

乳糜泻研究进展

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摘要: 乳糜泻是一种遗传易感个体因摄入含麸质蛋白的谷物(小麦、大麦和裸麦)及其制品而诱发的慢性自身免疫性肠病,影响着世界上约1%人口的健康,并呈增长趋势;在中国可能也存在乳糜泻“冰山”现象,发生率远比原先预计的高;然而目前,中国从事医疗卫生和食品工业的专业人员对乳糜泻的认识仍存在不足。本文着重介绍了国内外在乳糜泻的流行病学、发病机制、临床症状、诊断和治疗等方面的研究进展。全面了解乳糜泻的相关知识,提高对乳糜泻的意识,有助于推动中国对乳糜泻的预防和控制,促进无麸质食品的开发和研究。

关键词: 乳糜泻; 麸质蛋白; 基因

Recent advances in celiac disease

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ABSTRACT: Celiac disease (CD) is a chronic autoimmune enteropathy elicited in genetically predisposed individuals by exposure to containing gluten-containing grains (*i.e.*, wheat, barley, and rye), which is affecting about 1% of the world's population and the prevalence of CD is still increasing. In China, an unseen “celiac iceberg”, with the prevalence of CD in adults being higher than previously suggested, cannot be excluded. However, it is still lacking that awareness of CD among Chinese health professionals and food industry professionals. This review focused on the pathogenesis, clinical manifestations, diagnosis, and management of CD. We should raise the awareness of the health and societal impact of CD, develop prevention strategies to guarantee the health and quality of life of Chinese individuals suffering from CD, and promote the development of gluten-free food in China.

KEY WORDS: celiac disease; gluten; genes

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1 引言

小麦是全球第三大粮食作物, 年产量超 6 亿吨, 仅次于玉米和稻谷^[1]。小麦粉可被制作成面包、披萨、面条、馒头、饼干等食品, 而且小麦粉和小麦蛋白作为配料广泛用于食品加工中。小麦及其制品是重要的食物蛋白来源之一, 但同时小麦中所含麸质蛋白也可导致某些疾病^[2], 包括: (1) 由 IgE 所介导的小麦过敏: 典型的食物过敏、面包师哮喘、小麦依赖性运动诱发性过敏反应和接触性荨麻疹; (2) 与自身免疫相关的乳糜泻、谷蛋白共济失调和疱疹样皮炎; (3) 可能由固有免疫所介导的麸质蛋白敏感。

乳糜泻是一种携带有遗传易感基因的个体因摄入含麸质蛋白的谷物(如小麦、大麦和裸麦)及其制品而诱发的自身免疫性肠病, 又称为麦胶性肠病、非热带口炎性腹泻^[3]。乳糜泻的发病率在欧洲白种人中达 1%^[4]。在中国曾被认为极为罕见^[5], 但近几年来接连报道了多例乳糜泻病例, 且从中国人乳糜泻易感基因携带率和小麦消费量等方面分析, 结果显示中国人患病风险远比原先预计的高, 应引起人们的重视^[6]。本文着重介绍近年来对乳糜泻发病机制、临床症状、诊断和治疗方面的新进展, 以提高对乳糜泻的科学认识。

2 乳糜泻的流行病学研究

过去曾认为乳糜泻的发病有明显的地域分布和种族差异, 多见于欧洲和北美的白种人中。然而乳糜泻易感基因人类白细胞抗原(*human leukocyte antigen, HLA*)*DQ2* 和 *DQ8* 单倍型并不仅存在于欧洲人群中, 根据等位基因频率网络数据库(<http://www.allelefrequencies.net>)的检索结果显示南美洲、非洲和亚洲等人群也携带有 *HLA-DQ2* 和 *DQ8*, 而且由于全球小麦的消费量高且分布地域广泛, 乳糜泻发病可能涉及全球^[7]。

在西方普通人群中, 乳糜泻发病率约为 1%, 且在某些地区如瑞典 12 岁儿童(男女比例 1.06)中, 乳糜泻发病率更高, 可达 3%^[4,8]。最近的流行病学研究结果显示, 一些曾被认为乳糜泻发生率低的地区, 如中东、北非、印度等地, 其乳糜泻也较普遍^[9, 10]。在北印度儿童(平均年龄 5.6±3.6 岁, 男女比例 1.33)中乳糜泻发病率也达到 1%^[11]; 在伊朗 18~65 岁健康献血者(男女比例 3.76)中, 乳糜泻流行率为 0.6%, 与伊朗南部 6~12 岁儿童中的流行率相同^[12,13]; 在阿拉伯联合酋长国 16 岁以上的阿拉伯人群中(男女比例 1.09), 乳糜泻的血清学流行率为 1.17%^[14]; 而在沙特阿拉伯 16~18 岁的学生(男女比例 1.11)中, 乳糜泻血清流行率高达 2.2%^[15]。撒哈拉以南的非洲国家和远东等地区, 因人群易感基因频率低和低小麦消费量, 被认为乳糜泻极为罕见。但随着西方饮食习惯的全球性渗入, 使一些原本主要以消费大米为主的国家小麦消费量增加, 将导致这些地区将来

乳糜泻发病率可能增加^[16]。

我国曾被认为乳糜泻发病率极低^[5], 然而近年来接连报道了多例乳糜泻病例^[17-23], 此外, 对乳糜泻高危群体(慢性腹泻和腹泻型肠易激综合征患者)也进行了乳糜泻筛查研究, 结果显示: 在慢性腹泻成年患者中, 乳糜泻发病率大于 6.5%^[24,25], 而在具慢性腹泻症状的儿童中, 此发病率高达 11.9%^[26]; 73 名 20~64 岁的腹泻型肠易激综合征患者中, 有 6 人(8.2%)诊断为乳糜泻^[27]; 另一研究结果显示 282 名 18~23 岁的腹泻型肠易激综合征患者中, 5 例(1.77%)乳糜泻血清抗体检测阳性^[28]; 由此可见, 乳糜泻在中国并不罕见。

此外, 已有研究证实乳糜泻与性别存在一定的关联性, 乳糜泻多见于女性, 其患病率是男性的两倍, 在成人乳糜泻患者中, 男女比例甚至为 1:4^[29,30]。造成不同性别乳糜泻诊断率显著差异的原因可能有以下几点: 女性乳糜泻患者常具有与乳糜泻相关的症状, 而男性患者常无明显症状; 女性自身免疫性疾病的发生率高于男性; 女性更注重日常的健康体检^[31]。

3 乳糜泻的发病机制

乳糜泻是由遗传因素(易感基因)和环境因素(摄入麸质蛋白)共同作用而引发的自身免疫性肠病。

3.1 乳糜泻易感基因

大量有关乳糜泻易感基因的研究已证实乳糜泻主要与位于染色体 6p21 上的 *HLA-DQ* 基因密切相关。研究表明, 携带有 *HLA-DQ2.5(DQA1*0501-DQB1*0201)* 或 *HLA-DQ8(DQA1*0301-DQB1*0302)* 的人群患乳糜泻的风险是未携带者的 13 倍之多^[32]。90% 以上的乳糜泻患者携带有 *HLA-DQ2.5*, 而其余的绝大多数携带 *HLA-DQ8*^[32]。患乳糜泻的风险性还与携带易感基因的数量和种类有关。携带 *DQ2.5* 纯合子的个人, 患病的风险增加 4~6 倍^[33]。此外, 携带 *DQB1*0201* 等位基因的数量与乳糜泻血清标志物抗组织转谷酰胺酶(*tissue transglutaminase, tTG*)抗体水平和肠粘膜损伤程度呈正相关^[34,35]。携带有两个 *DQB1*0201* 等位基因的个体 *tTG* 抗体滴度高, 肠绒毛萎缩和腹泻症状更严重, 发病年龄轻, 经历无麸质饮食后, 绒毛萎缩恢复慢^[34, 35]。

尽管乳糜泻易感基因主要存在于 *HLA* 区域, 但 *HLA* 基因并非是乳糜泻唯一的相关遗传因素。据报道, 40% 携带有 *HLA-DQ2* 或 *HLA-DQ8* 的白种人中实际上仅有 3% 的人患上乳糜泻^[36]。*HLA* 基因对乳糜泻遗传率的贡献大约在 22% 至 44% 之间^[37], 显然, 还存在着其他与乳糜泻相关的遗传因素。研究已发现了 39 个乳糜泻关联的非 *HLA* 基因座, 包含有 115 个不同的基因, 其中参与免疫调节的细胞毒 T 淋巴细胞相关抗原 4 (*cytotoxic T lymphocyte-associated antigen-4, CTLA-4*) 基因、白介素(*IL*)*2/IL21*

炎、原发性胆汁性肝硬化)、非酒精性脂肪肝和非酒精性脂肪性肝炎^[55], 其中不明原因的转氨酶升高是最常见的, 也是乳糜泻最早出现的肝脏症状, 在某些患者中甚至是唯一的症状^[56,57]。据报道, 27%的成人乳糜泻患者和 36%的儿童乳糜泻患者并发有不明原因的转氨酶升高; 反之, 在成人和儿童不明原因的转氨酶升高症的患者中, 乳糜泻的发生率分别为 4%和 12%^[56,57]。在绝大多数病例中, 当患者执行严格的无麸质饮食后, 升高的转氨酶可恢复到正常水平^[56, 57]。

此外, 乳糜泻患者还可能并发疱疹样皮炎、口腔溃疡、牙齿变色或牙釉质脱落、复发性流产或不育、神经系统症状和精神疾病(如共济失调、癫痫、焦虑、抑郁、精神分裂症)等^[49, 58]。

5 乳糜泻的诊断

因成人和儿童患者乳糜泻的临床特征略有差异, 分别制定了相应的乳糜泻诊断指南^[59-62]。诊断方法主要包括血清学诊断、小肠组织活检以及对无麸质饮食的反应性。

5.1 血清学诊断

乳糜泻患者血清中存在着特异的乳糜泻血清标志物, 主要包括抗 EMA 抗体、抗 tTG 抗体、抗脱酰胺麦醇溶蛋白(deamidated gliadin peptide, DGP)抗体、AGA 抗体, 其中, AGA 抗体灵敏度和特异性低, 现已基本不用^[59,60], 目前临床上主要应用的是高特异性和灵敏度的抗 EMA 抗体和抗 tTG 抗体。抗 EMA 抗体特异性高于抗 tTG 抗体, 常作为乳糜泻血清学诊断的金标准, 但其检测方法为间接免疫荧光法, 操作繁琐费时, 检测人员需受专职培训, 结果可能受人为因素影响。抗 tTG 抗体检测采用操作简便的 ELISA 方法, 其灵敏度和特异性也与抗 EMA 抗体相近, 可达 95%~99%, 因此, 其成为目前最常用的乳糜泻血清学诊断方法^[63-65]。临床上也常联合检测抗 EMA 抗体和抗 tTG 抗体, 提高诊断的准确性^[66]。此外, 抗 DGP 抗体是随着乳糜泻发病机制的阐明而较新发现的一类乳糜泻血清抗体, 灵敏度高, 但特异性较差, 阳性预测值低, 常与抗 tTG 抗体联合使用, 若抗 DGP 抗体和抗 tTG 抗体检测均为阳性, 则可显著提高阳性预测值, 进而避免不必要的小肠活检, 被认为应是筛查和诊断乳糜泻最先采用的方法^[67, 68]。

以上乳糜泻血清学抗体均包括 IgA 和 IgG 两类抗体, 除抗 DGP 抗体外, 其余的均表现为 IgA 抗体的特异性高于 IgG 抗体, 因此, 一般检测 IgA 抗体^[7]。因可能存在选择性 IgA 缺乏的患者, 在诊断中, 需先检测血清中总 IgA 水平以排除 IgA 缺乏, 若存在 IgA 缺乏, 则应选用 IgG 抗体检测, 常选择检测抗 tTG-IgG 抗体、抗 EMA-IgG 抗体和抗 DGP-IgG 抗体^[59]。

5.2 小肠组织活检

小肠组织活检是诊断乳糜泻的金标准。但因绒毛萎缩等病理变化也可能见于其他疾病, 如病毒性腹泻、其他蛋白质过敏、淋巴细胞性小肠结肠炎等^[69]; 且轻症的乳糜泻患者肠黏膜病变程度低, 仅发生于局部, 活检取样时有可能未能采集到而被诊断为阴性; 再者, 组织活检有一定侵袭性, 轻症或无症状患者多不愿接受活检。因此, 目前世界胃肠病学组织推荐的乳糜泻诊断的金标准是: 小肠活检阳性, 同时乳糜泻血清学检测阳性才能确诊乳糜泻^[59]。

5.3 其他

对不愿接受小肠活检的乳糜泻可疑患者, 可先进行无麸质饮食治疗, 观察症状是否改善, 血清学抗体指标是否转阴; 再次摄入含麸质的食物后, 症状是否再次出现或加剧, 以此辅助诊断乳糜泻^[62]。此外, HLA-DQ 基因分型也可作为辅助的诊断手段, 用于当小肠组织活检结果与血清学检查结果不一致时, 根据基因检测结果, 进行乳糜泻排除诊断^[59]。

6 乳糜泻的治疗

患者终生无麸质饮食是治疗乳糜泻的最佳方法, 也是目前推荐的方法^[59]。然而因小麦麸质蛋白在食品工业中应用广泛, 患者在日常生活中常易误食含麸质蛋白的食品。为保证乳糜泻患者的饮食安全, 必需做到以下几点: (1) 建立无麸质产品生产链, 确保产品在生产、运输和销售过程中不受麸质污染; (2) 有效、准确地检测产品中的麸质蛋白含量; (3) 建立细致的无麸质产品的标签法。

此外, 目前也有一些新的治疗方法用于辅助无麸质饮食疗法, 主要包括^[70]: 酶制剂降解麸质蛋白、肠粘膜通透抑制剂或肠粘膜修复剂、tTG2 抑制剂和 HLA-DQ2/DQ8 阻断剂、炎症细胞因子抑制剂和抗炎治疗、诱导耐受、接种麸质蛋白肽疫苗、化学治疗和干细胞移植等。

7 展望

随着西方膳食模式快速广泛地渗入中国, 南北方饮食习惯的相互影响和融合, 中国人群的麸质蛋白暴露量快速增长^[6]。这导致中国人群患乳糜泻的风险性增加。然而, 目前我国从事医疗卫生和食品工业的专业人员对乳糜泻的认识仍不足, 有关乳糜泻和无麸质食品的研究欠缺。全面了解乳糜泻的相关知识, 及时追踪新进展, 提高对乳糜泻的意识, 有助于推动我国对乳糜泻的预防和控制, 防止其成为严重的公共卫生问题; 促进无麸质食品的开发和研究。

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