疫、自身抗体、中性粒细胞抗体、病原学检查,以及肥达试验、病原体宏基,均未见明显异常。胃镜结果见图2,结肠镜结果详见图3。余阳性检查见表2。

1.7 患儿2诊疗经过

入我科后考虑“1.极早发炎性肠病,2.中度贫血,3.口腔溃疡”,先后予万古霉素联合美罗培南抗感染,小百肽诱导缓解及补液治疗,住院期间患儿诉关节疼痛并出现散在皮疹。加用甲泼尼龙抗炎,奥美拉唑抑酸,补充钙及维生素,完善基因检测。后患儿临床症状好转出院。

1.8 患儿2预后

2个月后再次复查入院,基因报告:患儿新发位于X染色体的*ELF4*(exon5: c.465del; XLR)移码突变,突变导致终止码提前出现,致病性极高;患儿母亲为杂合携带者[5]。入院追问家族史情况,患儿母亲也有口腔同一部位反复溃疡病史,程度较患儿轻。复查胃镜:慢性非萎缩性胃炎伴糜烂。肠镜:回肠、结肠多发溃疡。复查病理见表2。继续予甲泼尼龙、肠内营养治疗,后加用硫嘌呤口服。门诊随访患儿2除口腔溃疡偶有复发外,其余一般情况良好。

1.9 2例患儿蛋白功能学验证[5]

2例患儿的蛋白功能学验证结果确认了*ELF4*变体的破坏性及致病性。

2 讨论

2.1 *ELF4*在免疫过程中的功能

*ELF4*基因(NM_001421.4)包含9个外显子,编码663个氨基酸,其编码蛋白称作ELF4转录激活因子。该转录因子是ETS(E-twenty six)亚家族成员,对免疫调节有重要作用[6]。ELF4转录因子参与穿孔素基因表达,影响NK及

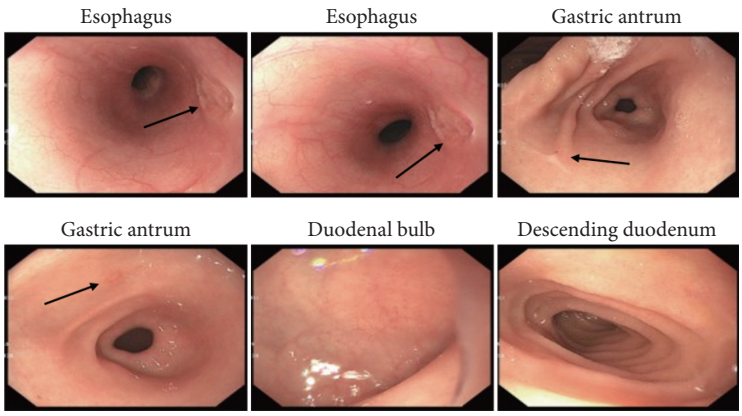

图 2 患儿2病情最严重时胃镜检查

Fig 2 Gastroscopic images of the patient 2 at the most severe stage of his illness

A shallow ulcer measuring approximately 0.4 cm×0.6 cm was observed at the lower end of the esophagus, with a small amount of white moss at its base and localized mild congestion and swelling in the mucosa. The gastric antrum mucosa was congested, with scattered red rash and mild punctate erosions, and a small shallow ulcer was seen at the small flexure, with mild congestion and swelling in the mucosa. No significant abnormalities were noted in other areas.

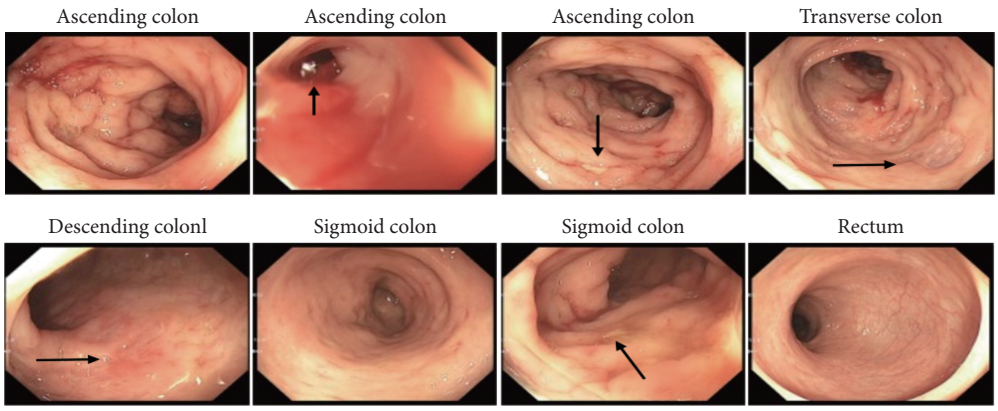

图 3 患儿2最严重时肠镜检查

Fig 3 Colonoscopic images of the patient 2 at the most severe stage

A marked narrowing of the intestinal lumen was visible in the ascending colon approximately 45 cm from the anus. The mucosa was significantly swollen, partially obstructing the intestinal lumen. The biopsy is brittle and easily bleeds when touched. Multiple flat ulcers were observed in the transverse, descending, sigmoid, and rectal colons. The ulcers had irregular shapes and were covered by white moss. The surrounding mucosa showed mild swelling and hyperplastic changes. The ulcers were segmented and evenly distributed.

表 2　患儿2阳性辅助检查总结

Table 2　Summary of auxiliary examinations with positive results in patient 2

Inspection item	First hospitalization (2022.07)	Second hospitalization (2022.10)
Inflammatory markers	CRP 98.7 mg/L, ESR 34 mm/1 h; Fecal calprotectin 733 μg/g; Inflammatory factors IL-1β 14.2 pg/mL (< 5 pg/mL), IL-8 515 pg/mL (< 62 pg/mL), IL-2R 220.00 U/mL (223-710 U/mL), IL-6< 2.00 pg/mL (< 5.9 pg/mL), and TNF-α 13.10 pg/mL (< 8.1 pg/mL)	IL-1β< 5.00 pg/mL (< 5 pg/mL), IL-8 6.25 pg/mL (< 62 pg/mL), IL-2R 220.00 U/mL (223-710 U/mL), IL-6< 2.00 pg/mL (< 5.9 pg/mL), and TNF-α 5.33 pg/mL (< 8.1 pg/mL)
Other infection indicators	Fecal routine examination showed presence of pyocytes and phagocytic cells and positive fecal occult blood test.	Fecal occult blood positive
Immunity-related indicators	Alexin C1q 38.92 mg/dL (1.18-2.38 mg/dL); Antibody to IBD: ASCA-IgG positive	/
Imaging examination	MRE showed abnormal signal in the small intestine, ileocecal region, and multi-segmental colorectal wall, with some walls slightly thickened. There was an increase in mesenteric lymph nodes, some of which were enlarged. The fat space between the ileocecal mesenteries was slightly blurred, consistent with the radiographic findings of inflammatory bowel disease.	Roughly normal
Pathological biopsy	Minimal lymphocytic infiltration was observed in the esophageal mucosa. The gastric antrum mucosa showed mild inflammation, and the duodenal mucosa had mild lymphoid tissue hyperplasia. The ascending colon mucosa had mild chronic inflammation accompanied by lymphoid tissue hyperplasia, while the transverse colon mucosa was mildly inflamed, with active changes (+), visible crypt abscesses and crypt inflammation, accompanied by shallow ulcers. The descending and sigmoid colon, as well as the rectal mucosa, showed mild chronic inflammation, accompanied by focal erosions and mild lymphoid tissue hyperplasia.	Mild chronic inflammation with mild lymph tissue hyperplasia was present in the esophagus, stomach, and duodenum mucosa. Slight chronic inflammation with lymph tissue hyperplasia was observed in the colon mucosa, including distortions of crypts and mild crypt inflammation. In the descending colon, sigmoid colon, and rectal mucosa, mild chronic inflammation with focal erosions was observed, accompanied by lymph tissue hyperplasia.

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MRE: magnetic resonance enterography

NK-T细胞发育[7], 调节CD8$^+$ T细胞的增殖[8], 抑制Th17细胞分化[9], 诱导Ⅰ型干扰素抗病毒[10], 维持白介素1受体拮抗剂(IL1RN)抗炎基因的表达并抑制TREM1的上调[1]。总之ELF4转录因子是炎症反应的负性调控因子, *ELF4*基因发生突变将会导致炎症失控。

2.2　ELF4蛋白功能学与临床表征的关联

已知ELF4转录因子可抑制Th17细胞分化并诱导Ⅰ型干扰素产生。Th17细胞通过分泌IL-17促进中性粒细胞募集及炎症反应[11]。Ⅰ型干扰素既能通过诱导IL-27限制Th17细胞的发育[12], 又能抑制致热原IL-1的产生[13]。我们推测*ELF4*突变体因无法驱动上述过程, 所以导致2例患儿反复发生黏膜炎症及发热。此外*ELF4*在小鼠和人类结肠中均存在高表达[14]。*ELF4*敲除小鼠不仅出现了肠道炎症的加剧还伴有ILC3数量和功能的明显下降[15]。研究

发现ILC3可通过IL-22诱导黏蛋白和再生基因(REG)蛋白产生,这两种蛋白在肠道黏膜的保护修复中发挥着重要作用[16]。因此*ELF4*的正常表达有助于抑制结肠炎的发生[15]。这也就解释了为什么DEX患儿腹部症状频发。

2.3 DEX病例临床表征

目前报道的11例DEX患儿临床表现多样。常见的症状包括口腔溃疡、贫血、炎症性肠病、发热、反复呼吸道感染、肛周溃疡、关节炎、血管炎。部分患儿还伴随全身多系统损害[1, 3-4]。

2.4 DEX与白塞病、克罗恩病的异同点

DEX是一种新发现的单基因炎症失调性疾病,表现为早发性黏膜炎症、消化道炎症及消化道外症状。白塞病是一种全身慢性血管性炎症,其临床特点包括复发性口腔阿弗他溃疡、生殖器溃疡、眼部炎症、胃肠道炎症及关节炎、皮肤病等[17]。而炎症性肠病是一组慢性非特异性肠道炎症疾病,临床上包括溃疡性结肠炎和克罗恩病。其中克罗恩病可累及从口腔到直肠的全消化道,以腹痛、慢性腹泻及肠梗阻为主要表现,部分患者也可出现如皮疹、关节炎及眼部炎症等肠外症状[18]。单从临床症状难以精准区分三者。

此次报道的2例患儿部分症状如口腔及肛周溃疡与白塞病类似,消化道症状与病理活检又高度符合炎症性肠病。这也是我科初期诊断考虑白塞病、克罗恩病和极早发炎症性肠病的原因。

但三者也具有不同之处。与白塞病相比两DEX患儿均无眼炎症状且针刺反应均阴性。与克罗恩病相比两患儿炎症指标更轻微,自身抗体较少阳性,溃疡更表浅,镜下增生亦不明显。就溃疡好发部位而言,DEX表现为全结肠均匀受累,白塞病好发于回盲部,而克罗恩病好发于末端回肠。就消化道内镜特点而言,我院DEX患儿镜下见多个表浅、形态不规则的溃疡,而肠白塞病镜下以圆形、局灶性分布、边界不连续且黏膜无鹅卵石样外观的溃疡为主[19]。就病理活检而言,DEX以非特异性炎症为主,白塞病和克罗恩病分别以显著血管性炎症及增生性炎症为主。

2.5 DEX治疗展望

在治疗中患儿1和患儿2在糖皮质激素使用基础上采用了前者联合美沙拉嗪,后者联合巯嘌呤及肠内营养的治疗方式,两者临床症状均得到缓解。结合*ELF4*基因功能,关于DEX患儿的治疗我们也有以下思考。①或可制备适用于人类的含小鼠TREM-1细胞外结构域和人免疫前蛋白-g(IgG1)FC部分的融合蛋白产物(mTREM-1/IgG1)。*ELF4*突变体难以直接抑制TREM-1炎症因子的放大,研究发现用mTREM-1/IgG1预处理的小鼠不仅能阻止TREM1与其配体相结合,还可有效降低小鼠体内炎症因子TNF-α、IL-1β的水平[20]。患儿2病程中TNF-α及IL-1β指标均升高明显。适用于人类的mTREM-1/IgG1产物或有助于缓解病情。②可使用IL1RN、IL-12p40阻断剂或肿瘤坏死因子(TNF)阻断剂进行治疗。阿那白滞素(Anakinra,一种IL1RN的重组体)、乌司奴单抗(Ustekinumab,IL-12p40阻断剂)和阿达木单抗(Adalimumab,TNF阻断剂)分别对3例国外DEX患者的有效治疗[1]提示必要时也可将其用于国内患者。③需重视蒙脱石对腹痛、腹泻明显的DEX患儿的使用。蒙脱石是一种天然铝镁硅酸盐黏土,可以通过吸附肠道的细菌、病毒改善腹泻[21]。实验发现口服蒙脱石粉可以防止*ELF4*下调,并减轻结肠黏膜中DNA的损伤[15]。

我院报道的2例患儿随访时间短,缺乏远期预后评估,其临床特点仍待补充。目前DEX患儿的诊治并未形成统一标准,建议完善该罕见病诊治指南。突变*ELF4*基因与DEX疾病的临床关联仍有待广大医务工作者积极探索。

* * *

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Author Contribution WANG Nan is responsible for conceptualization, formal analysis, investigation, methodology, writing--original draft, and writing--review and editing. XIE Yongmei is responsible for funding acquisition, project administration, resources provision, supervision, and writing--review and editing. WANG Zhiling is responsible for supervision and writing--review and editing. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

利益冲突 所有作者均声明不存在利益冲突

Declaration of Conflicting Interests All authors declare no competing interests.

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（2023 – 07 – 16收稿, 2024 – 02 – 03修回）

编辑　刘　华