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儿童急性坏死性脑病免疫学治疗进展

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摘　要

儿童急性坏死性脑病(ANEC)是一种十分少见的暴发性急性脑病。通常以病毒感染相关的高热症状起病，随后迅速恶化，出现嗜睡、昏迷等进行性意识障碍表现，并伴有抽搐及局灶性神经功能缺损表现。该病起病急、病情重、发展迅速，本病预后极差，死亡率高，目前尚无针对ANEC的特异性治疗方法，通常以免疫治疗和对症支持治疗为主。早期诊断和干预对挽救患儿生命，减少病后后遗症状，提高患儿病后生活质量具有重要价值。本文回顾了近年来ANEC的相关研究进展，并重点对ANEC免疫学治疗主要研究进展进行综述，以期对ANEC的诊疗提供新的思路与方法。

关键词

急性坏死性脑病，儿童，细胞因子风暴，免疫治疗

Research Progress in the Immunological Treatment of Acute Necrotizing Encephalopathy of Childhood

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Abstract

Acute necrotizing encephalopathy of childhood (ANEC) is a rare form of fulminant acute

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encephalopathy. It usually starts with high fever symptoms related to viral infection, and then rapidly worsens, showing progressive consciousness disorders such as drowsiness and coma, accompanied by seizures and focal neurological deficits. The disease has acute onset, severe disease and rapid development, extremely poor prognosis and high mortality. At present, there is no specific treatment for ANEC, usually immunotherapy and symptomatic supportive therapy. Early diagnosis and intervention are of great value in saving the lives of the sick children, reducing the sequelae after the disease and improving the quality of life. This paper reviews the relevant research progress of ANEC in recent years, and focuses on the progress of ANEC immunology, in order to provide new ideas and methods for the diagnosis and treatment of ANEC.

Keywords

Acute Necrotizing Encephalopathy, Children, Cytokine Storm, Immunotherapy Treatment

1. 引言

儿童急性坏死性脑病(acute necrotizing encephalopathy of childhood, ANEC) 1995 年被首次命名，是儿童十分少见的一类疾病[1]-[3]，该病好发于 6~18 个月的婴幼儿，起病急骤、病情危重、发展迅速，预后极差，死亡率可达 40%，其中大概有 70%的 ANEC 患儿在起病 1 周内死亡[4] [5]，据报道，15%~35%的幸存者遗留有严重的如意向性震颤、步态共济失调、偏瘫、四肢瘫痪、手足徐动、构音障碍、眼外运动异常和智力迟钝等[2] [6] [7]神经系统后遗症，只有不到 10%的患者有轻微的神经系统后遗症或没有神经功能缺陷[8]。该病发病原因及发病机制复杂，在众多的机制中，当前主要以病毒感染诱发的免疫失调为 ANEC 发病的关键核心，临床尚无特效治疗药物，常以免疫调节治疗和生命支持及对症治疗为主。早期诊断和干预对挽救患儿生命、减少病后后遗症、提高患儿病后生活质量具有重要价值。

2. 发病机制

目前本病的发病机制尚未完全明确，ANEC 常有前驱感染的诱因，病毒感染较为多见[9]-[16]，支原体、新冠病毒感染后的儿童急性坏死性脑病也有报道[4] [17]-[20]。除上述的病毒感染以外，也出现接种百日咳、白喉、破伤风类毒素等疫苗[21] [22]、肺炎链球菌等细菌感染[23]及应用非甾体类药物[21] [22] [24]等所导致的 ANE 的报道。研究表明，继发于疫苗接种的 ANE 患者与抗体依赖性增强作用及疫苗接种失败有关[24] [25]，各种病原、疫苗接种及非甾体类药物应用等导致的 ANEC 临床表现无明显差异[24] [26]。同时也有相关报道提示基因易感性也能导致该病[27]-[32]。

2.1. 细胞因子风暴

病毒感染之后由机体过度免疫反应所激起的“细胞因子风暴”是当前研究最多、认可度最高的主流假说。病毒感染后，细胞因子风暴瞬间被激活，机体内会产生大量的细胞因子，会损伤血管内皮和破坏血脑屏障，继而导致脑水肿、神经系统微血管血栓形成和神经细胞死亡，加剧脑组织的损伤，诱发 ANEC [33]；同时还可能引发全身性的免疫失衡，导致肝功能不全、急性肾功能衰竭、休克和弥散性血管内凝血等严重并发症，产生类似全身性炎症反应综合征(SIRS)的表现[34]-[36]。

有研究指出在 ANEC 患儿外周血或脑脊液中可见升高的细胞因子如白介素(interleukin)-6、肿瘤坏死

因子 α (tumor necrosis factor-α, TNF-α)、干扰素 γ (interferon-gamma)等，其中最为多见的为 IL-6 和 TNF-α [27] [35]-[37]。IL-6 的生理水平可能提供神经保护，而在病理条件下，较高水平或者过表达的 IL-6 具有神经毒性[38]，而 TNF-α 可以损害中枢神经系统的内皮细胞，并通过激活 Ca^{2+}/CaMKII/ERK/NF-κB 信号通路增加基质金属蛋白酶-9 的表达。细胞因子风暴在神经系统中不直接损害血管壁，而是可以通过胰蛋白酶以及基质金属蛋白酶-9 的活化作用，水解并破坏血脑屏障(BBB)中的蛋白质，增加血管的通透性，进一步引发脑细胞的水肿、出血和坏死[18] [36] [39]。

在对 ANEC 患儿外周血淋巴细胞进行流式细胞术分析发现，在疾病的恢复阶段，CD56 自然杀伤细胞(NK)的比例有所上升，而这一类细胞能够生成大量的细胞因子，这也提示 NK 细胞可能与 ANEC 的病因机制有所关联[20]。

2.2. 遗传易感性

截止目前也有研究认为基因突变也可导致该病，可能是由环境刺激从而造成该病在遗传易感人群中发病发展，而患者生长发育一般在发病前并无特殊临床表现。2003 年一个被定位于 2q12.1-2q13 [31]的常染色体显性遗传并多代发病的 ANE 家系[30]被初次发现并报道，2009 年发现与这一染色体相关的 RANBP2 基因突变为该病致病基因，并将 RANBP2 基因突变相关的急性坏死性脑病命名为急性坏死性脑病 1 型(acute necrotizing encephalopathy type 1, ANE1) [27]。RANBP2 基因的突变有可能引发细胞内线粒体的功能异常，同时也可能对抗原的呈递、细胞因子的信号传递、免疫反应以及血脑屏障的维持等多个方面产生影响[27]。同时有研究表明 ANE1 患儿复发后，由于脑干多次受累以及颅内病变范围的扩大，从而导致神经系统功能恶化，预后较首次发病也明显变差[32]。

CPT II 基因突变也被证实与 ANEC 发病存在一定关联，并与其不良预后也存在一定相关性[28]。CPTII 基因突变将导致线粒体脂肪酸 β-氧化的先天性代谢障碍[40]，致使能量功能中断，尤其影响腺苷三磷酸(adenosine triphosphate, ATP)高消耗器官，而脑毛细血管内皮的线粒体密度高于外周，对 ATP 的需求更多，这可能是 ANEC 患者出现脑水肿的原因之一[27]。CPTII基因突变形成的不耐热表型在高体温时活性严重降低且半衰期明显缩短，即使轻微病毒感染，也可增加患者发热的易感性[41]。

此外也有报道提到电压门控性钠离子通道 α1 亚基(sodium voltage-gated channel alpha subunit 1, SCN1A)、人类白细胞抗原(human leukocyte antigen, HLA) DRB/HLA DQB、Toll 样受体 3 (toll-like receptor 3, TLR3)、3-甲基巴豆酰‐辅酶 A 羧基酶(3-methylcrotonyl-CoA carboxylase, MCC)等基因与 ANEC 相关，但是否是家族性急性坏死性脑病的易感基因，或是急性坏死性脑病中的新分型，仍需进一步深入研究验证[29] [42]。

3. 临床表现与诊断

ANEC 无特征性的临床表现，通常表现为高热后迅速出现抽搐、意识障碍等神经系统症状，临床病程通常分为三个阶段，分别为感染前驱期、急性脑病期、后遗症期[4]。前驱的表现主要包括感染中毒样症状，例如持续的发热、咳嗽、喉咙疼痛等上呼吸道感染现象，腹泻、腹痛、呕吐等消化系统症状、皮疹等也有报道。急性脑病期通常发生在前驱症状出现后 1~3 天，表现为神经系统功能进行性恶化，多伴有高热、惊厥、进行性意识障碍、休克等严重表现[43]，此期患儿可在神经系统症状发生后的几小时内出现意识水平的波动和变化，通常进行性意识障碍发生在惊厥发作后，并逐渐到达高峰，出现如肌张力改变、瞳孔扩大、弥散性血管内凝血、多器官功能障碍甚至噬血细胞综合症等严重并发症[44]-[46]。该期为导致患儿死亡的主要时期。部分患者在症状得到有效控制后会进入恢复期，该期以意识逐渐恢复为主要标志，大部分幸存者会遗留不同程度的神经系统后遗症，极少部分患儿只有轻微神经系统后遗症或完全康复。

但并非所有 ANEC 患儿都会出现上述三个阶段，部分患者在出现神经系统症状之前没有明显的前驱期。

ANEC 的诊断标准最初是在 1995 年由日本学者提出[3]，并在 2009 年被进一步完善和补充[27]：(1) 出现前驱病毒感染表现合并反复的惊厥或意识进行性恶化的症状；(2) 影像学出现包括双侧丘脑、脑干被盖上部、小脑髓质、内囊等区域在内的对称性多部位病灶受损表现；(3) 脑脊液检查中出现蛋白总量升高而细胞数无明显改变的病理变化；(4) 血清转氨酶呈现出不同水平的上升，并伴随着乳酸脱氢酶、肌酸激酶和尿素氮的增高，但一般情况下并不会有血氨升高的表现；(5) 家族中曾出现有类似神经系统感染症状的患者；(6) 有复发性脑病并伴有发热症状的患者。

4. 治疗

该病发病原因多样，发病机制复杂，在众多的机制中，当前主要以病毒感染诱发的免疫失调为 ANEC 发病的关键核心，现尚无治疗该病的特效药，通常以免疫调节治疗和对症支持治疗为主。

4.1. 免疫调节治疗

4.1.1. 静脉输注类固醇激素治疗

类固醇激素既可以通过抑制促炎基因表达及促炎因子的转录从而减少促炎因子的释放，又可以增强抗炎基因的表达，同时通过促进血管紧张素转化酶和中性内肽酶的合成，降解缓激肽，从而通过降低血管通透性来稳定血脑屏障，减轻血管源性水肿[47]，故静脉注射类固醇激素是当前临床治疗 ANEC 的一线治疗手段，但是否使用类固醇类激素、激素治疗的时机、剂量及疗程均无统一意见。有研究指出类固醇药物的使用包括甲基强的松及地塞米松对于细胞因子风暴介导的脑病均有效，且疗效无明显差异[43]，但也有研究认为，接受类固醇治疗的患者预后反而更差[48]。王叶青等人回顾性纳入 38 例儿童急性坏死性脑病病例，按不同治疗剂量分为 2 mg/(kg·d)、10 mg/(kg·d)及 20~30 mg/(kg·d) 3 个治疗组，得出大剂量甲泼尼龙冲击治疗[20~30 mg/(kg·d)]是 ANEC 患儿预后的独立保护因素[4]。Okumura 等人研究发现脑干尚未受累的患儿在发病早期即应用类固醇类药物和免疫球蛋白可能通过改变细胞因子谱改善 ANEC 患儿的预后，然而在脑干病变患儿中，即使在发病后 24 h 内使用类固醇类药物，其疗效也不明显[43] [49]。

4.1.2. 静脉输注丙种球蛋白治疗

静脉输注丙种球蛋白也可通过抑制免疫活性细胞的活化和抑制炎性细胞因子的产生发挥抗炎作用，但 Okumura 等人认为丙种球蛋白单一给药效果欠佳，丙种球蛋白在 ANEC 中对于减少细胞因子作用特异性较低，可能无法抑制高细胞因子带来的后果[43]。但在接受类固醇激素和托珠单抗的患者基础上加用丙种球蛋白治疗的患者在 6 个月时存活的几率是前者的两倍，这可能间接表明丙种球蛋白确实在减少 ANEC 的神经炎症中起作用，因此丙种球蛋白与其他免疫疗法联合使用，可以明显发挥其协同增效作用[50] [51]。

4.1.3. 血液净化疗法

血浆置换是用新鲜血浆或血浆替代品与患者的血浆与进行交换，被认为可以通过清除血液中的高分子量颗粒来改善炎症状况，包括循环中的炎症颗粒，如细胞因子、抗体和免疫复合物等[52]。而 ANEC 与细胞因子持续升高及免疫损伤相关，故血浆置换理论上对 ANEC 有效[53]。故早期积极血浆置换也可通过抑制细胞因子风暴、改善脑代谢从而达到改善神经系统预后的目的[54]。国内一项多中心回顾性研究纳入 29 例明确诊断为 ANEC 的患儿，分为血浆置换组和非血浆置换组，观察患儿治疗前后体内相关有害物质的清除情况及预后，发现血浆置换可在短期内降低血清 C 反应蛋白和降钙素原水平，改善肝功能，提高患儿生存率，改善 ANEC 的预后[55]。同时也有一些研究表明，持续肾脏替代治疗可以减少炎症细胞因子，从而减轻对大脑的毒性作用[56]，尤其是高剂量的持续肾脏替代治疗可更有效地去除循环中细胞

因子水平，但血液膜滤除细胞因子治疗 ANEC 仍有争议，患者可能会出现严重的电解质紊乱，且高剂量持续肾脏替代治疗增加了抗生素清除，并可能由于合并严重细菌感染导致更高的死亡率，同时该治疗对于患儿预后的改善并无提示作用[57]。

4.1.4. IL-6 受体拮抗剂治疗

ANEC 发病机制与细胞因子风暴相关，尤其血清 IL-6 水平在症状出现时对脑病的诊断和其严重程度有预测价值。血清 IL-6 水平可能在脑病发病前几小时升高，同时高水平 IL-6 浓度可能提示进展为脑病。血清 IL-6 水平的时间进程也是判断临床严重程度和治疗疗效的有效指标，有研究显示 IL-6 显著升高到 15,000 pg/mL 后，几乎没有患儿存活，血清 IL-6 最高水平越低，中枢神经系统后遗症越轻[35]。托珠单抗作为全球首个针对 IL-6 受体的人源化单克隆抗体，是 IL-6 受体拮抗剂(IL-6R)，通过竞争性结合 IL-6R，阻断 IL-6 与 IL-6R 结合，减少对炎症和先天免疫反应的下游效应。在正常情况下，托珠单抗不能穿越血脑屏障，但是爆发性的炎症反应破坏了血脑屏障，因此托珠单抗可以进入大脑发挥作用[58]。Koh 等通过监测 3 例 ANEC 患儿分别在脑病发生后 18、20、32 小时内、外周血 IL-6 未显著升高时使用托珠单抗 8~12 mg/kg 给药的单次治疗后外周血 IL-6 水平、预后情况以及 Lee 等比较了接受免疫治疗的各种组合与危重 ANEC 患儿的预后得出在类固醇和免疫球蛋白治疗的基础上，托珠单抗的早期使用具有神经保护作用，因此越早使用托珠单抗越能降低 ANEC 患者死亡率[59]，但短期预后的改善并无明显差别[49] [60] [61]，也有报道显示托珠单抗对严重 ANEC 的短期及长期结局具有有益影响[61]。然而国内有一项多中心回顾性研究报道了危重 ANEC (ANE 评分 ≥ 5 分)患儿入院 24 小时内使用托珠单抗治疗(8 mg/kg)与未使用托珠单抗治疗相比病死率并无明显统计学差异[59]。

虽然免疫调节治疗可以减轻炎症和组织损伤，但也阻碍正常的免疫功能，增加对感染的易感性，故免疫调节治疗的潜在益处应该与相关的风险进行权衡，因此，在免疫调节治疗之前，应密切监测免疫功能和不良反应，严格控制药物的剂量和方案，以确保治疗的安全性和有效性。

4.2. 其他治疗

除了上述治疗外，一些对症治疗也至关重要。亚低温治疗治疗也被认为是治疗 ANEC 的一种特殊方法。Yokota 等人提出了流感相关性脑病的病理生理假说。治疗性亚低温降低了人类脑损伤后全身和颈内血浆 IL-6 水平。早期亚低温治疗可能具有抗细胞因子作用，可减轻细胞因子风暴引起的脑损伤。同时亚低温治疗也被用来通过减少脑水肿来控制颅内压[62]。对于 CPTII突变所导致的不耐热表型的病例，及时应用轻度治疗性低温可能迅速恢复酶活性，减轻线粒体能量代谢障碍[63]。故 ANEC 患儿应在发病早期就接受亚低温治疗，能极大程度降低体内细胞因子水平从而改善预后[61]。由于 ANEC 具有基因易感性，故对于 ANEC 病例，都应考虑进行遗传分析，作为长期治疗的潜在手段。ANE1 主要是由于线粒体功能障碍而影响脑部能量代谢活跃区域发病。而基因突变如 RANBP2、CPTII均可引发线粒体功能障碍，导致能量代谢衰竭[27] [40]。因此，采用包含 B 族维生素、左卡尼汀、辅酶 Q10 等药物的线粒体鸡尾酒疗法，可能有助于改善线粒体氧化磷酸化的松散耦联[64]。国内病例报道指出，早期应用线粒体鸡尾酒疗法可显著改善患儿病情[65] [66]。鉴于免疫调节治疗 ANEC1 的复杂性，线粒体鸡尾酒疗法可能成为其治疗的重要辅助手段[40] [67]。同时积极控制体温、降低颅压、镇静止惊、呼吸支持及维持血流动力学等生命支持治疗等。积极的康复训练对于一些遗留神经系统后遗症状的 ANEC 患儿也起到了改善病后生存质量的重要作用。此外，由于多数 ANEC 继发于流感病毒感染后，虽尚未证实流感疫苗对 ANEC 的发病率和死亡率有直接影响，但可以限制流感病毒相关性 ANEC 的发病率[68] [69]，因此加强儿童流感疫苗接种至关重要。对于流感病毒感染的 ANEC 患儿，应尽早使用神经氨酸酶抑制剂，如奥司他韦、扎那米韦或帕拉

米韦，可能会降低死亡率，改善疾病的长期预后[70]。

由于 ANEC 较为罕见，有关研究和诊疗经验也相对有限。随着医学技术的不断进步，近年来涌现出越来越多关于 ANEC 的研究报道，并且随着学者们对 ANEC 研究的不断开展，ANEC 相关研究已经取得长足的进展，然而当前对于 ANEC 的发病机制尚不明晰，ANEC 治疗方式仍存在较多争议，且治疗手段匮乏、治疗效果不一，仍需进一步临床循证医学证据支持。在未来，希望开展更多关于 ANEC 其发病机制及诊疗的研究，以期对 ANEC 进行提供更加准确的诊断和有效的防治，以挽救患儿生命，减少病后后遗症状，提高患儿病后生活质量。

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