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儿童急性坏死性脑病治疗研究进展

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摘　要

儿童急性坏死性脑病(acute necrotizing encephalopathy of children, ANEC)多见于病毒感染诱发，临床以意识水平迅速发生障碍、惊厥发作为主要表现，目前发病机制暂不清楚，目前普遍认为与细胞因子风暴有关，基因易感性也在发病中起到一定作用。急性坏死性脑病早期缺乏特异性临床表现，严重威胁儿童生命，目前暂无特殊治疗方式，除对症支持治疗外，控制细胞因子风暴同样重要，主要包括丙种球蛋白、糖皮质激素、IL-6阻滞剂(托珠单抗)等被用于治疗该病，早期及时控制细胞因子风暴有助于改善患儿预后，但仍遗留较高的致残率，需进一步研究对于急性坏死性脑病的治疗方式，从而提高生存率和降低致残率。

关键词

急性坏死性脑病，儿童，发病机制，诊断，治疗

Research Progress on the Treatment of Acute Necrotizing Encephalopathy in Children

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Abstract

Acute necrotizing encephalopathy in children (ANEC) is often induced by viral infection. The main clinical manifestations are rapid disturbance of consciousness and convulsion. At present, the pathogenesis is not clear. It is generally believed that it is related to cytokine storm, and genetic susceptibility also plays a certain role in the pathogenesis. Acute necrotizing encephalopathy is the lack of specific clinical manifestations in the early stage, which seriously threatens children's life. At present, there is no special treatment. In addition to symptomatic support treatment, it is also important to control cytokine storm, mainly including gamma globulin, glucocorticoid, IL-6 blocker (trozumab). Early and timely control of cytokine storm is helpful to improve the prognosis of children, but it still leaves a high disability rate. It is necessary to further study the treatment of acute necrotizing encephalopathy so as to improve the survival rate and reduce the rate of disability.

Keywords

Acute Necrotizing Encephalopathy, Children, Pathogenesis, Diagnosis, Treatment

1. 引言

儿童急性坏死性脑病(acute necrotizing encephalopathy of children, ANEC)是一种全球分布且罕见的疾病，最初由 1995 年 Mizuguchi 等人最初发现，临床以发热、抽搐、意识障碍及多脏器功能衰竭为主要表现，以及影像学表现为对称性多灶性脑损害，主要累及双侧丘脑、脑干背盖、大脑白质、小脑等，幸存者多遗留神经系统障碍，其病死率大约 30%，但仍有 10%的患者可痊愈，并无任何神经系统症状[1] [2]。本文将从流行病学、发病机制、诊断标准、治疗、预后等方面对其进行探讨。

2. 流行病学

目前尚无针对急性坏死性脑病的流行病学研究，ANE 最初发现于日本和台湾儿童，故怀疑该病可能与种族因素有关[3]。但后来西方国家也有相关报道，包括一些成人病例[4]，表示该病发生与种族因素无关。本病全年均可发病，多见于冬季，男女发病率并无明显差异。该病多认为继发于病毒感染，包括甲型流感和乙型流感、新型甲型流感(H1N1)、副流感、水痘、人疱疹病毒-6 和疱疹病毒 7 型(HHV-6 和 HHV-7)、肠道病毒、轮状病毒、单纯疱疹病毒、柯萨奇 A9 病毒和麻疹等[2] [5] [6] [7] [8]，其中流感病毒、人疱疹病毒-6 最为常见。另外，自 2019 年新型冠状病毒在全球流行，新型冠状病毒相关性急性坏死性脑病已逐渐成为儿童重症和死亡的原因之一[9] [10] [11] [12]。除上述病毒感染外，ANE 还可继发于肺炎支原体[13]及白喉、破伤风类毒素和全细胞百日咳疫苗接种等[14]。尽管有个案报道提示脑脊液中可能存在某些病毒的 PCR 检查呈阳性，但通过尸体解剖及病理检查并未发现脑炎相关线索，因此并不认为是一种病毒性脑炎[15] [16] [17]，因此普遍认为该病与感染后宿主免疫应答引起细胞因子风暴有关。

3. 发病机制

目前急性坏死性脑病的发病机制暂不清楚，目前普遍认为与细胞因子风暴有关，细胞因子风暴是由

细胞因子和白细胞正反馈共同组成，似乎是 ANE 的共同特征。该病的病理特征为病变部位血脑屏障破坏，伴脑出血、细胞坏死和损伤，但无中性粒细胞、淋巴细胞等炎症细胞浸润。有研究发现在 ANE 患者中发现细胞因子升高，故提出“细胞因子风暴”在该疾病发病机制中发挥核心机制的可能性[18]。细胞因子风暴可导致全身症状，如肝功能损害、急性肾功能不全、休克和弥散性血管内凝血(Diffuse intravascular coagulation, DIC)，在神经系统中可改变血管通透性而导致脑损伤[19]。此外，已有多项研究表明 ANE 患者血清和脑脊液的细胞因子升高，包括 TNF-α、IL-6、L-10、IL-15、IL-1、IFN-γ 等，其中 TNF-α 和 IL-6 最为重要[1] [20] [21]。有研究表明在脓毒症相关性脑病中 IL-6 和 TNF-α 等升高的细胞因子可破坏血脑屏障，随后增加血管通透性导致脑水肿、点状出血和坏死[22] [23]。Haorun Huang 等人对 22 例开颅患者进行脑脊液 IL-6 检测并用动物模型证实，发现高浓度 IL-6 会引起的下丘脑损伤从而损伤认知功能[24]，而 TNF-α 可导致血脑屏障通透性增加，可能会损害中枢神经系统内皮细胞[25]。

此外，除环境因素，ANE 的发生也与遗传因素有关，Neilson 及其同事在核孔蛋白基因 RANBP2 中发现了 ANE 的遗传易感性[26]，该基因突变为常染色体显性遗传伴不完全外显率。RANBP2 基因突变可能影响细胞内线粒体运输或能量产生和脂质过氧化，并影响包括病毒进入、抗原呈递、细胞因子信号传导、免疫应答和血脑屏障维持等功能[18]。但并非所有的复发或家族性 ANE 与 RANBP2 基因有关，编码电压门控钠离子通道 α 1 亚单位(sodium voltage-gated channel alpha 1, SCNIA)和肉碱棕榈酰转移酶 II (carnitine palmitoyl transferase II, CPT2)的基因突变也与 ANE 有关[27] [28]。部分人类白细胞抗原基因型(human leukocyte antigen, HLA)与 ANE 易感性之间似乎也有关联[29] [30]。但这些并不足以解释 ANE 的发病机制。

4. 诊断标准

急性坏死性脑病是以高热后急性脑功能障碍为特点，其前驱症状根据不同病原体感染从而不同，如咳嗽、咳痰等呼吸道症状，呕吐、腹泻的消化道症状，严重者甚至还会出现全身炎症反应综合征，随病情进展可很快发生严重颅高压、脑疝，进而出现脑功能衰竭甚至脑死亡，其存活者往往会经历三个阶段，包括前驱期、急性脑病期、恢复期[1] (见表 1)。由于 ANE 患儿的症状、体征及辅助检查结果缺乏特异性，ANE 的诊断主要基于临床症状和典型的神经影像学表现，因此只有在排除其他类似疾病之后才能明确诊断[2] [31]。颅脑 MRI 为最具诊断意义的影像学检查，但因 CT 检查耗时短，可作为危重症急性坏死性脑病的初始检查。

Table 1. Progress in clinical manifestations of acute necrotizing encephalopathy
表 1. 急性坏死性脑病临床表现进展

前驱期	急性脑病期	恢复期
高热或超高热、咳嗽、呕吐、腹泻、皮疹等表现	惊厥发作(多发生在 24~72 小时)、昏迷、意识进行性障碍等	多数为遗留神经系统后遗症(瘫痪、发育迟缓、癫痫等)，少数恢复完全康复(大约 10%)

ANE 的诊断标准在 1995 年由 Mizuguchi [2]等人提出：(1) 感染性疾病发热后短期内出现抽搐、意识障碍等急性脑病症状；(2) 脑脊液蛋白升高，无细胞数增多；(3) 影像学提示多灶性对称性病变，主要累及双侧丘脑、基底节区、脑室周围白质、内囊、脑干被盖等；(4) 血清转氨酶不同程度升高，乳酸脱氢酶、肌酸激酶和尿素氮亦有增高，无高氨血症；(5) 排除其他类似疾病(代谢性、感染性、中毒性、自身免疫性等)。其中急性脑功能障碍和双侧丘脑对称性损害为诊断的必要条件。

随着家族性或复发性急性坏死性脑病(ANE1)的提出，Neilson [26]等在原本的 ANE 诊断标准上做出补充，增加了以下三条诊断标准：(1) 家族中有相似的神经系统症状者；(2) 复发性脑病伴发热者；(3)

头颅 MRI 显示病灶也可累及以下部位：颞叶内侧、岛叶、屏状核、外囊、杏仁核、海马、乳状体、脊髓。

5. 治疗

目前对于 ANE 患儿并无特效治疗方法，主要采取以免疫调节、生命支持为主的综合治疗。免疫调节治疗主要包括糖皮质激素和丙种球蛋白、托珠单抗、低体温等，对抑制细胞因子风暴有一定效果。

5.1. 糖皮质激素和丙种球蛋白

由于细胞因子风暴在疾病过程中的潜在作用，以大剂量糖皮质激素或静脉注射免疫球蛋白(intravenous immunoglobulin, IVIG)最常用。Okumura [32]等人在研究中发现对于不合并脑干损伤的 ANE 患儿，早期(24 h 内)使用大剂量糖皮质激素(甲泼尼龙 30 mg/kg·d，持续 3 天)与较好的预后有关。最近有一篇研究也表明早期使用大剂量类固醇激素与较好的预后有关[33]。我国一项单中心回顾性研究表明大剂量甲泼尼龙(20~30 mg/kg·d)冲击治疗和丙种球蛋白(2 g/kg·d，3~5 天滴注)是预后的保护性因素，其中大剂量甲泼尼龙冲击治疗是预后的独立保护因素[34]。另外，我国一项多中心回顾性研究表明存活组应用大剂量激素(20 mg/kg)比例高于死亡组，可能会改善 ANE 患儿预后[35]。同样，对于复发的 ANE1 患者，在发病 24 小时内用 20 mg/kg·d 的甲基强的松龙治疗 5 天，然后用甲基强的松龙 2 mg/kg·d 治疗 6 周，与未予以免疫调节治疗的患者相比，有更好的改善及恢复[36]。因此早期(48 h 内)大剂量使用甲基强的松龙(20~30 mg/kg·d，持续 3~5 后减量)可能有利于改善患儿预后，但仍缺乏大量多中心、随机对照实验，其具体剂量、疗程以及是否联用尚未达成国际共识。

5.2. 托珠单抗

由于 IL-6 在细胞因子风暴较为重要，高浓度具有神经毒性作用，因此控制 IL-6 水平可能成为 ANE 的治疗方法。有一项研究发现对累及脑干而无 RanBP2 基因突变的高危 ANE (ANE-SS = 5)患者，在神经系统出现症状后 18~32 小时使用托珠单抗(针对 IL-6 受体的单克隆抗体)，在随访过程中 2 名患者完全康复，1 名患者出现轻度功能障碍，考虑病初与大量出血有关，表明早期使用托珠单抗可能有助于改善预后[37]。另外有研究发现早期(24 小时内)使用托珠单抗有利于改善预后以及托珠单抗联合甲泼尼龙、丙种球蛋白可提高 ANE 患者的生存率[38] [39]。总之，早期联合使用托珠单抗可作为 ANE 患者的附加治疗。但 IL-6 在抗感染的免疫反应中起关键作用，因此 IL-6 阻滞剂(如托珠单抗)可能会增加患者感染的风险，在治疗过程中需密切关注患者感染迹象。但托珠单抗的具体剂量和方案应根据患儿疾病类型和患者自身情况而不同。

5.3. 亚低温

亚低温可降低大脑代谢和脑血流量，并且具有抗炎作用[40]。亚低温能够减少促炎因子 NF-κB 的核转录，并降低 ANE 患者促炎因子水平，包括 IL-6 和 TNF-α，从而起到抗细胞因子作用[41]。有病例报道显示低体温联合其他抗炎药物可用于治疗 ANE，并获得较好的预后[42]。但亚低温可能会引起包括心律失常、凝血功能障碍等潜在风险，因此在治疗过程中需谨慎选择患者、仔细全面评估。

5.4. 丝氨酸蛋白酶抑制剂

丝氨酸蛋白酶在炎症反应中起关键作用[43]，因此阻断其活性可减轻炎症反应。尿胰蛋白酶抑制剂/乌司他丁是一种丝氨酸蛋白酶抑制，在日本被广泛用于治疗急性脓毒血症和 DIC [44] [45]，后者往往是 ANE 常见的临床特征。在脓毒血症动物模型中，用丝氨酸蛋白酶抑制剂治疗可减少 TNF-α、IL-6 和多种其他炎症介质[46]。乌司他丁可抑制 p38 MAPK 磷酸化，从而减少 TNF-α 相关基因的表达[47]。

目前，乌司他丁已在人体中进行评估。在脓毒血症患者中，乌司他丁被证明可以降低 TNF-α 和 IL-6 以及其他促炎介质的水平，同时增加抗炎因子 IL-10 抗炎水平[44] [45]。另外，内源性蛋白酶抑制剂在肝脏内合成，但 ANE 患者常常合并肝功能损害[48]，因此 ANE 患者可能因肝功能损害而减少蛋白酶抑制剂的释放，从而可能进一步加剧免疫反应，丝氨酸蛋白酶抑制剂可能成为治疗 ANE 药物，但仍需要进一步研究。

总之，早期开始免疫调节治疗，可改善其预后，除以上方法，血液净化疗法也可清除血液中的炎症介质，多种方法的联合治疗效果可能优于单一治疗方法。

6. 预后

ANE 是一种进展的、高致死率、高致残率的疾病，其预后较差，其死亡率大约为 30%~40%，存活者多遗留不同程度的神经功能障碍，包括局灶性无力、眼外异常、肌张力障碍/痉挛，或共济失调，极少部分能完全康复。神经系统后遗症往往与大脑受累部位和程度有关，需要支持性治疗[49]。回顾近年的研究发现，年龄 < 2 岁、脑干受累、脑脊液蛋白升高、MRI 提示出血或空洞、延迟治疗等通常提示预后不良[5] [50] [51] [52]。另外，为了更好评估 ANE 的严重程度和预后，Yamamoto [51]等提出的 ANE 严重程度评分(ANE-SS，表 2)和 Wong [53]等提出的 MRI 评分，多项研究显示 ANE-SS 和 MRI 评分可用于评估患者预后[5] [35] [54] [55]。

Table 2. Acute necrotizing encephalopathy severity score in children
表 2. 儿童急性坏死性脑病严重程度评分

项目	得分
休克	3
年龄 > 48 月龄	2
脑干损伤	2
血小板计数 < 100×10^9/L	1
脑脊液蛋白 > 60 mg/dL	1

0~1 分为低风险、2~4 分为中风险、5~9 分为高风险。

综上所述，ANE 是一种罕见且快速进展的坏死性脑病，其发病机制暂不清楚，人们普遍认为是免疫介导相关性脑病，该病预后较差，随着时间推移可能会出现完全康复，其诊断依据主要是基于临床特征和双侧丘脑对称性病变的影像学特征，而排除其他疾病是诊断该病的前提条件。目前正在进行的 ANE 治疗研究主要是围绕抗细胞因子治疗有关，特别是针对 IL-6，但仍需要进一步研究。临床医生需进一步提高对该病的认识，及早诊断和治疗可能有利于改善患儿预后。

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