饮食对自闭症的影响研究进展

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摘要 自闭症是一种发育障碍类疾病, 患者常出现严重的行为异常, 丧失语言能力和社交交往能力, 生活基本不能自理, 并且可能需要持续一生的治疗. 随着发病率的攀升, 自闭症已经给患者家庭和社会造成了严重的社会和经济负担. 自闭症的病因和机理尚未完全明晰, 尚缺有效的治疗或干预方法. 目前的研究表明, 饮食与自闭症关系密切, 不良的饮食习惯, 食物中的有害物质, 对营养物质的吸收、利用和代谢异常, 可能影响免疫、内分泌和能量代谢系统, 最终影响大脑的发育. 食物是肠道微生物的重要影响因素, 而肠道微生物对人体健康至关重要, 且通过微生物-肠道-脑轴(菌肠脑轴)影响大脑的正常工作和发育. 食物中的营养、促生长物质及本身负载的微生物为肠道微生物的生长和组成提供了充足的物质基础. 饮食干预不仅能改善自闭症患者的营养状况, 还能缓解一些胃肠道症状以及睡眠、刻板、自残、多动和暴躁等异常行为, 甚至社交和语言能力等也有所好转. 其中, 给自闭症患者服用益生菌, 在明显改善患者的肠道菌群的同时, 自闭症症状得以改善. 因此, 将肠道微生物作为自闭症的诊断和干预靶标正在引起广泛关注, 饮食、肠道微生物与自闭症的关系正在成为当前的研究热点.

关键词

自闭症
饮食
益生菌
肠道微生物
菌肠脑轴

自闭症(autism或autistic disorder)又称孤独症, 是生物性障碍类疾病, 可导致严重的社交行为变化, 主要表现为社交障碍、沟通困难、重复和刻板行为以及言语发育迟缓. 阿斯伯格综合征(Asperger syndrome)、童年瓦解性障碍(childhood disintegrative disorder)和其他待分类的广泛发育障碍(pervasive developmental disorder not otherwise specified, PDD-NOS)等与自闭症或经典自闭症谱系障碍统称为自闭症谱系障碍(autism spectrum disorder, ASD)^[1]. 各国报道的ASD患病比例不同, 英国约为1.57%^[2], 在韩国高达2.64%^[3], 且患病人数逐年明显增加, 据美国疾病控制与预防中心统计, 截止到2013年, 美国6~17岁的孩子中, 每50个孩子中就有1个患有ASD, 并且男性患病比例是女性的4~5倍^[4]. 我国缺乏相关

流行病学调查结果, 据估计约1%的儿童患ASD. 随着发病率的持续升高^[5], ASD已经成为精神类致残的首要疾病, 给家庭和社会造成了巨大的社会和经济负担^[6]. 然而, ASD的病因尚未确定, 也缺乏有效的治疗手段^[7,8].

近年来的研究表明, ASD与饮食关系密切. 饮食影响肠道微生物的数量和构成, 而肠道微生物直接影响肠脑, 通过对肠脑到头脑的干预或将成为当前最安全 and 最基本的ASD治疗方法之一. 本文将对ASD和饮食相关致病因素和相应的治疗方法进行综述, 以期医疗及科研人员和ASD患者家庭提供参考.

1 饮食习惯与自闭症

由于ASD患者对感官刺激异常敏感, 导致患者

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普遍挑食, 据估计有超过90%的ASD儿童存在饮食问题^[9]. ASD儿童通常只吃五六种食物, 普遍拒绝各种水果、蔬菜和蛋白质, 更偏爱零食和高脂肪、高碳水化合物类及加工食品^[10,11]. ASD儿童的营养物质摄入水平和骨密度比正常儿童显著降低, 且缺乏维生素、微量元素、必需氨基酸以及必需脂肪酸等^[12]. 挑食还导致ASD儿童缺乏纤维素, 容易引起胃肠道功能紊乱, 特别是便秘^[13]. 此外, 典型的西方化饮食习惯也可能促进ASD的发生^[14]. 需要指出的是, 零食或加工食品中的防腐剂、保鲜剂、香味剂、抗氧化剂等都属于儿童不宜的添加物.

母亲的饮食习惯也会影响孩子的饮食习惯^[15]. ASD发病的高风险时间是出生前、期间或出生后不久^[16]. 在孩子生长发育的关键时期, 对外界环境更敏感, 各种影响因素都可能对孩子的大脑和神经发育造成影响. 研究发现, 母亲孕期食用含可卡因和酒精的食物会提高孩子患病风险^[7]. 母亲在围产期摄入高脂肪、高糖饮食会对后代的中枢奖赏系统的发育产生不良影响, 使后代更偏向高脂、高糖的垃圾食品^[17]. 而在孕前和孕早期补充叶酸能降低后代患ASD的风险^[18,19]. 此外, 母亲对孩子的喂养习惯也会影响孩子的健康, 过多的食用方便食品和加工食品, 为迎合孩子的喜好过多提供高糖高脂等美味食物都会对孩子产生不利影响. 因此, 要改变ASD儿童的饮食习惯, 降低后代患ASD的风险, 孕妇更要注意自己的饮食习惯和喂养习惯, 在孩子出生后也要时刻注意培养孩子良好的饮食习惯.

2 营养物质与自闭症

食物中的营养物质对维持人体正常的生理和心理健康至关重要. 临床研究发现, 缺乏维生素和矿物质等多种营养物质会导致心理和行为发生改变, 例如, B族维生素和微量元素对脑组织健康和记忆等至关重要, 营养物质缺乏可能对大脑的正常工作产生影响^[20-22]. ASD的发生可能正是由于营养物质的异常引起的.

营养物质已经超越了营养作用, 良好的营养能降低婴儿的出生缺陷^[23]. ASD儿童维生素和微量元素的缺乏程度与ASD严重程度相关^[24]. 补充维生素和微量元素, ASD患儿睡眠情况和肠道症状明显好转^[25]. 口服维生素和微量元素3个月后, ASD儿童的甲基化水平、谷胱甘肽、氧化水平、硫酸盐化水平、

三磷酸腺苷(adenosine triphosphate, ATP)、烟酰胺腺嘌呤二核苷酸(nicotinamide-adenine dinucleotide, NADH)和烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide adenine dinucleotide phosphate, NADPH)等都明显升高, 并且多动和发脾气等行为与安慰剂组相比明显减少^[26,27]. ASD患者服用维生素B6和镁后, ASD儿童的症状得到改善, 警觉性有所提高, 消极、自残、刻板的行为明显减少^[28]. 注射甲基维生素B12能明显改善ASD患者的社会交往行为、语言能力和其他行为问题^[29].

缺乏必需脂肪酸的典型西方饮食可能促进精神疾患的发生^[30]. Omega-3不饱和脂肪酸对中枢神经系统的发育和正常功能具有重要作用^[31,32], 而ASD患者体内大多缺乏不饱和脂肪酸^[33,34], 并且给ASD患者服用Omega-3不饱和脂肪酸6周后, ASD儿童在刻板、多动和不当言论等方面表现良好^[35], 干预12周, ASD儿童的多动行为明显减少^[36]. 然而, 也有研究表明大剂量的补充Omega-3不饱和脂肪酸效果并不理想^[37].

其他营养补充剂, 如谷氨酰胺(glutamine)、低聚糖(prebiotic oligosaccharides)以及L-精氨酸(L-arginine)^[38]、左旋肌肽(L-carnosine)^[39]、抗坏血酸(ascorbic acid, 维生素C)^[40]等对ASD症状也有改善作用.

3 食物代谢与自闭症

ASD儿童的营养状况除受食物中营养物质的影响, 还受食物在胃肠道中的代谢影响. 9%~91%的ASD儿童有胃肠道疾病症状^[41], 包括小肠结肠炎^[42]、胃炎、食管炎^[43]、肠道通透性增加^[44]、双糖酶活性不足^[45]等, 另有约1/2伴有腹泻和便秘^[27,46]. 胃肠道异常将导致ASD儿童对营养物质消化和吸收受到影响. 有36.7%的ASD儿童肠道通透性增加(gut leakage, 肠漏), 使毒性物质易透过肠道进入血液系统, 再透过血脑屏障影响大脑发育^[47]. ASD儿童氧化应激水平升高, 能量运输能力下降、硫酸盐化作用和解毒能力降低; 血液中生物素、谷胱甘肽、红细胞活性腺苷甲硫氨酸、血尿苷、血ATP、红细胞NADH、红细胞NADPH、血硫酸盐以及血色氨酸等明显降低, 而氧化应激生物标记物和血谷氨酰水平显著升高^[48]. 此外, 粪便中的多种短链脂肪酸和氨的含量也显著升高^[49]. 综合来看, 饮食可能通过蛋白质和氨基酸代谢、能量代谢、脂肪酸代谢、氧化还原/甲基化等代谢通路以及肠道微生物对ASD产生影响(图1).

[illegible]

大脑中的多种神经递质都与食物中的氨基酸代谢密切相关。色氨酸(tryptophan)是五羟色胺(serotonin; 5-Hydroxytryptamine, 5-HT)、喹啉酸(quinolinic acid, QA)和犬尿酸(kynurenic acid, KA)的前体物质^[59]。5-HT的水平能影响睡眠障碍和情感障碍等ASD症状^[60]。ASD儿童的5-HT合成能力与正常儿童相比有明显差异^[61]。且30%~40%的ASD儿童外

半胱氨酸(cysteine)在体内可代谢产生硫酸盐(sulfate),参与解毒、儿茶酚胺的失活和合成脑组织、黏蛋白的硫酸盐化等多种代谢途径。血液中神经递质、类固醇、黏多糖、酚类、氨基酸和多肽等物质都与硫酸盐代谢有关,通常ASD儿童血液中的硫酸盐

含量较正常人低^[67], 而ASD患者的尿液硫酸盐、亚硫酸盐、硫代硫酸盐比正常人高, 硫氰酸盐的含量却比正常人低^[68]. 可能大量的硫酸盐随尿液排除体外, 导致ASD儿童血液中硫酸盐含量较正常人低.

谷氨酸、半胱氨酸和甘氨酸等可结合为具有抗氧化和解毒作用的, 含有巯基活性基团的还原型谷胱甘肽(reduced glutathione, GSH), GSH脱巯基后可生成氧化型谷胱甘肽(oxidized glutathione, GSSG). 缺乏GSH会减弱机体的抗氧化能力, 造成机体损伤, GSH/GSSG的比例决定了体内氧化还原状态, 对自由基的清除、氧化还原状态的平衡、蛋白质氧化还原状态的维持、酶活性和细胞膜完整性的保持、信号转导、解毒以及细胞的分化和凋亡具有重要作用. 研究发现, 甲基代谢和叶酸代谢过程能影响GSH/GSSG的比例^[69], 并且大多数ASD儿童体内GSH的量偏低, 而GSSG偏高, GSH/GSSG的比例明显降低^[19].

3.2 氧化还原/甲基化(redox/methylation)与自闭症

食物中充足的叶酸、甲硫氨酸和半胱氨酸有助于维持身体正常的氧化还原状态. 甲硫氨酸(methionine, 蛋氨酸)是必需氨基酸, S-腺苷甲硫氨酸(S-adenosylmethionine, SAM)是甲基供体, 脱去甲基后可生成S-腺苷高半胱氨酸(S-adenosylhomocysteine, SAH), 继续代谢可生成同型半胱氨酸(homocysteine)和腺苷(adenosine). 半胱氨酸是通过依赖叶酸的甲基化循环途径由同型半胱氨酸分解产生的. 在体内, GSH是通过甲硫氨酸转硫基途径合成, 半胱氨酸是GSH合成的限制氨基酸, 因此, GSH的合成需要足够的叶酸、蛋氨酸和SAM提供的半胱氨酸^[70]. SAM和GSH具有协同作用, 它们之间相互影响决定了体内的氧化还原水平, 而体内氧化还原失去平衡可能导致ASD^[71]. 可能的影响机制是体内氧化和抗氧化的失衡会引起活性氧(reactive oxygen species, ROS)的产生, ROS在体内积累会对DNA、RNA、蛋白质、脂质、碳水化合物等产生化学修饰和功能改变, 从而导致细胞功能出现障碍. GSH相关的酶(谷胱甘肽过氧化物酶及谷胱甘肽还原酶)能帮助机体清除ROS, 因此, 通过改变ASD患者体内的氧化还原状态可能有助于ASD的好转.

ASD患者体内的氧化水平要高于正常人, 而甲基化活动则明显比正常人少, SAM/SAH的比例作为甲基化能力的指标, 在ASD患儿体内, SAM和

SAM/SAH比率都显著降低, 可引起DNA、RNA、蛋白质和磷脂的低甲基化(hypomethylation), 导致基因和蛋白表达下降, 从而降低酶的活性和减少膜磷脂成分, 影响细胞的正常功能^[69]. ASD的氧化还原甲基化假说(redox/methylation hypothesis)认为儿童体内氧化应激反应异常, 导致异常的甲基化引起ASD^[72]. 不仅ASD儿童, 他们的父母也存在类似的甲基化能力和依赖GSH的抗氧化和解毒能力代谢异常^[73].

3.3 能量代谢与自闭症

大脑是人体消耗能量最多的器官, 特别是大脑发育过程需要大量能量, ASD儿童更倾向于脂肪、淀粉类高热量的食物^[10,11,74], 推测可能正是ASD儿童体内的能量代谢出现了问题. 如前所述, ASD儿童的NAD⁺和NADPH等参与线粒体能量代谢的物质明显减少, 缺乏能量供给的大脑可能促使ASD儿童选择高能量的食物. 此外, ASD患者血清中肉毒碱(carnitine)和丙酮酸(pyruvic acid)的含量明显降低, 而丙氨酸和氨的量明显升高^[75]. 肉毒碱能将长链脂肪酸送入线粒体参与能量代谢, 而丙酮酸是能量代谢过程中的中间产物, 在无氧环境下可通过无氧呼吸过程产生很少的能量并生成乳酸. 通过磁共振波谱(magnetic resonance spectrum, MRS)分析对ASD儿童进行检测发现, 他们血液中乳酸明显增加, 而脑中的N-乙酰-天冬氨酸(N-acetyl-aspartate, NAA)含量明显降低^[76]. 上述结果表明, ASD儿童体内的能量代谢异常, 能量供给不足, 还有可能缺氧, 导致脑中神经代谢出现紊乱并损伤神经系统.

3.4 脂肪酸代谢与自闭症

孩子出生前和出生后的大脑发育过程需要大量的不饱和脂肪酸, 脂肪酸代谢异常或不足将影响大脑发育, 增加患ASD的风险^[77], 而ASD患者体内确实缺乏Omega-3不饱和脂肪酸^[33]. 此外, 向大鼠(*Rattus norvegicus*)体内注射丙酸, 能引起社会行为障碍等自闭症样(autism like)异常行为, 用乙酸钠等其他类型的短链脂肪酸也可引起类似的异常行为^[78]. 丙酸(propionic acid, PPA)是一种由肠道微生物代谢产生的短链脂肪酸, 常被用作食物防腐剂.

4 食物不耐受/过敏与自闭症

食物中的某些成分可能引起食物不耐受或过敏.

减少或杜绝某些食物能减轻ASD患者的某些症状,因此,ASD儿童对某些食物成分不耐受或过敏可能影响了大脑发育导致ASD^[44]。有研究发现,对伴有胃肠功能紊乱的ASD患者禁食敏感食物4和14周后能有效改善ASD症状,但长期效果不明显^[79]。此外,ASD儿童体内存在免疫功能异常或过敏反应,他们的免疫球蛋白抗体IgG, IgE和IgA水平普遍偏高^[80,81]。

约有60%的ASD患者伴有一定程度的免疫异常症状^[82,83],约有46%的ASD患儿的家庭成员中有2名以上曾经患有自体免疫性疾病,患病人数越多则儿童患ASD的风险也越高^[84]。有意思的是,精神分裂症、抑郁症和强迫症等也都与自体免疫相关^[85,86],因而推论,ASD也可能是一种自体免疫性疾病。

ASD还与免疫因子和神经肽,如精氨酸加压素(arginine vasopressin)等相关^[82]。ASD儿童血浆中细胞转化生长因子 $\beta 1$ (transforming growth factor $\beta 1$, TGF $\beta 1$)和白介素23(interleukin 23, IL-23)比对照组明显减少,并且TGF- $\beta 1$, IL-23和IL-17(interleukin 17)的含量与ASD的严重程度负相关^[87]。ASD儿童血液中热休克蛋白(heat shock protein 70, HSP70)、细胞转化生长因子 $\beta 2$ (transforming growth factor $\beta 2$, TGF- $\beta 2$)、半胱天冬酶7(caspase 7)以及肿瘤坏死因子 γ (INF- γ)比对照组明显升高^[88]。此外,ASD儿童体内免疫球蛋白IgG4显著高于对照组,推测可能ASD儿童体内存在慢性应激^[89]。

“卫生假说”(hygiene hypothesis)认为,太干净的环境对人体健康不一定有好处,容易使儿童远离微生物和寄生虫,处于免疫系统发育过程中的儿童缺少了微生物和寄生虫的刺激,导致免疫系统异常,引起过敏和哮喘等免疫系统疾病^[90-92]。ASD与过敏和哮喘具有相近的发病趋势、性别偏好和城乡差异,并且都跟免疫密切相关^[93]。可能的机制是,ASD儿童生活的环境太过干净,减少了他们被微生物“接种”的机会,导致免疫系统发育异常,异常的免疫系统能影响大脑发育,从而影响ASD儿童的行为、语言和社会交往。然而,现在这方面的研究才刚起步,未来有可能通过让ASD儿童多接触点“脏东西”,或者通过免疫刺激来促进免疫系统的发育,有望为ASD的治疗提供新的方向。

5 食品添加剂和生物异源物质与自闭症

食品添加剂可能增加ASD的风险。人工色素、防

腐剂等常用的食品添加剂对儿童的大脑发育有不利影响,食品中的色素或苯甲酸钠等能导致儿童多动症^[94]。调查显示,2005~2010年,美国6~21岁的人群中,患有ASD的比例升高了91%,而其罪魁祸首可能是一种人工甜味剂——果葡糖浆(high fructose corn syrup, HFCS),过多的果葡糖浆摄入会导致锌、钙、铜和磷等微量元素的摄入失衡^[95]。最近的研究显示,食品乳化剂(dietary emulsifiers)能通过影响肠道微生物引起结肠炎和代谢综合征^[96]。

杀虫剂、农药、添加剂和防腐剂等食物中常见的生物异源物质(xenobiotics)会对人体产生伤害。随着环境污染、食物和饮水中可能残留砷、铅、汞、镉、锑和锰等重金属,这些重金属会对人的神经系统产生毒害,重金属和生物异源物质能引起人体代谢异常^[7,97-99]。铅和汞这2种环境中常见的重金属在ASD儿童体内的含量显著高于对照组^[100],ASD儿童血液和尿液中重金属含量更高^[101]。此外,麻疹、腮腺炎和风疹(measles-mumps-rubella, MMR)三联疫苗注射^[102]及疫苗中含有的防腐剂硫柳汞(thimerosal)可能导致ASD。正常情况下,人体能将汞转变为无毒的乙基汞(ethylmercury)排出体外,而一些肠道微生物能将汞转变为有神经毒性的甲基汞,可引起脑萎缩,破坏神经系统^[103]。用抗生素清除大鼠肠道中的微生物后,组织中汞的含量会增加,并且甲基汞的比例也明显增加^[104],表明肠道微生物能将本身无毒的物质转化为有毒的物质。也有研究发现接种疫苗并不能增加患ASD的风险^[105]。虽然仍未有定论,世界卫生组织也已不再鼓励在疫苗中使用硫柳汞作为防腐剂^[106],然而,以往的研究并没有将肠道微生物的代谢考虑进去,为谨慎起见,有必要继续对硫柳汞的安全性进行评估。

6 肠道微生物与自闭症

6.1 肠道微生物与肠脑

肠道里的神经细胞数量比脊髓里的还多,与大脑的神经细胞数量相当,并且细胞类型、神经递质及感受器都与大脑极其相似^[107],肠道也被称为人的“第二大脑”或“肠脑”^[108]。肠脑与大脑之间通过脑肠轴(brain-gut-axis)双向互通^[109],影响中枢神经系统,对人的情感、认知和行为产生影响^[110,111]。ASD也可能受脑肠轴的影响^[112,113]。

近年来的研究发现,人体中存在2000 g左右的微生物,总数量是人体自身细胞数量的10~100倍,编码的基因数量是人体自身的300多倍,被称为人体的“第二基因组”或“被遗忘的器官”^[114~116].肠道微生物能帮助人体消化和吸收营养物质,合成某些维生素和生物活性物质,维护人体免疫系统,抵御病原微生物的侵入,血液中大约70%的物质来自肠道^[117],其中36%的小分子物质是由肠道微生物产生的^[118].肠道微生物的平衡一旦被打破将可能导致多种疾病^[119~121].肠道微生物不仅影响人体的生理健康,也会影响人的心理和行为^[122,123],其影响机制可能通过血液系统、内分泌系统和神经系统,并且它们之间相互影响构成了微生物-肠道-大脑轴(microbiome-gut-brain axis, 菌肠脑轴)^[124~126].

随着检测技术的发展,现在可以方便地通过高通量测序技术检测肠道微生物.研究发现,粪便中有超过90%的DNA序列来自肠道微生物,这些微生物主要来源于2个门:拟杆菌门(Bacteroidetes)和厚壁菌门(Firmicutes),可以通过拟杆菌属(*Bacteroides*)、普氏菌属(*Prevotella*)和瘤胃球菌属(*Ruminococcus*) 3个属的微生物相应比例来确定个体的肠型(enterotypes)^[127].而肠型是相对稳定的,几乎不受饮食等因素的影响,可用于区分不同个体的肠道微生物组成特点^[128].研究发现,ASD患者常缺乏普氏菌属(*Prevotella*)的肠型^[129].

6.2 肠道微生物影响大脑发育

人一生中肠道微生物是变化的,从婴儿出生后微生物开始定植,1岁左右才趋于稳定,到3岁左右才接近成人^[130].而ASD的发生也是在1岁以前开始出现症状,多在3岁以内发病,这与婴儿肠道菌群发育过程的时间节点相似^[131].虽然,一般认为婴儿的肠道在出生后才开始有菌定植^[130],但最近的研究发现母体子宫中的胎盘内也可检测到微生物^[132],可能婴儿在子宫里已经开始了与微生物相互影响.不同的出生方式影响体内定植的微生物和婴儿的健康状况^[133],剖腹产和顺产的婴儿,肠道菌群存在显著差异^[134~136],而剖腹产是诱发ASD的影响因素之一^[137].这可能是由于不同的出生方式使婴儿接触微生物的时机和部位不一样,导致定植在肠道中的微生物也不一样.此外,不同的喂养方式也会导致肠道微生物不同,母乳喂养的婴儿与吃配方奶的婴儿肠道微生物

的组成显著不同^[138].细菌会通过母亲的哺乳方式和乳汁传递给孩子,早期从母亲乳汁中获取的有益微生物不足,细菌的传递受到影响可能导致后期的肠道问题,而肠道微生物的异常可能引起ASD症状.所以,个体的发育不仅由自身的基因决定,还受体内定植的肠道微生物的影响,婴儿肠道早期定植的微生物出现异常可能会干扰大脑发育,继而引发ASD.

6.3 肠道微生物影响自闭症

目前发现,一些肠道微生物的异常可能跟ASD相关^[139].肠道微生物的整体组成或者某些类型的菌群都可能对ASD产生影响^[140].梭菌属(*Clostridium*)细菌可产生神经毒性物质或其前体物质,一些晚发型自闭症(late-onset/regressive autism)患者肠道菌群明显紊乱,破伤风梭菌(*Clostridium tetani*)产生的破伤风毒素(tetanus antitoxin)异常高^[120,141],并且梭菌属和瘤胃球菌属(*Ruminococcus*)细菌数量明显高于对照组^[120].还有研究发现,ASD患者体内的梭状芽孢杆菌(*Clostridium bolteae*)是正常对照组的46倍,梭状芽孢杆菌(*Clostridium*) clusters I and XI则分别是正常对照组的9和3.5倍^[142],并且ASD儿童肠道中的溶组织梭菌(*Clostridium histolyticum*)比例明显偏高^[143].

为了抑制肠道中的梭菌,人们尝试使用万古霉素(vancomycin)和甲硝唑(metronidazole)这2种广泛用于厌氧菌感染的抗生素,发现它们确实能明显改善ASD症状^[144],其中万古霉素能清除肠道中的艰难梭菌(*Clostridium difficile*)和大部分革兰氏阴性厌氧菌.口服万古霉素几乎不被人体吸收,只对肠道微生物发挥作用,并且停药后ASD症状易出现反复,推测可能是由于某些肠道微生物在抗生素的作用下产生了孢子,停药后孢子就会活化成细菌继续影响肠道和神经系统.

除梭菌外,脱硫弧菌属(*Desulfovibrio*)和萨特菌属(*Sutterella*)也可能跟ASD相关.大约50%的ASD儿童肠道中可检测到脱硫弧菌,超过50%的伴有胃肠功能障碍的ASD儿童肠道中存在萨特菌,而正常人中几乎没有^[145,146].脱硫弧菌可引起硫代谢异常,而ASD儿童血液中硫含量确实较低,而尿液中硫含量较高^[68].萨特菌属于产碱菌科(Alcaligenaceae),能抵抗胆碱,约占肠道全部细菌的1%~7%^[147,148],目前,萨特菌和脱硫弧菌是如何影响ASD的还不清楚.

ASD还可能与真菌的过度增殖有关. ASD儿童使

用抗真菌素, 如制霉菌素(nystatin)、氟康唑(fluconazole)和酮康唑(ketoconazole)后, 真菌得以抑制, ASD症状也有所改善^[149]。白色念球菌(*Candida albicans*)是酵母菌(yeast)的一种, 属于真菌, 能引起肠炎和阴道炎, 这种菌能产生一种类似 γ -氨基丁酸(GABA)的物质—— β 丙氨酸^[150], 能透过血脑屏障与GABA竞争, 影响GABA的正常功能^[151,152]。而ASD患者体内 β 丙氨酸显著高于正常人^[153]。因而, 推测ASD患者肠道中的白色念球菌产生了大量 β 丙氨酸, 进入血液系统并透过血脑屏障进入大脑, 与抑制性神经递质GABA进行拮抗, 大脑加速产生GABA, 过量的GABA使大脑在社会交往方面受到抑制从而导致ASD^[154]。益生菌能显著抑制ASD患者体内真菌的过度增殖, 明显改善ASD症状。研究发现, ASD患者尿液中真菌感染的标志物质D-阿拉伯糖醇(D-arabitol, DA)的含量显著高于正常人, 嗜酸乳杆菌能显著降低ASD儿童尿液中DA的数量以及D-阿拉伯糖醇与L-阿拉伯糖醇(L-arabitol, LA)的比例(DA/LA), 并且ASD儿童的眼神交流、社会交往和反馈行为等得以明显改善^[155]。

ASD患者肠道中的厚壁菌门和拟杆菌门的比例与正常人也不同, 他们肠道中拟杆菌门的含量更高, 而正常人厚壁菌门的含量更高, 并且放线菌门(Actinobacteria)和变形菌门(Proteobacteria), 脱硫弧菌属和*vulgatus*拟杆菌属在严重ASD患者中也都明显增多^[156]。粪杆菌属(*Faecalibacterium*)和瘤胃球菌属(*Ruminococcus*)在PDD-NOS患儿和健康对照儿童粪便样品中含量更多; 而喜热菌属(*Caloramator*)、八叠球菌属(*Sarcina*)和梭状芽胞杆菌属在ASD儿童粪便中最多; 与健康对照相比, 毛螺旋菌科(Lachnospiraceae)的组成与PDD-NOS患儿显著不同, 特别是与ASD儿童差异更大; 除真细菌(*Eubacterium siraeum*)外, 真杆菌科(Eubacteriaceae)在ASD儿童粪便中最少; 拟杆菌属在PDD-NOS和ASD患儿粪便中几乎是最高的; 肠杆菌科(Enterobacteriaceae)在ASD儿童粪便中最多; 而ASD儿童粪便中双歧杆菌(*Bifidobacterium*)与健康对照儿童相比明显减少^[157]。除此之外, ASD儿童粪便中萨特菌(*Sutterella*)比对照组要明显增多, 而伴有功能性胃肠疾病的ASD儿童毛圈瘤胃球菌(*Ruminococcus torques*)比无功能性胃肠疾病的明显增多^[158]。ASD儿童普氏菌属(*Prevotella*)、粪球菌属(*Coprococcus*)和未分类的韦荣球菌科(Veillonellaceae)

明显减少, 并且肠道菌群多样性与ASD症状相关性比与肠道症状的严重程度的相关性更强^[129]。由此推论, 肠道菌群紊乱可能是ASD的诱因。然而ASD患者的胃肠道症状并不一定会引起菌群异常, 伴有胃肠道症状的ASD患者和没有胃肠道症状的ASD患者之间的肠道微生物并没有显著差异^[159]。

ASD模型小鼠(*Mus musculus*)表现出胃肠道通透性增加的症状, 采用脆弱拟杆菌(*Bacteroides fragilis*)处理自闭症样小鼠后, 肠道通透性明显改善, 同时自闭症样行为也有改善^[160]。在ASD儿童体内也发现了类似的结果, 他们粪便中拟杆菌门/厚壁菌门的比例明显下降, 而乳酸菌和脱硫弧菌属的数量明显增加, 并且脱硫弧菌属与ASD的严重程度直接相关。在给予益生菌之后, ASD儿童体内拟杆菌门/厚壁菌门的比例, 脱硫弧菌属和双歧杆菌属细菌比例均得以恢复^[161]。上述结果表明, 通过益生菌干预肠道菌群, 能改善自闭症样行为, 也从另一方面说明ASD可能是肠道菌群异常导致的。

近年来, 用益生菌或其代谢产物对ASD儿童进行干预来改善肠道微生物平衡状态方面的研究取得了一些进展, 研究发现, 给33名ASD患者服用含有5种益生菌的胶囊和一种来自乳酸菌细胞裂解物的免疫激活剂21 d后, 有88%患者的语言沟通、社会交往、感觉、认知意识以及身体健康和行为等方面的症状明显改善; 48%的患者腹泻症状明显减轻; 52%的患者便秘症状明显好转^[162]。但是, 这个研究并没有对被试设置纳入和排除标准, 也没有设置对照组。另一研究显示, 短双歧杆菌(*Bifidobacterium breve*)可减轻ASD患者的胃肠道症状, 给20位3~16岁伴有便秘的ASD孩子服用4周短双歧杆菌后, 其便秘症状都得到了明显改善, 排便频率增多, 粪便硬度和粪尿失禁频率降低, 并且腹痛症状减少^[163]。给ASD儿童每天3次服用益生菌产品4个月后, ASD儿童肠道菌群得以恢复, 并且梭菌属和脱硫弧菌属细菌的增加可能是导致ASD的原因^[161]。然而, 这一研究样本量少, 选取的样本类型单一, 也没有设置对照组和安慰剂组。因此, 上述几个研究显示了对肠道微生物进行干预在治疗ASD方面的积极意义, 但并没能充分解答所有问题, 仍需要更多的、严格控制的研究。

6.4 食物影响肠道微生物

食物在塑造和维持肠道微生物方面具有决定作

用^[164], 而肠道微生物又能进一步帮助人体从食物中获得更多的营养物质. 食物和营养影响肠道微生物组成, 不同的饮食习惯肠道微生物组成也不同^[165]. 动物源食物和植物源食物能在一天之内影响肠道微生物, 可引起不同肠道微生物的改变, 并且这种改变除了受食物本身影响外, 还受食物上负载的共生微生物的影响^[166]. 肠道微生物除受饮食影响外, 还受种族和生活环境的影响. 研究发现, 韩国、日本、美国和中国人群肠道微生物之间差异较大, 而同一国家的人群之间差异不大^[167]. 欧洲儿童的现代饮食与非洲农村儿童富含纤维素的饮食造成了他们肠道微生物菌落间的显著差异, 非洲农村儿童拟杆菌多, 厚壁菌少, 并且善于水解纤维素和木质素的普氏菌属(*Prevotella*)和木聚糖菌属(*Xylanibacter*)更多, 短链脂肪酸也更多, 而肠杆菌明显不足^[168]. 可能正是这种菌落构成保证了非洲农村儿童可以从富含纤维的食物中获得足够的能量, 并且保护他们免于炎症和肠道疾病.

食物中的抗性淀粉(如纤维素、半纤维素和胶质等)、寡糖(如寡果糖和菊粉等)、不溶性糖类等植物多糖类碳水化合物不能被人体消化、分解和吸收, 而肠道微生物能将它们转化为乙酸、丙酸和丁酸等短链脂肪酸(short-chain fatty acid, SCFA), 并为宿主提供能量和多种营养物质^[169]. 其中, 丁酸是结肠细胞的最主要能量来源, 具有抑制结肠癌、防止感染、降低氧化应激和增强结肠免疫屏障等作用^[170].

在人们治疗ASD的实践中出现了一些饮食疗法. 其中, 特殊碳水化合物饮食(the specific carbohydrate diet, SCD)疗法尽可能减少饮食中未消化的淀粉和多糖, 从而抑制酵母菌以及其他有害微生物的生长, 减少产生的神经毒性物质伤害大脑. 在抑制有害菌生长的同时, 还提供促进有益菌增殖的方法, 帮助肠道菌群恢复健康, 提高患者的行为、感知和语言发展能力^[171]. 而肠道和心理综合征饮食(gut and psychology syndrome diet, GAPS)疗法则包括了主要的SCD成分, 但允许使用淀粉和糖, 还提倡发酵食品、益生菌和自制食品, 特别强调了营养补充剂的作用, 目的是促进ASD儿童肠道菌群的平衡, 并不仅抑制有害菌的增殖, 可用于改善多种消化系统异常以及相应的心理问题^[172].

婴儿出生后的第一口食物可能远比人们认为的重要. 母乳除了为婴儿提供发育所需的各种营养物

质以及一些保护性因子之外, 还包含人体共生微生物以及促进免疫和微生物生长的物质. 研究发现, 1990~2011年, 北京儿童哮喘患病率呈上升趋势, 而纯母乳喂养达到6个月的儿童, 其哮喘发病率显著降低^[173]. 最近的研究表明, 母乳中含有多种共生微生物, 是婴儿体内常见的乳酸菌和双歧杆菌等有益微生物的绝佳来源^[174,175], 而配方奶中缺乏这些物质, 尤其是母乳中的共生微生物. ASD儿童常在1岁以内就出现一些异常状况, 而这一时期也正是肠道微生物建立的关键时期, ASD儿童在肠道症状出现的同时, 肠道微生物可能已经紊乱, 紊乱的肠道微生物可能通过脑肠轴或者菌肠脑轴参与了ASD的发生^[112].

虽然, 目前的研究发现ASD与肠道菌群之间存在联系, 但并不清楚肠道菌群是ASD的发病原因还是结果, 或者只是一种混淆因素. 后续研究仍需进一步扩大样本数量, 采用更严格的实验方法, 并在研究肠道微生物的基础上, 检测肠道微生物的代谢产物的变化以及神经活性物、毒性物质、氧化还原水平、氧气、氢气、短链脂肪酸和生物活性肽等物质的含量, 进一步明确肠道微生物影响ASD的机制^[176]. 益生菌已被广泛用于改善肠道微生物组成, 干预或治疗各种肠道问题, 将益生菌用于治疗ASD已经显示出了明显的优势和潜力, 将会成为未来研究的热点.

7 小结与展望

ASD受遗传和环境共同影响, 饮食是其中重要的影响因素. 饮食对ASD的影响是多方面的, 一方面, 食物中的某些物质可能引起ASD儿童出现食物不耐受或过敏, 其中的某些添加剂和生物异源物质也可能对大脑造成伤害; 另一方面, 食物中的各种营养物质满足了ASD儿童生长发育必需的各种营养需求, 并为大脑的发育提供了充足的能量和生物活性物质. 此外, 食物中的各种成分通过影响ASD儿童的免疫、能量和内分泌代谢等过程参与ASD的发病. 食物还为肠道微生物提供了充足的营养和促生长物质, 食物本身的微生物也能影响肠道微生物的组成, 并通过脑肠轴影响大脑正常的工作和发育. 虽然发现了一些与ASD相关的肠道微生物, 由于该病病因复杂, 可能并不属于传统医学认为的一种病原体(pathogen)对应一种疾病, 单一的肠道微生物可能并不是ASD的病源, 而符合由于肠道微生物生态系统遭到破坏的疾病的特点. 碍于检测手段和对肠道微

生物的有限了解, 还不能得出一致结论. 从目前的研究结果推测可能的致病机理是肠漏导致某些有害物质进入人体, 这些有害物质可能通过菌肠脑轴进一步影响血脑屏障的通透性从而影响大脑的正常发育(图2). 而可以预期的是, 肠道微生物将会是ASD研究的重点方向.

虽然, 目前还没有治疗ASD核心症状的有效方法, 但并不缺乏治疗ASD的方法, 常见的治疗方法有行为干预法、特殊教育法、药物治疗法、生物医学干预法以及心理干预法等^[177]. 还有一些补充和替代疗法(complementary and alternative medicines), 如抗生素、抗真菌、抗病毒药物、胃肠道药物、营养补充剂、限制或特殊饮食、分泌素、螯合剂、高压氧、免疫球蛋白等生物相关疗法, 还有非生物相关疗法, 如听觉整合培训、针灸疗法、颅骨疗法、按摩和气功疗法、互动节拍器疗法、灵气疗法、自然疗法、经颅刺激疗法和瑜伽等^[177,178]. 此外, 将肠道微生物作为靶标的食物、益生菌、益生元、合生元、活生素(postbiotics, 指益生菌产生的对宿主具有生物活性的细菌产物或代谢副产物, 国内尚无正式译名, 或也可称为益生素、后生素等)^[179]、粪菌移植(fecal microbiota trans-

plantation, FMT)^[180]等方法也被逐步用于ASD的治疗, 其中, 大多数ASD儿童都尝试过限制或特殊饮食疗法, 主要包括GF/CF饮食、SCD、GAPS、低草酸饮食(low oxalate diet)、生酮饮食(ketogenic diet)和法因戈尔德饮食(the Feingold diet)^[181]. 这些饮食方式的理论和方法各异, 但大都获得了一些患者家庭的认可. 据估计, 50%~70%的ASD儿童进行过生物相关疗法, 然而, 由于食物干预法本身的特点, 很难对其进行双盲实验验证, 上述疗法大多缺乏严格的安全性和有效性评估^[182], 仍需要增加样本量并采取纵向比较研究^[183].

对ASD的常规治疗通常是基于行为疗法、饮食疗法与药物治疗的组合疗法. 而饮食疗法相比其他疗法更经济、更安全、几乎没有可预见的风险和副作用, 能与其他疗法同时使用, 所以更易被家长或社会福利团体采用. 适当的饮食能帮助患者减轻疾病的严重程度, 改善心理和胃肠道症状^[181]. 但饮食干预通常耗时较长, 干预效果难以评估, 而ASD患者对食物比较挑剔, 有可能出现喂食困难, 导致难以坚持. 因此, 需要科学家、医生、营养学家以及美食家共同对饮食干预方法进行优化, 开发方便有效的监测方法,

图2 (网络版彩色) ASD可能的致病机理

Figure 2 (Color online) Potential pathogenesis of ASD

设计科学合理易于接受的食物配方并进行严格的安全性和有效性评估。

防治ASD应该遵循一定的原则,依据饮食、肠道微生物与ASD的关系,本研究组总结了以下防治原则。

(i) 个性化原则。采取个性化的治疗方式和个性化的饮食干预方法。不同个体的遗传背景、菌群组成和生活环境各异,因此,最理想的治疗方式是根据不同ASD儿童的特点采取个性化的治疗和干预措施,最终达到“精准治疗”。在进行干预或治疗之前对ASD儿童进行发病状态、肠道菌群、肠道健康状况以及营养状态等进行检测和评估,再根据每个人的结果,在治疗方式上根据孩子的症状和发病严重程度采取个性化的治疗方案,在饮食干预方面也要根据孩子自身的营养吸收状况、肠道微生物组成和孩子的食物口味喜好设定个性化的食谱。

(ii) 多样性原则。治疗方法多样,食物选择多样,增加肠道菌群的多样性。治疗ASD的方法多种多样,但相关的研究却明显滞后,各种方法的有效性和安全性评估仍很欠缺,但这并不表示这些干预方法没有效果,因此,建议家长给ASD儿童积极尝试不同的疗法或者采取多种疗法组合。在进行饮食干预时

也要遵循多样性原则,多样化的食物不仅能为ASD儿童提供多样化的全面的营养物质,并且能提供多样化的微生物和促进多样化微生物的增殖。此外,由于ASD儿童的肠道微生物多样性较低,因此需要尽可能地增加肠道微生物的多样性,例如,多给孩子吃富含益生元和益生菌的发酵食物或服用一些益生菌,同时尽量限制或避免使用抗生素,不吃含酒精或加工食品;经常带孩子到户外活动,让孩子多接触土壤,以获得更多的环境微生物。

(iii) 越早越好的原则。诊断和干预越早越好,甚至在孩子出生前就进行预防。对ASD治疗的经验是诊断和干预越早越好。由于ASD的发病难以很快逆转,甚至有些症状可能会持续一生,因此,任何时候对ASD进行干预都不晚,但是越早诊断和干预孩子的病情进展越慢,干预效果也越好。ASD可能在胎儿时期或母亲怀孕时就已经开始了,甚至母亲在怀孕之前就已经具有了生ASD儿童的高风险因素,因此,应该提早预防,在怀孕前或怀孕期间尽早咨询相关医生或专家,同时密切关注母亲怀孕前和怀孕期间的肠道微生物,饮食和营养状况,降低剖腹产机会,坚持母乳喂养等,都是降低ASD风险的积极举措。

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Influence of diet on autism

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Autism is a heterogeneous group of neurodevelopmental disorders, characterized by severe behavioral abnormalities, language and social communication difficulties, and unusually restricted, repetitive behaviors and interests. Some autistic children cannot take care of themselves, and the course of the disease may last for the person's lifetime. The prevalence of diagnosed autism has rapidly increased over the last several decades, and the disorder has caused a serious social and economic burden to patients' families and the society at large. The etiology and mechanism of autism are most likely the result of complex interactions between genetic and non-genetic risk factors. However, these are yet to be completely elucidated and effective treatment methods or interventions are required. The present research shows a close association between diet and autism, poor eating habits, harmful substances from food, abnormalities in nutrient absorption, and utilization and metabolism; all of these may affect the immune, endocrine, and metabolic systems, and finally affect brain development. The intestinal microbiota is significantly influenced by diet and is essential for human health. In particular, it can affect the brain's normal operation and development through the microbiome-gut-brain axis. Nutrients, growth-promoting substances, and microbes in the diet provide adequate material base for the growth and maintain the composition of the intestinal microbiota. An intervention in the diet may not only improve the nutritional status of autistic patients but also relieve some gastrointestinal symptoms as well as improve sleep, inflexibility, self-injuring behavior, hyperactivity, irritability and other abnormal behaviors; in addition, social and language skills are also improved. Specifically after probiotic treatment, the intestinal microbiota and autism-like behaviors are all significantly improved. Therefore, as autism causes widespread concern, probiotic interventions and the relationship between diet, intestinal microbiota, and autism are becoming research hotspots.

autism, diet, probiotics, intestinal microbiome, microbiome-gut-brain axis

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