·特约稿·

全身型幼年特发性关节炎发病机制及治疗进展

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摘 要 全身型幼年特发性关节炎(sJIA)是幼年特发性关节炎(JIA)的一种特殊类型,临床以发热、淋巴结肿大、关节炎、皮疹和浆膜炎为特征,与其他类型相比是最急性和最严重的一种类型,病死率高。近期研究表明,sJIA 的系统炎症与固有免疫系统功能失调有关,属于自身炎症性疾病,固有免疫系统的失调致炎症细胞因子的增加而产生相应的临床症状。白细胞介素(IL)-1 和 IL-6 在 sJIA 的发病机制中发挥了主要作用,而且用 IL-1 和 IL-6 拮抗药治疗 sJIA 取得了较好的疗效。

关键词 关节炎,幼年特发性,全身型;发病机制;白细胞介素

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Advances in the Pathogenesis and Treatment of Systemic Juvenile Idiopathic Arthritis

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ABSTRACT Systemic juvenile idiopathic arthritis (sJIA) is a special type of JIA. It is an inflammatory condition characterized by fever, lymphadenopathy, arthritis, rash and serositis. It is the most acute and severe type, which has a disproportionately high morbidity compared with other subtypes. In sJIA, systemic inflammation has been associated with dysregulation of the innate immune system, suggesting that it is an autoinflammatory disorder. Dysregulation of the innate immune system in sJIA results in increased production of inflammatory cytokines, leading to the distinctive clinical features of the disease. IL-1 and IL-6 play a major role in the pathogenesis of sJIA and treatment with IL-1 and IL-6 inhibitors has shown to be highly effective.

KEY WORDS Arthritis, juvenile idiopathic, systemic; Pathogenesis; Interleukin

幼年特发性关节炎(juvenile idiopathic arthritis, JIA)是儿童时期最常见的慢性风湿性疾病,全身型幼年特发性关节炎(systemic juvenile idiopathic arthritis, sJIA)约占 JIA 中 10%,但各地报道差异较大,从 8%至 54%不等[1-3]。与其他类型 JIA 比较,sJIA 具有独特的临床表现,如发热、皮疹、脾脏增大、淋巴结肿大,实验室检查异常(白细胞升高、血小板升高、贫血、血沉增快、C 反应蛋白升高等),与巨噬细胞活化综合征密切相关。其发病机制尚未完全明确,近期研究表明,固有免疫系统的功能失调可能是 sJIA 发病的重要机制,sJIA 是一种自身炎症性疾病。

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1 发病机制

1.1 触发因素

1.1.1 遗传因素 多项研究表明,少/多关节炎型 JIA 与 HLA 基因相关[4-6],提示少/多关节炎型 JIA 属于获得性免疫学疾病。而 sJIA 与 HLA 基因无关,其基因效应只涉及启动子元素和基因编码 IL-6 和巨噬细胞抑制因子(macrophage inhibitory factor, MIF)的细胞因子/趋化因子[7-10],白细胞介素(IL)-6 基因启动子位置上的一个单核苷多态性(-174)与 sJIA 有关[9-10],IL-6 的基因多态性可致 sJIA 中 IL-6 的过度表达。此外,MIF 基因的 5'侧翼多态性也与 sJIA 相关,患儿血清和滑膜液中高水平 MIF 可导致患儿长期功能损害[7-8]。与 IL-6 和 MIF 基因多态性的相关性提示 sJIA 是一个固有免疫异常所至的疾病。

1.1.2 环境因素 ①感染:感染可能是触发自身炎症性疾病的最重要因素,已经证实细小病毒 19 感染与 sJIA 发病和病情恶化有关[11]。②疫苗:疫苗接种是否

会诱发 JIA,目前尚不能确定。有 1 例 sJIA 患儿接种减毒的水痘疫苗后病情加重的报道[12]。

1.2 *吞噬细胞替代分泌失控*　吞噬细胞包括单核细胞、巨噬细胞和粒细胞。在 sJIA 中,吞噬细胞分泌的前炎症细胞因子 IL-1、IL-6、IL-18 和前炎症蛋白 S100A8、S100A9、S100A12 较其他炎症性疾病显著升高[13-15],IL-6 除外,所有这些分子都由所谓的替代分泌途径分泌,它完全不同于通过内质网和高尔基体进行的细胞内转运机制[16],替代分泌途径失控可致前炎症细胞因子和蛋白质释放而引起 sJIA 的多系统炎症。

1.3 *吞噬细胞异常激活*　在 sJIA 中吞噬细胞异常激活可致前炎症细胞因子(IL-6、IL-1、IL-18)和前炎症蛋白质(S100A8、S100A9、S100A12)分泌。

1.3.1 *前炎症细胞因子*　已证实 sJIA 体内激活的单核细胞分泌的 IL-1 明显高于对照组[17]。IL-1 作用于骨髓刺激粒细胞形成而使外周血粒细胞增多;大脑 IL-1 受体可激活下丘脑体温调节中枢而致发热;IL-1 还可激活内皮细胞引起 sJIA 的皮疹和 IL-6 产生[18]。IL-6 的水平在 sJIA 患儿血清和滑膜液中均明显高于其他型别 JIA,IL-6 升高与疾病活动和疾病的系统表现(如发热、血小板升高、小细胞贫血、生长落后、关节破坏和骨质疏松等)相关[14,19-20],IL-6 还刺激肝脏介导急相蛋白的产生。此外,血清 IL-18 水平在 sJIA 中较其他型别 JIA 明显升高[13],它是影响炎症过程的另一个重要的细胞因子。

1.3.2 *前炎症 S100 蛋白*　前炎症 S100 蛋白包括 S100A8、S100A9 和 S100A12,是由吞噬细胞特异性地分泌,又称骨髓相关蛋白(myeloid-related proteins, MRPs),是钙结合蛋白[21]。在 sJIA 中超常高的巨噬细胞特异性 S100 蛋白与疾病活动度密切相关,而且在其他类型炎症性关节炎和其他自身免疫学疾病、感染性疾病中都不会出现[15,22-23]。因此,这些 S100 蛋白可作为 sJIA 最好的生物标记物,血清 S100A8/S100A9 水平可以作为 sJIA 与感染、淋巴瘤等疾病进行鉴别诊断的指标。

1.4 *自身炎症性疾病*　鉴于上述发病机制及临床特征,sJIA 是一种自身炎症性疾病,而不是抗原驱动的淋巴细胞介导的自身免疫性疾病。sJIA 多系统的炎症,如发热、皮疹、关节炎、淋巴结肿大、肝脾肿大等是因为从激活的吞噬细胞和内皮细胞释放细胞因子失控而产生。

2　sJIA 的诊断

sJIA 可以在儿童时期任何阶段发病,在 1 ~ 5 岁有一个发病高峰期,男女发病率相当[24-25]。sJIA 的临床诊断:每次发热 2 周以上或是否伴发关节炎,伴有下列症状至少一项(一过性皮疹、淋巴结肿大、肝脏或脾脏肿大、浆膜炎),需排除感染和肿瘤[26]。40% 的 sJIA 患儿经过一个循环的病程后在数月内获得永久性缓解,少数患儿在经过多次循环的病程后获得完全缓解,约半数患儿有严重的、持续的疾病过程,可发生严重并发症,如淀粉样变性、巨噬细胞活化综合征等,病死率高。研究表明,下列指标提示预后不良:难以控制的持续发热、激素依赖、血小板增高、多关节炎、起病 3 ~ 6 个月内有关节损伤[27]。

3　治疗

3.1 *经典/传统治疗*　目前的治疗是基于 2013ACR 推荐指南[28],NSAIDs 作为第一线药的地位不确定,特别是对严重病例,而对发热和医生总体评分 ≥7 的 sJIA 患儿首选糖皮质激素治疗,对用 NSAIDs 治疗超过 2 周仍有持续发热的患儿也选择糖皮质激素治疗[29];甲氨蝶呤(methotrexate, MTX)推荐用于活动性关节炎患儿,而对于有发热而无关节炎的患儿不推荐[30];静脉注射糖皮质激素冲击治疗用于严重的及难治性的 sJIA,可迅速发挥较强的抗炎作用,同时减少长期中大剂量应用糖皮质激素的不良反应,常用药物为甲基强的松龙,剂量每次 10 ~ 30 $mg \cdot kg^{-1}$,最大量每次 1 g,每日一次,疗程 3 ~ 5 d。

3.2 *抗 IL-1 治疗*

3.2.1 *阿那白滞素(anakinra)*　阿那白滞素为重组、非糖基化的人 IL-1 受体拮抗剂,能竞争性地抑制 IL-1 与 IL-1 I 型受体结合,从而阻滞在器官和组织中表达的 IL-1 的生物活性。阿那白滞素在 sJIA 中的有效应用首次报道于 2004 年的 2 例经典方案治疗失败的病例[31],另外多个临床研究证实阿那白滞素治疗 sJIA 有效[32-33]。

3.2.2 *卡那单抗(anakinumab)*　卡那单抗为人源性的抗 IL-1β 单克隆抗体,临床研究表明[34],1/3 的 sJIA 在单次接受卡那单抗治疗 15 d 后可达到临床缓解,坚持卡那单抗治疗,1/3 的患儿可停用激素,半数以上的患儿糖皮质激素减量。

3.2.3 *利纳西普(rilonacept)*　利纳西普是抗 IL-1 的融合蛋白,可与 IL-1α 和 IL-1β 结合。研究表明,利纳西普可使 35% ~ 40% 的 sJIA 患儿达到 ACR 儿童 70 应答[35];另一项研究表明,sJIA 患儿应用利纳西普 3 个月后,ACR 儿童 30、ACR 儿童 50、ACR 儿童 70 应答分别达到 78.3%,60.9% 和 34.8%。

3.3 *抗 IL-6 治疗*　托珠单抗(tosilizumab)是一种重组人源化 IL-6 受体单克隆抗体,可阻断可溶性和跨膜

IL-6 受体。托珠单抗有效地治疗 sJIA 首次报道于 2005 年[34],11 例中的 10 例 sJIA 患儿的疾病活动度获得明显减轻;TENDER 研究中,112 例 sJIA 纳入研究,用托珠单抗治疗 1 年后,ACR 儿童 70、ACR 儿童 90 应答分别达到 80% 和 59%,48% 的患儿无活动性关节炎,52% 的患儿停用糖皮质激素[36]。

3.4 抗 TNF 治疗 TNF-α 抑制剂在大多数型别的 JIA 治疗中有效。RUSSO 等[37]证实仅 24% sJIA 患儿对抗 TNF 治疗有反应,13% 的患儿达到稳定缓解,这种疗效结果令人非常不满意。这种极为有限的治疗效果提示 TNF-α 在 sJIA 的发病机制中仅发挥次要作用。

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