

儿童食物蛋白过敏性结肠直肠炎诊断研究进展

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摘 要

食物蛋白过敏性结肠直肠炎(FPIAP)是婴儿期最常见的过敏性疾病之一。由于其发病早,发病率高,FPIAP对患儿及家庭带来了极大身心负担。因此,早期诊断及干预对于FPIAP患儿来说至关重要,但目前临床早期诊断FPIAP仍存在困难,进一步寻找FPIAP早期有效诊断方法或许是未来的研究方向。该文就目前FPIAP诊断相关研究进展进行综述,为FPIAP的进一步研究提供参考。

关键词

食物蛋白过敏性结肠直肠炎, 诊断, 婴儿

Advances in the Diagnosis of Food Protein Induced Allergic Proctocolitis in Children

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Abstract

Food Protein-Induced Allergic Proctocolitis (FPIAP) is one of the most common allergic diseases in infancy. Because of its early onset and high incidence, FPIAP brings great physical and mental burden to children and their families. Therefore, early diagnosis and intervention are very important for children with FPIAP. However, it is still difficult to diagnose FPIAP in early clinical stage at present. Further searching for effective early diagnosis methods of FPIAP may be the direction of future research. This article reviews the current research progress in diagnosis of FPIAP, and provides reference for further study of FPIAP.

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Keywords

Food Protein Induced Allergic Proctocolitis, Diagnosis, Infant

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1. 引言

食物蛋白过敏性结肠直肠炎(Food Protein-Induced Allergic Proctocolitis, FPIAP)是一种因外源性蛋白质引起的非 IgE 介导的结肠、直肠炎性病变为特征的疾病,以血便为主要表现,多发生于婴儿早期[1]。尽管 FPIAP 确切的患病率尚不清楚,但一项纳入了 13,019 名新生儿的队列研究提示, FPIAP 在其中的患病率总体为 0.16% [2],是最常见的非 IgE 介导的食物蛋白过敏性疾病之一[3]。据报道,与正常人群数据相比,非 IgE 介导食物过敏患儿在接受消除食物治疗后,其健康相关生活质量(Health Related Quality of Life, HRQoL)评分明显降低,特别是在身体、情绪和心理社会功能领域[4],同时其家庭活动及生活质量也会受到影响[5]。既往曾患 FPIAP 的患儿,在之后发生功能性胃肠道疾病的可能性也更高[6]。FPIAP 尚无明确的诊断标准,其诊断一般是基于临床,除食物激发试验(Oral Food Challenge, OFC)被认为是诊断的必要条件外,目前还难以对 FPIAP 进行早期识别与鉴别[7] [8]。因此,寻找特异性较高的检查手段对于 FPIAP 的早期诊断与干预都有明显临床价值,现本文综述 FPIAP 诊断方法近年来的相关研究进展。

2. 血液相关标志物

过敏性疾病是包括体液免疫和细胞免疫的一种超敏反应,涉及到全身多个系统[9]。因此实验室检查在一定程度上有助于支持 FPIAP 的诊断,但目前在 FPIAP 患儿血液检测中发现的如贫血、低蛋白血症等表现特异性均不高[10],因此能否在血液中找到特异性足够高的标志物成为了学者们关注的重点。

2.1. 嗜酸性粒细胞

发生食物蛋白过敏时,过敏原由抗原呈递细胞传递给肥大细胞,随后肥大细胞可分泌一系列介质,其中组胺可刺激内皮细胞及上皮细胞释放嗜酸性粒细胞活化趋化因子,促进嗜酸性粒细胞等细胞的浸润,而婴儿早期未完全发育的肠道在明显的嗜酸性粒细胞浸润下可能会显著改变细胞的紧密连接,导致肠道的渗透性增加,因此嗜酸性粒细胞被认为可能是食物蛋白过敏诱导的细胞免疫应答中的直接靶细胞[11] [12],同时血液中嗜酸性粒细胞的增多与胃肠道食物过敏症状严重程度之间也存在一定相关[13]。Arik [14]等发现,在食物蛋白过敏患儿中, FPIAP 患儿的外周血中嗜酸性粒细胞较对照组中其他过敏患儿明显升高。Cetinkaya [15]等研究显示, FPIAP 患儿血中嗜酸性粒细胞都能观察到增多,重度 FPIAP 的患儿升高的程度更大。因此,血液中的嗜酸性粒细胞增高与许多因素有关,包括食物过敏、药物反应、感染、NEC 等[16],在排除其他可能原因后,嗜酸性粒细胞计数仍可考虑作为临床筛查 FPIAP 的生物标志物。

2.2. 平均血小板体积及血小板压积

由于血小板表面表达有高亲和力受体,虽然这些受体表达水平可变,且并不存在于所有血小板中,但也因此过敏性疾病患者的血小板能对过敏原产生反应而活化,同时血小板还能迁移到组织中并与免疫细胞相互作用,从而在免疫反应过程中起到桥梁的作用[17] [18]。平均血小板体积(Mean Platelet Volume,

MPV)被认为是血小板活化的标记物,在哮喘、荨麻疹等许多过敏性疾病的评估中得到了应用[19] [20],因此其与 FPIAP 之间的关系也受到了学者关注。一项研究显示,在 59 名确诊了 FPIAP 的患儿中,平均血小板体积和血小板压积(Platelet Crit, PCT)较对照组显著升高,同时在随访过程中发现未获得过敏耐受的患儿中的值显著高于已获得过敏耐受患儿[21],表明 MPV 与 PCT 不仅有检测 FPIAP 的价值,同时还可对预后的评估提供帮助。但由于研究样本较少,同时既往也没有相关学者做过类似研究,故其能否作为诊断 FPIAP 的生物标志物可能还需要进一步大样本的研究来明确。

3. 粪便相关标志物

非 IgE 介导的食物过敏的特征是肠道炎症及通透性增加,从而粒细胞向肠腔内释放,导致肠道内环境发生变化。同时由于目前缺乏可靠的检验,因此学者们对寻找粪便相关生物标志物的兴趣越来越大[22]。

3.1. 钙卫蛋白

粪便钙卫蛋白(Fecal Calprotectin, FC)是一种钙和锌的结合蛋白,属于钙结合蛋白这一家族,这些蛋白质会在肠道发生炎症时从胃肠道中释放,有研究发现,钙卫蛋白浓度和肠粘膜炎症水平相关[23]。因此,FC 与 FPIAP 之间的关系成为了学者们关注的重点。Zhang [24]等进行的关于 FC 与牛奶蛋白过敏的 meta 分析,共纳入了 12 项研究,包括 310 例患儿与 217 例对照组,最后发现 FC 可作为诊断非 IgE 介导牛奶蛋白过敏患儿的可靠生物标志物。Rycyk [25]等纳入 34 名确诊 FPIAP 患儿和 27 名对照组患儿的研究发现,与被诊断胃肠道功能性疾病的性别与年龄相匹配的对照组相比,FPIAP 患儿粪便中 FC 水平明显升高,行 ROC 曲线分析后发现截断值在 486 $\mu\text{g/g}$ 时特异性最高为 92%。也有文献报道,粪便 FC 的测量或许可用于早期炎症性的疾病的鉴别诊断,但对于患儿的临床结局或食物耐受状况意义不大[26]。Roca [27]等发现虽在早期过敏患儿粪便中 FC 含量高于健康婴儿,但无统计学意义。Diaz [28]等也在关于非 IgE 介导的牛奶蛋白过敏研究中发现,过敏婴儿与对照组婴儿粪便中的 FC 浓度无统计学差异。因此,还需要更多研究来证实 FC 作为诊断 FPIAP 生物标志物的临床价值。

3.2. 嗜酸性粒细胞源性神经毒素

嗜酸性粒细胞性神经毒素(Eosinophil-Derived Neurotoxin, EDN)是由肠道中的嗜酸性粒细胞激活后分泌的,其浓度水平与嗜酸性粒细胞的活化和脱颗粒作用相关[29] [30]。据报道,EDN 不仅是反应嗜酸性粒细胞活性的一个有价值的生物标志物,也是包括食物过敏、特应性皮炎、哮喘、过敏性鼻炎等多项过敏性疾病的有用筛查工具[31]。有研究发现,在 FPIAP 患儿粪便中通过直肠拭子和直肠活检 2 种方式获得的 EDN 值对比对照组患儿粪便中 EDN 的值均显著升高,其 P 值分别为 0.025 及 0.010 [32]。Kalach [33]等测定多种粪便标志物,最终发现 EDN 的 ROC 曲线截断值在 2818 ng/g 时的敏感性和特异性分别为 55% 和 81%。Rycyk [25]等研究也提示 EDN 在诊断 FPIAP 上与粪便 FC 联合检测时效果比单独检测更好,其联合检测的敏感性和特异性分别达到了 88.9%和 84%,提示 EDN 可作为诊断 FPIAP 的生物标志物。但由于以上研究的样本量较少,尚不能完全说明 EDN 的诊断价值,因此有必要进行更大样本的研究来阐述其作用。

4. 肠道菌群

越来越多的证据表明,肠道微生物群的失调要早于食物过敏原致敏的发生,甚至早期肠道微生物丰富度减低与后来食物致敏的可能性增加是相关的,肠道微生物群可能成为 FPIAP 等过敏疾病新的生物标志物来源[34]。Martin [35]等研究 160 名患儿的 954 例粪便样本,其中 81 名婴儿患 FPIAP,79 名婴儿作为对照组,在 FPIAP 患儿中发现了肠杆菌中一个未知属别的细菌的相对丰度增加,甚至在症状出现前就

已经有所增加,同时还发现一个未知梭菌属细菌的相对丰度减少,而在 FPIAP 缓解时,乳杆菌的数量会增加。在一项纳入了 62 名婴儿的前瞻性研究中,FPIAP 患儿粪便中放线菌门构成比显著降低,变形菌门构成比明显增加;双歧杆菌属和瘤胃球菌属构成比明显降低,梭状芽孢杆菌属和志贺氏菌属构成比明显增加[36]。Berni 等[37]发现,FPIAP 患儿粪便拟杆菌和厚壁菌的相对丰度有所增加。Baldassarre [38]等使用益生菌治疗 FPIAP 患儿,并发现 GG 乳酸杆菌可以通过改变肠道菌群组成来改善 FPIAP 症状。以上这些研究发现肠道菌群与 FPIAP 之间的存在一定联系,但目前就这一方面尚无准确的定论。由于婴儿早期肠道微生物的组成是高度动态的,因此可能需要更深入的研究来证实相关推论。

5. 其他可能标志物

除上述之外,还有其他许多的潜在标志物,如 IgG、IgG4、血清 IgE、肿瘤坏死因子(Tumor Necrosis Factor- α , TNF- α)、粪便隐血等。IgG、IgG4 虽然在成人研究中进行了试验,但是还没有任何证据表明其在儿童期诊断非 IgE 介导的食物过敏的有效性,一般与胃肠道通透性及炎症标记物合用于研究中[7]。FPIAP 等非 IgE 介导的食物过敏患儿通常缺乏特异性 IgE,但一些 FPIAP 患儿仍有可能出现与 IgE 致敏相关的过敏性疾病,如特应性皮炎等,因此指南建议是否行特异性 IgE 测定或皮肤点刺试验,应基于患儿过敏史及正发作的过敏症状[3]。TNF- α 是慢性炎症性疾病中的关键细胞因子,Ozen [39]等发现在小于 6 个月及大于 1.5 岁这 2 个年龄段 FPIAP 患儿中,TNF- α 的值都显著高于非 FPIAP 患儿,也有研究显示,FPIAP 患儿粪便中 TNF- α 的值虽然较对照组有升高,但差异无统计学意义[21]。粪便隐血检测因具有无创性、花费少及易获得结果等特点,在 FPIAP 患儿中经常使用。Concha [40]等发现 FPIAP 患儿的粪便隐血阳性率有 84%,在对照组中粪便隐血阳性率也有 34%。提示尽管粪便隐血阳性率足够高,但是在正常儿童中亦有假阳性,故相较于诊断价值,其筛查价值可能更值得关注。

6. 腹部彩超

由于彩超具有无创性、无放射性、相对经济便捷等一系列优点,因此评估其在 FPIAP 患儿诊断相关的应用的研究逐渐增多。一项回顾性研究共包括 13 例诊断为 FPIAP 婴儿,13 名婴儿中有 12 名婴儿的超声结果异常,其阳性表现为肠壁增厚及血管增多,尤其是降结肠和乙状结肠[41]。Jimbo [42]等对 16 例非 IgE 介导的胃肠道食物过敏患儿的研究发现,100%的患儿的超声结果显示出肠壁增厚和蠕动不良,而这些表现在可疑过敏食物排除后消失。腹部彩超在 FPIAP 患儿中的应用价值,提示其不仅可以用于排除其他器质性疾病,同样也能作为一个潜在的辅助诊断手段应用,但由于目前研究较少,可能还需更多研究来证明其临床应用价值。

7. 内镜检查

尽管 FPIAP 的诊断多数是基于临床的,但内镜检查仍是诊断 FPIAP 的金标准。FPIAP 患儿进行活检时,可见伴有淋巴结增生的局灶性红斑,活检的特征表现包括在淋巴结附近的直肠及乙状结肠有明显的嗜酸性粒细胞浸润和脱颗粒[43]。有时过敏性结肠炎行内镜检查可能会显示出非特异性症状,且 FPIAP 病灶较为局限,因此必须进行多次活组织检查才能诊断[44]。通常只有在症状持续不缓解或强烈怀疑其他可能诊断时,才应进行内镜检查,目前指南认为组织学诊断标准为固有层伴有炎症且嗜酸性粒细胞浸润(范围为 5 至 > 50 个/HPF) [3]。

8. 小结与展望

近年来,随着 FPIAP 的发病率呈上升的趋势,人们对 FPIAP 的认识也逐渐提高,对于早期识别 FPIAP 的检查手段也成为了人们研究的热点。尽管目前关于 FPIAP 诊断方法的研究取得了许多进展,但大多数

都处于一个初步的研究, 目前仍没有发现敏感性及特异性较高的非侵入性检查手段。因此, 更大样本、多中心的研究或许是未来的研究方向。

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