

食用小麦后运动诱发过敏反应的研究进展

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摘要: 食用小麦后运动诱发的过敏反应(WDEIA)是一种罕见的,但可能是严重的由IgE介导的食物过敏。单独摄入小麦并不会引起任何症状。然而,当摄入小麦后伴随运动、服用非甾体抗炎药、摄入乙醇时,将引发瘙痒、荨麻疹、血管性水肿、呼吸困难、低血压等过敏反应症状,严重者可致过敏性休克。为避免严重过敏反应,及时准确诊断尤为重要。然而由于对该疾病的认识不足,常被误诊或诊断延迟。作者较全面地介绍了WDEIA的流行病学研究、发病机制、临床症状及其诊断和治疗等方面的研究进展,将有助于提高对WDEIA的意识,以便及早诊断,有效防治。

关键词: 过敏反应;流行病学;发病机制;诊断;治疗

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Research Progress on Wheat-Dependent Exercise-Induced Anaphylaxis

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Abstract: Wheat-dependent exercise-induced anaphylaxis (WDEIA) is a rare but potentially severe IgE-mediated food allergy. The symptoms are not induced by the intake of wheat alone. However, if ingestion of wheat is accompanied by the triggering factors such as exercise, non-steroidal anti-inflammatory drugs, alcohol and infection, allergic symptoms are elicited, including pruritus, urticaria, vascular edema, dyspnea, hypotension and even anaphylaxis. To avoid serious allergic reactions, timely and accurate diagnosis is particularly important. However, diagnosis is often missed or delayed due to the lack of knowledge concerning WDEIA. This review focused on the epidemiology, pathogenesis, clinical symptoms, diagnosis and therapy of WDEIA, aiming to raise the awareness of WDEIA and to improve the early diagnosis and effective prevention and treatment.

Keywords: anaphylaxis, epidemiology, pathogenesis, diagnosis, therapy

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食物依赖运动引起的过敏反应 (Food-Dependant Exercise-Induced Anaphylaxis, FDEIA) 是摄入食物后进行运动而导致的一种特殊类型的过敏反应。1983 年 Kidd 等首先提出 FDEIA 概念^[1]。而 Kushimoto 等于 1985 年首先报道了小麦相关的 FDEIA。这种疾病被称为小麦依赖运动诱发的过敏反应 (Wheat-Dependant Exercise-Induced Anaphylaxis, WDEIA)^[2]。

小麦具有很高的营养价值和适口性,可以加工成许多食物,如面包、啤酒等。然而,小麦越来越被认为是引起免疫介导的食物过敏的主要诱因之一,包括 IgE 和非 IgE 介导的食物过敏。IgE 介导的小麦过敏可分为呼吸过敏(面包师哮喘和鼻炎)、小麦食品过敏和 WDEIA^[3-4]。WDEIA 患者仅能耐受小麦制品的摄入,但当同时存在其他辅助增强因素,如运动、感染等,会出现严重的 I 型过敏反应^[5-8]。为科学地认识并有效防治 WDEIA,作者主要介绍 WDEIA 的流行病学、发病机制、临床症状及其诊断和治疗方法。

1 流行病学研究

小麦是诱发 FDEIA 的最常见的食物。Silvade 报告了斯里兰卡两个过敏反应诊所在 2011—2015 年共 19 例 FDEIA 患者的回顾性研究,19 例患者均有小麦依赖性运动诱发的过敏反应^[9]。2012 年,在日本横滨地区的初中生中,FDEIA 的发病率为 0.018%,学生男女比例为 1:1,致病食物分别为甲壳动物($n=5$)、小麦($n=4$)和未知($n=5$),WDEIA 占 28.57%^[10]。这与之前的研究没有显著性差异^[11]。而横滨地区的小学生 FDEIA 的患病率为 0.004 7%,明显低于初中生,其中 WDEIA 占 50%^[12]。有研究发现韩国首尔国立大学医院 2000—2006 年过敏病人发病率为 0.014%,其中 18 例被诊断为 FDEIA,致病食物为小麦($n=14$)、苹果、虾($n=1$)、未知($n=2$),WDEIA 占 77.78%^[13]。随后在 2013 年有关韩国成人小麦过敏的报告中,6 例小麦过敏中有 3 例是 WDEIA,占 50%^[14]。

WDEIA 可以在任何年龄表现出来,且多见于没有任何食物过敏史的青少年和成年人^[15]。WDEIA 在成人中的发生频率高于儿童,主要发生在 18~30 岁的年龄范围内^[16-17]。有研究对 2010—2014 年在北京协和医院确诊为 WDEIA 的 283 名患者的性别、来

源地及发病年龄进行统计分析,发现 54%(153/283) 的患者为男性;81.2% 的患者来自以小麦为主食的中国北方,其中 96 名患者来自北京,占总人数的 33.9%;32 名患者来自湖北,占总人数 11.3%;29 名患者来自内蒙古,占总人数的 10.2%;第一次发生过敏反应的平均年龄为(34.1±13.5)岁^[18]。

2 发病机制

WDEIA 在小麦过敏原和辅助因素共同作用下表现出过敏症状。运动、服用非甾体抗炎药以及感染等辅助因素可促进肥大细胞脱颗粒、释放组胺;增加肠道通透性,促进过敏原的吸收^[19],而使患者出现过敏症状。

2.1 过敏原和致敏表位

小麦蛋白质占小麦籽粒质量的 10%~15%,根据蛋白质在盐中的溶解度可分为两部分:1)水/盐溶性组分包括白蛋白和球蛋白,占总蛋白质质量的 15%~20%;该组分包括淀粉酶/胰蛋白酶抑制剂(AAI)亚基以及其他蛋白质,如脂质转移蛋白(LTP)^[20];2)水/盐不溶性组分(麸质蛋白)包括麦醇溶蛋白和麦谷蛋白,约占小麦蛋白质质量的 80%,其中麦谷蛋白约占这一比例的一半^[21-23]。麦醇溶蛋白根据电泳率的不同,又分为 α/β 、 γ 、 ω 型;而麦谷蛋白根据相对分子质量的大小,分为高相对分子质量麦谷蛋白亚基(HMW-GS)和低相对分子质量麦谷蛋白亚基(LMW-GS)^[24]。

据报道,小麦麸质蛋白中的 α/β -麦醇溶蛋白, γ -麦醇溶蛋白, $\omega 5$ -麦醇溶蛋白,LMW-GS 和 HMW-GS 是导致 WDEIA 的过敏原^[25-27],其中 $\omega 5$ -麦醇溶蛋白和 HMW-GS 是主要过敏原,且部分过敏原的 IgE 结合表位序列已从日本和欧洲 WDEIA 患者中鉴定得到(见表 1)。

2.2 辅助因素

2.2.1 运动 诱发 WDEIA 最重要和最普遍的辅助因素是身体活动。诱发过敏所需的运动强度因人而异。有研究表明^[18],大多数反应发生在低强度运动(如散步等)之后。Wong 等人^[30]指出,相对较低的运动强度(步行 15 min)即可在 WDEIA 患者中引起反应。运动可以通过以下几种不同的途径起作用:1)在运动过程中,转谷氨酰胺酶(TG2)可能被激活,这导致小麦肽段和 TG2 之间的缀合,随后与 IgE 结合^[37],但是这种缀合物在循环中的存在仍未被证实;

表 1 导致小麦依赖运动诱发的过敏反应(WDEIA)的过敏原及其 IgE 结合表位

Table 1 Allergen and IgE-binding epitopes identified as associated with wheat-dependent exercise-induced anaphylaxis(WDEIA)

过敏原	名称	相对分子质量/ $\times 10^3$	WDEIA 相关表位
Tri a 19	$\omega 5$ -醇溶蛋白 ^[24,29]	49~55	QQX ₁ PX ₂ QQ ^[30-32]
Tri a 20	γ -醇溶蛋白 ^[24,26]	31~35	QPQQPFQ ^[33]
Tri a 21	α/β -醇溶蛋白 ^[24,26]	28~35	
Tri a 26	高相对分子质量谷蛋白亚基 ^[24,25]	67~88	QQPGQ, QQPGQGGQ, QQSGQGQ ^[34]
Tri a 36	低相对分子质量谷蛋白亚基 ^[24,35]	32~39 ^[28]	

2)剧烈运动时产生乳酸等酸性代谢产物,导致血液 pH 值降低,可能增强肥大细胞活性;此外,运动还可增高体温,促进肥大细胞等炎症反应细胞释放炎症介质^[16,38];3)运动和乙酰水杨酸能增加胃肠道通透性,并促进过敏原吸收到循环血液中^[39];4)运动引起肠道局部渗透压增加,肥大细胞脱颗粒,从而增加肠道通透性^[40-41];5)运动期间血流再分布可能携带过敏原至组织,其中含有对这些过敏原不耐受的肥大细胞,这可能是导致运动期间过敏反应的原因^[42]。

2.2.2 乙酰水杨酸和其他非甾体抗炎药(NSAIDs)在某些情况下,WDEIA 不是由摄食小麦和运动相结合诱导的,而仅是因摄入小麦制品并服用了非甾体抗炎药乙酰水杨酸所诱发^[43],且低剂量的乙酰水杨酸就足以诱发 WDEIA^[44]。研究表明,乙酰水杨酸是引起 WDEIA 患者严重过敏反应的重要辅助因素。研究人员报告了 20 例服用乙酰水杨酸后出现严重过敏反应的 WDEIA 病例^[45]。除乙酰水杨酸外,吲哚美辛、布洛芬和双氯芬酸钠等非甾体抗炎药可能诱发 WDEIA^[46-48]。

非甾体抗炎药可与肠道黏液层和细胞表面磷脂双层相互作用,线粒体氧化磷酸化解偶联,导致肠细胞损伤和肠道通透性增加;抑制环氧合酶(COX),减少微血管的血流量,且在胃酸、胃蛋白酶、胆汁、肠道细菌等侵害性因子作用下,导致胃肠道损伤(炎症、糜烂和溃疡)^[49];损伤胃肠道的细胞紧

密连接,通透性增加,促进过敏原的吸收^[39,50],辅助诱发 WDEIA。此外,非甾体抗炎药可通过增加 Syk 激酶活化来加速组胺释放^[48,51]。

2.2.3 乙醇和感染乙醇也可以作为诱发 WDEIA 的辅助因素^[52],据报道它可以增加胃过敏原吸收并增加组胺释放^[53]。乙醇还可能通过氧化应激引起肠道通透性增加^[54]。此外,感染尤其是早期阶段或临床轻度形式,可作为辅助因素来增加过敏反应。与其他辅助因素相比,感染更加危险,因为无法避免或被预防^[55]。

3 临床症状

WDEIA 的症状通常在小麦摄入后短时间内由身体活动引起,但在极少数情况下可能会发生延迟发作^[56]。相反,如果在运动后很快摄入食物,也可能出现症状^[57]。WDEIA 事件的发生频率因病人而异,从单一发作到多次发作^[58],临床表现和严重程度也各不相同。WDEIA 的典型症状是瘙痒、局部或全身性荨麻疹、血管性水肿,这些症状在运动后几分钟内就会出现,并可发展为呼吸困难、胃肠道症状、低血压以及过敏性休克^[8,16,59]。

4 诊断

WDEIA 的准确诊断对于避免进一步的严重反应是非常重要的。然而,由于疾病的罕见性,诊断时间滞后非常频繁^[8]。事实上,WDEIA 经常被误诊为其他更常见的疾病,如荨麻疹、运动性过敏反应或特发性过敏症^[8]。诊断工具可分为体内试验,如皮肤点刺试验(SPT)和激发试验;体外试验,包括嗜碱性粒细胞活化试验(BAT)、组胺释放试验(HRT)和小麦蛋白特异性 IgE 试验。

对于疑似 WDEIA 的诊断,可能需要进行激发试验,即口服小麦制品后在跑步机上进行最大限度的运动,以确认诊断^[8,55],这有助于了解病理机制,在诊断不明确的情况下尤为重要。然而,激发试验只能确认约 70% 的患者的诊断^[60-61],并且因为不能很好地控制给予的食物量和诱导反应所需的运动强度,风险性高^[8,62-63]。而且试验结果阴性也并不能完全排除 WDEIA,因为在受控制的激发试验中并未考虑其他辅助因素的影响,如运动强度、花粉接触、非甾体类抗炎药物或乙醇的摄入。因此,当血清小麦蛋白特异性 IgE 抗体检测结果为阳性并且临床病史

提示 WDEIA 时,诊断时并不需要常规进行激发试验。

血清中过敏原特异性 IgE 抗体的测定,较常使用 ImmunoCAP,它是过敏原特异性 IgE 抗体体外检测的金标准,可通过荧光酶联免疫测定法 (FEIA) 测定小麦蛋白的血清 IgE 抗体^[64]。有研究发现重组 ω 5-醇溶蛋白特异性 CAP 的灵敏度为 80%,而小麦提取物和麸质蛋白 CAP 的灵敏度分别为 48% 和 56%^[65]。此外,由 ImmunoCAP 检测 ω 5-醇溶蛋白与小麦蛋白的血清特异性 IgE,并计算两者对数值的比值,该比值具有 100% 的敏感性和特异性,可用于 WDEIA 患者的诊断^[66]。此外,与任何过敏性发作一样,急性发作后 WDEIA 患者的血清类胰蛋白酶水平升高,如果在急性反应后 6 h 内测定类胰蛋白酶含量,也有助于确定诊断^[15]。

WDEIA 建议的临床诊断标如下:当患者出现以下 1、2、3、4 或 1、2、3、5 症状时,极有可能是 WDEIA^[16,18]。

1. 当运动前摄入小麦制品,运动期间出现过敏反应体征和症状。
2. 患者在摄入小麦制品后 6 h 内进行运动时发作。
3. 小麦提取物特异性 IgE 阳性,尤其是麸质和(或) ω 5-醇溶蛋白,麸质和(或)醇溶蛋白的皮肤点刺试验呈阳性。
4. 在避免食用小麦制品或在食用小麦相关食品后 6 h 内避免运动,未发生 WDEIA。
5. 未进行运动,但在其他辅助因素如服用非甾体抗炎药(NSAIDs)、摄入乙醇的参与下出现症状。

5 治疗

5.1 避免小麦摄入或其与辅助因素的结合

对在低阈值(如体育活动)激发情况下即可诱发症状的或出现严重反应的患者,以及从事高职业要求(飞行员、警察等)的患者,推荐无麸质饮食;而在不太严重的情况下,避免小麦摄取与辅助因素结合可能就足够了,如仅在剧烈运动后发作者,建议其空腹运动或者运动前 4~6 h 避免摄入小麦制品,并随身携带急救药品^[16,67]。此外,由于小麦蛋白与来自黑麦、大麦和燕麦的相应蛋白质的交叉反应性,

患者是否还需避免摄入其他含谷蛋白的谷物,目前尚不明确。

5.2 药物作用

某些药物可预防 WDEIA 的发作。有报告显示盐酸奥洛他定和酮替芬可抑制 FDEIA 的过敏反应,其中激发食物包含小麦^[68]。Choi 报告了一例 WDEIA,患者在食用小麦前服用酮替芬,激发实验为阴性且没有出现呼吸困难等症状,成功预防了 WDEIA^[69]。口服色氨酸钠(SCG)对于预防 WDEIA 的发作也有效^[70]。Inoue 等的研究表明米索前列醇能够抑制阿司匹林引起的 WDEIA 患者血清醇溶蛋白的升高,抑制过敏原的吸收,从而抑制过敏反应^[71]。韩国 WDEIA 病例使用了 INF- γ 口服免疫疗法治疗后,患者可自由食用含小麦的食物^[72]。

5.3 紧急措施

WDEIA 的紧急治疗措施包括在早期警告信号出现时立即停止体力活动,一旦发生严重过敏反应,症状较轻时可以口服或肌注抗组胺药物,当出现呼吸困难、血压降低等症状时,需立即使用肾上腺素进行抢救^[16]。此外,应指导患者如何使用肾上腺素自动注射器。使用自动注射器装置给予肾上腺素是有效的急救措施,剂量为 0.15 mg 或 0.30 mg,注入股外侧肌(大腿外侧)。根据美国国立卫生研究院的指南,0.15 mg 肾上腺素自动注射器应用于体质质量小于或等于 25 kg 的儿童,包括体质质量小于 10 kg 的健康婴儿;如果需要,可以在至少间隔 5 min 后再给予相同剂量^[73]。

6 展望

WDEIA 是一种相对罕见但可能导致严重过敏反应的食物过敏形式,目前尚欠缺详细的数据,但报道的病例数越来越多,特别是在亚洲和欧洲地区。与小麦过敏不同,WDEIA 可耐受小麦制品的摄入,只有在伴随有运动等辅助因素的共同作用下才会发作,然而因诱发所需运动强度的个人差异性,以及其他辅助因素的多样性,使其易被误诊或延迟诊断。因此全面了解 WDEIA 的相关知识,跟进研究新进展,提高对 WDEIA 的意识,将有助于尽早诊断和有效防治。

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科 技 信 息

澳新拟批准一种麦芽糖 α -淀粉酶作为加工助剂

据澳新食品标准局(FSANZ)消息,2021年6月18日,澳新食品标准局发布160-21号通知,其中A1210号申请,申请将来自转基因酿酒酵母的麦芽糖 α -淀粉酶(maltogenic alpha amylase)作为加工助剂。

[信息来源]食品伙伴网.澳新拟批准一种麦芽糖 α -淀粉酶作为加工助剂[EB/OL]. (2021-6-21). <http://news.foodmate.net/2021/06/597219.html>