

综述

婴幼儿铁缺乏症与脑发育障碍相关性研究

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[摘要] 铁缺乏症(ID)是儿童期最为常见的微量元素缺乏症。胎儿晚期、新生儿和婴幼儿期是大脑发育的关键时期, 这些阶段的铁缺乏可导致大脑发育的不可逆性损害, 包括情感行为异常、认知功能下降和注意力缺陷等脑功能异常表现, 并可能持续至成人阶段, 必须引起足够的重视。该文就生命早期铁缺乏导致大脑发育障碍的主要机制以及干预措施等研究进展进行综述。[中国当代儿科杂志, 2018, 20(11): 964-967]

[关键词] 铁缺乏症; 神经发育; 认知功能; 行为异常; 儿童

Association between iron deficiency and brain developmental disorder in children

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Abstract: Iron deficiency (ID) is the most common trace element deficiency in childhood. Recent studies have shown that late fetus period, neonatal period, and infancy are important periods for brain development, and ID during these periods may cause irreversible damage to brain development, including abnormal emotion and behavior, cognitive decline, and attention deficit, which may still be present in adulthood. Therefore, it should be taken seriously. This article summarizes the research advances in major mechanisms involved in brain developmental disorder due to ID in the early stage of life and related intervention measures.

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Key words: Iron deficiency; Neurodevelopment; Cognitive function; Abnormal behavior; Child

铁缺乏症(iron deficiency, ID)是儿童期最为常见的微量元素缺乏症之一, 严重者可进展为缺铁性贫血(iron deficiency anemia, IDA)^[1-3]。据世界卫生组织资料显示, 发展中国家儿童ID和IDA的发病率分别为30~40%和10~20%, 婴幼儿高于年长儿, 发达国家儿童IDA发病率也达10%^[1-5]。铁是体内重要微量元素, 除参与血红蛋白合成, 也是肌红蛋白、某些代谢关键酶、免疫系统活性调控以及组织构成等的重要组成部分。因此, ID可能影响多个器官系统^[5-9]。近年来国外研究发现, 自胎儿晚期至2~3岁内的ID可明显影响儿童早期的大脑发育, 导致持续性心理行为异常和智力发育落后, 若铁剂治疗滞后则可能难以使其逆转^[1-5, 10-16]。本文主要就近年来婴幼儿ID和IDA所致脑发育受

损, 导致情感行为和智力发育落后的主要机制及其临床表现、防治建议等进行综述。

1 铁的分布与功能

人体内总铁含量约为3~5 g, 其中70%为功能铁, 另30%为储存铁。90%以上的功能铁参与血红蛋白和肌红蛋白构成; 其余则为铁依赖性代谢关键酶(核苷酸还原酶、过氧化物酶、过氧化氢酶和细胞色素C氧化酶等)的重要成分, 参与能量代谢、消化和免疫功能, 以及维持其他微量元素代谢平衡。因此, ID也可能导致儿童生长发育落后、消化功能不全、免疫功能下降和其他营养素缺乏^[5-9]。

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2 铁代谢与生命早期脑发育的相关性

铁在神经元和各类胶质细胞中广泛存在,其中基底神经节、海马和纹状体等部位的铁浓度最高,参与髓鞘形成、脑神经元能量代谢和以多巴胺为主的神经递质合成。铁缺乏可导致大脑皮质、髓质、小脑、脑桥和海马等铁含量降低和功能发育障碍^[1-3,10-12]。

在人类生命过程中有三个ID易感期,即胎儿晚期/新生儿期、婴幼儿期和青春发育期。青春期中脑已发育成熟,此阶段ID所致脑功能障碍可以逆转^[1,13]。而胎儿/新生儿期和婴幼儿期是大脑发育旺盛的关键时期,一旦出现脑组织缺铁,可能导致脑发育不可逆损伤,并持续到成年^[1-3,12-14]。故需要重视生命早期缺铁对大脑发育的潜在损伤^[1-4]。

3 铁缺乏致大脑发育障碍的主要机制

3.1 能量代谢缺陷

大脑为高代谢耗能脏器,在发育旺盛阶段代谢和能量需求更大,因此对于各种含铁酶的依赖更为明显^[1,5]。婴幼儿ID和IDA可降低大脑发育阶段所需物质的合成以及有氧代谢和能量供应能力,导致大脑结构和功能发育受损,尤其是海马、前额叶皮质和前扣带皮层等。例如,生命早期ID对海马的影响表现为神经代谢能量有效性不足,生长因子表达降低和树突发育异常,导致记忆力(尤其是长程记忆功能)受损和学习能力下降^[15-20]。而且婴幼儿脑发育受损一旦发生,将可能难以逆转,因此海马发育障碍所致的学习能力和记忆力下降等缺陷将持续到成年^[1,5]。

3.2 髓鞘合成障碍

髓鞘合成高度依赖于能量代谢^[1-2]。人类髓鞘合成始于胎儿期,主要由少突胶质细胞合成。ID可导致铁依赖性代谢关键酶的功能下降,降低营养代谢和生物产能,以及正常脑血管网络生成,使少突胶质细胞合成髓鞘的能力受抑^[20-23]。此外,含铁酶参与髓磷脂中脂肪酸的合成,ID可改变髓磷脂的脂肪酸谱以及编码髓鞘生成的结构蛋白(如髓鞘碱性蛋白)的基因表达,导致髓鞘合成延迟或低髓鞘化、突触结构异常和神经生长因子表达减少,从而降低大脑神经突触效能、神经递质释

放和信息传导速度等。上述损害在海马、纹状体和小脑等部位表现尤为明显^[23-26]。

3.3 神经递质代谢受损

研究显示,婴幼儿ID所致大脑神经递质的远期不良影响主要为儿茶酚胺等单胺类神经递质受损,尤以多巴胺代谢受损为主^[1-3]。ID可通过抑制铁依赖性合成酶,如酪氨酸羟化酶而抑制多巴胺合成及其相关区域功能成熟,多发生于铁高度集中的大脑区域(如纹状体、黑质、腹中脑),也可见于中脑皮质边缘通路和黑质纹状体通路等部位,其受损严重程度与ID持续时间和严重程度明显相关^[25-28]。多巴胺能神经递质受损也与神经髓鞘发育不良共同作用,导致神经网络传递作用下降,导致不同程度认知功能下降和行为异常^[26-27]。

4 ID所致的行为和智力发育受损表现

4.1 情感行为异常

(1)适应能力差:如面对新的情境表现出过度犹豫和谨慎,甚至恐惧。也无法根据新的环境,有效自我调整活动规律。学龄期儿童可表现出畏惧或厌烦上学,有社会退缩、攻击性、违纪等不良行为^[1,28-32]。(2)情感和情绪异常:社交能力下降,有孤独倾向,不合群。缺乏积极的情感和言语表达,也缺乏对于情绪的自我调节能力,并可出现抑郁或焦虑情绪^[29-33]。(3)相关疾病易感性:成年期焦虑抑郁症和精神分裂症的患病率可能增高^[1,30]。

4.2 注意力缺陷

纹状体黑质和额叶的多巴胺神经传递功能缺陷可导致自我行为控制和执行功能下降^[1-2]。有研究^[31-35]显示,生命早期存在ID和IDA的患儿,在学龄期可表现出注意力缺陷,包括视觉和听觉注意力缺陷、难以专注、观察反应能力下降。此外,自我控制能力较低、容易冲动、行动缺乏目的性和计划性,注意缺陷多动障碍发病率明显增高。

4.3 学习能力下降

生命早期存在ID和IDA的患儿因脑发育障碍,可导致青少年期的平均智商水平偏低,与新生儿和婴幼儿期没有铁缺乏的青少年智商水平的差距随年龄的增长而加大^[29,34]。同时,因髓鞘生成障碍和多巴胺神经递质功能缺陷,神经网络传导能力下降,注意力缺陷,记忆力下降,反应能力和自

我纠错能力下降,并缺乏探索兴趣,表现出学习困难尤其在数学等需要逻辑推理学科的困难^[34-37]。

4.4 电生理异常

早产儿和生后6个月内铁缺乏的患儿,即可伴有听觉脑干诱发电位潜伏期延长,这些患儿在4周岁的视觉诱发电位的潜伏期较既往无ID或IDA的对照组儿童延长;在学龄期仍有听觉和视觉诱发电位潜伏期延长。这些电生理异常与生命早期缺铁导致的髓鞘形成障碍和神经传导速度降低,以及单胺类神经递质功能缺陷有关^[2,37-41]。

5 铁缺乏的干预

在人体铁代谢过程中,铁元素优先满足血红蛋白合成,ID达到一定严重程度,才导致贫血,故IDA为ID的后期结果。所以,ID与IDA为同一疾病的不同阶段^[1-3,10-12]。

预防儿童ID或IDA的方案包括:①母亲孕期补铁:健康孕妇每天补充元素铁30~60 mg,患有IDA的孕妇需要每日补充120 mg。对40000名孕妇的荟萃分析^[1,42]显示,母亲孕期补充铁剂还可使低出生体重儿和早产儿的发生率降低。②新生儿出生时的脐带处理:新生儿娩出时延迟30~45 s结扎脐带,并于结扎之前夹紧近母体端的脐带,向新生儿端挤压脐带,可使新生儿获得更多脐血以增加铁的储存^[1,43]。③婴儿期补铁:《儿童缺铁和缺铁性贫血防治建议》^[44]提出,早产儿需在出生后2~4周起预防性口服铁剂(每日1~2 mg/kg)。母乳喂养的足月儿在生后4~6个月起及时添加富含铁的辅食;国际上^[1,42]提出母乳喂养的足月儿生后1~6个月每天补充元素铁7~7.5 mg可降低ID和IDA发病率,并有助于婴幼儿视觉敏感度和精神运动发育。混合喂养或人工喂养者建议用含铁配方乳,及时添加含铁辅食,必要时适当补充铁剂(每日1 mg/kg)。④幼儿期应注意营养均衡,避免挑食和偏食。一般采用含二价铁元素的亚铁制剂口服,如富马酸亚铁和琥珀酸亚铁等(元素铁每日2~6 mg/kg)。同服维生素C有助于铁剂吸收,各类乳制品不宜与铁剂同时服用,以免影响铁剂吸收。对于IDA患者血红蛋白恢复正常后需要继续服用铁剂2个月以补足储存铁。

6 结语

胎儿/新生儿和婴幼儿期缺铁可能导致因大脑发育障碍所致的不可逆性行为、认知功能下降,并与ADHD等儿童心理行为疾病明显相关,需要引起足够重视,予以及时合理干预。

[参 考 文 献]

- [1] Cusick SE, Georgieff MK, Rao R. Approaches for reducing the risk of early-life iron deficiency-induced brain dysfunction in children[J]. *Nutrients*, 2018, 10(2): 227-240.
- [2] Algarin C, Karunakaran KD, Reyes S, et al. Differences on brain connectivity in adulthood are present in subjects with iron deficiency anemia in infancy[J]. *Front Aging Neurosci*, 2017, 9: 54.
- [3] Mudd AT, Fil JE, Knight LC, et al. Early-life iron deficiency reduces brain iron content and alters brain tissue composition despite iron repletion: A neuroimaging assessment[J]. *Nutrients*, 2018, 10(2): 35-52.
- [4] Iglesias L, Canals J, Arija V, et al. Effects of prenatal iron status on child neurodevelopment and behavior: A systematic review[J]. *Crit Rev Food Sci Nut*, 2018, 58(10): 1604-1614.
- [5] Wenger MJ, DellaValle DM, Murray-Kolb LE, et al. Effect of iron deficiency on simultaneous measures of behavior, brain activity, and energy expenditure in the performance of a cognitive task[J]. *Nutr Neurosci*, 2017, 7(3): 1-10.
- [6] Hassan TH, Badr MA, Karam NA, et al. Impact of iron deficiency anemia on the function of the immune system in children[J]. *Medicine*, 2016, 95(47): e5395.
- [7] Lachowicz JI, Nurchi VM, Fanni D, et al. Nutritional iron deficiency: the role of oral iron supplementation[J]. *Curr Med Chem*, 2014, 21(33): 3775-3784.
- [8] Hussain SQ, Ashraf M, Wani JG, et al. Low hemoglobin level a risk factor for acute lower respiratory tract infections (ALRTI) in children[J]. *J Clin Diagn Res*, 2014, 8(4): 1-3.
- [9] Kim A, Nemeth E. New insights into iron regulation and erythropoiesis[J]. *Curr Opin Hematol*, 2015, 22(3): 199-205.
- [10] Wallin DJ, Tkac I, Stucker S, et al. Phlebotomy-induced anemia alters hippocampal neurochemistry in neonatal mice[J]. *Pediatr Res*, 2015, 77(6): 765-771.
- [11] Zamora TG, Guiang SF, Georgieff MK, et al. Iron is prioritized to red blood cells over the brain in phlebotomized anemic newborn lambs[J]. *Pediatr Res*, 2016, 79(6): 922-928.
- [12] Doom JR, Georgieff MK. Striking While the iron is hot: Understanding the biological and neurodevelopmental effects of iron deficiency to optimize intervention in early childhood[J]. *Curr Pediatr Rep*, 2014, 2(4): 291-298.
- [13] Blanton C. Improvements in iron status and cognitive function in young women consuming beef or non-beef lunches[J]. *Nutrients*, 2013, 6(1): 90-110.

- [14] Georgieff MK. Iron assessment to protect the developing brain[J]. *Am J Clin Nutr*, 2017, 106(Suppl): S1588-S1593.
- [15] Rao R, Ennis K, Oz G, et al. Metabolomic analysis of cerebrospinal fluid indicates iron deficiency compromises cerebral energy metabolism in the infant monkey[J]. *Neurochem Res*, 2013, 38(3): 573-580.
- [16] Kennedy BC, Wallin DJ, Tran PV, et al. Long-term brain and behavioral consequences of early-life iron deficiency[M]// *Fetal Development*. Springer International Publishing, 2016: S43-S48.
- [17] Meechorn MD, Cheng AY, Liu H, et al. Perinatal nutritional iron deficiency permanently impairs hippocampus-dependent trace fear conditioning in rats[J]. *Nutr Neurosci*, 2005, 8(3): 195-206.
- [18] Blegen MB, Kennedy BC, Thibert KA, et al. Multigenerational effects of fetal-neonatal iron deficiency on hippocampal BDNF signaling[J]. *Physiol Rep*, 2013, 1(5): e00096.
- [19] Black MM, Quigg AM, Hurley KM. Iron deficiency and iron-deficiency anemia in the first two years of life: strategies to prevent loss of developmental potential[J]. *Nutr Rev*, 2011, 69(Suppl 1): S64-S70.
- [20] Bastian TW, Santarriaga S, Nguyen TA, et al. Fetal and neonatal iron deficiency but not copper deficiency increases vascular complexity in the developing rat brain[J]. *Nutr Neurosci*, 2015, 18(8): 365-375.
- [21] Tran PV, Fretham SJ, Carlson ES, et al. Long-term reduction of hippocampal BDNF activity following fetal-neonatal iron deficiency in adult rats[J]. *Pediatr Res*, 2009, 65(5): 493-498.
- [22] Hübner NS, Mechling AE, Lee HL, et al. The connectomics of brain demyelination: functional and structural patterns in the cuprizone mouse model[J]. *Neuroimage*, 2017, 146: 1-18.
- [23] Tran PV, Fretham SJ, Wobken J, et al. Gestational-neonatal iron deficiency suppresses and iron treatment reactivates IGF signaling in developing rat hippocampus[J]. *Am J Physiol Endocrinol Metab*, 2012, 302(3): 316-324.
- [24] Patton SM, Coe CL, Lubach GR, et al. Quantitative proteomic analyses of cerebrospinal fluid using iTRAQ in a primate model of iron deficiency anemia[J]. *Dev Neurosci*, 2012, 34(4): 354-365.
- [25] Brunette KE, Tran PV, Wobken JD, et al. Gestational and neonatal iron deficiency alters apical dendrite structure of CA1 pyramidal neurons in adult rat hippocampus[J]. *Dev Neurosci*, 2010, 32(3): 238-248.
- [26] Golub MS. Recent studies of iron deficiency during brain development in nonhuman primates[J]. *Biofactors*, 2010, 36(2): 111-116.
- [27] Greminger AR, Lee DL, Shrager P, et al. Gestational iron deficiency differentially alters the structure and function of white and gray matter brain regions of developing rats[J]. *J Nutr*, 2014, 144(7): 1058-1066.
- [28] Doom JR, Richards B, Caballero G, et al. Infant iron deficiency and iron supplementation predict adolescent internalizing, externalizing, and social problems[J]. *J Pediatr*, 2018, 195: 199-205.
- [29] Lozoff B, Smith JB, Kaciroti N, et al. Functional significance of early-life iron deficiency: Outcomes at 25 years[J]. *J Pediatr*, 2013, 163(5): 1260-1266.
- [30] Nielsen PR, Meyer U, Mortensen PB. Individual and combined effects of maternal anemia and prenatal infection on risk for schizophrenia in offspring[J]. *Schizophr Res*, 2016, 172(1-3): 35-40.
- [31] Skogli EW, Andersen PN, Hovik KT, et al. Development of hot and cold executive function in boys and girls with ADHD: A 2-year longitudinal study[J]. *J Attention Disorders*, 2014, 21(4): 305-315.
- [32] Lantrip C, Isquith PK, Koven NS, et al. Executive function and emotion regulation strategy use in adolescents[J]. *Appl Neuropsychol Child*, 2016, 5(1): 50-55.
- [33] Rodrigue KM, Daugherty AM, Haacke EM, et al. The role of hippocampal iron concentration and hippocampal volume in age-related differences in memory[J]. *Cerebral Cortex*, 2013, 23(7): 1533-1541.
- [34] Prakash J, Prabhavathi SN. Iron deficiency anemia in growing years and its effect on cognition: A review[J]. *Inter J Child Health Nutr*, 2014, 3(4): 1-10.
- [35] Lukowski AF, Koss M, Burden MJ, et al. Iron deficiency in infancy and neurocognitive functioning at 19 years : Evidence of long-term deficits in executive function and recognition memory[J]. *Nutr Neurosci*, 2010, 13(2): 54-70.
- [36] Fretham SJB, Carlson ES, Georgieff MK, et al. The role of iron in learning and memory[J]. *Adv Nutr*, 2011, 2(2): 112-121.
- [37] Droby A, Yuen KSL, Muthuraman M, et al. Changes in brain functional connectivity patterns are driven by an individual lesion in MS: a resting-state fMRI study[J]. *Brain Imaging Behav*, 2016, 10(4): 1117-1126.
- [38] Schieffer KM, Connor JR, Pawelczyk JA, et al. The relationship between iron deficiency anemia and sensorineural hearing loss in the pediatric and adolescent population[J]. *Am J Audiol*, 2017, 26(2): 155-162.
- [39] Algarin C, Peirano P, Garrido M, et al. Iron deficiency anemia in infancy: Long lasting effects on auditory and visual systems functioning[J]. *Pediatr Res*, 2003, 53(2): 217-223.
- [40] Algarin C, Nelson CA, Peirano P, et al. Iron-deficiency anemia in infancy and poorer cognitive inhibitory control at age 10 years[J]. *Dev Med Child Neurol*, 2013, 55(5): 453-458.
- [41] Marek S, Hwang K, Foran W, et al. The contribution of network organization and integration to the development of cognitive control[J]. *PLoS Biol*, 2015, 13(12): e1002328.
- [42] Wang M. Iron deficiency and other types of anemia in infants and children[J]. *Am Fam Physician*, 2016, 93(4): 270-278.
- [43] Bora R, Akhtar SS, Venkatasubramanian A, et al. Effect of 40-cm segment umbilical cord milking on hemoglobin and serum ferritin at 6 months of age in full-term infants of anemic and non-anemic mothers[J]. *J Perinatol*, 2015, 35(10): 832-836.
- [44] 中华儿科杂志编辑委员会, 中华医学会儿科分会血液学组, 中华医学会儿科分会儿童保健学组. 儿童缺铁和缺铁性贫血防治建议 [J]. *中华儿科杂志*, 2008, 46(7): 502-504.

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