

小于胎龄儿的追赶生长与认知发育

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摘要: 小于胎龄(SGA)儿常有较差的认知发育结局,尤其是追赶生长失败的SGA儿。研究发现,SGA儿的追赶生长与其认知发育结局有关。了解SGA儿的追赶生长规律及与认知结局的关系,对及时识别异常的生长轨迹和早期干预以改善其认知发育具有重要意义。本文从体重、身长/高和头围3个维度阐述了SGA儿追赶生长与认知发育的关系,为SGA儿出生后体格生长提供参考,促进其实现良好的追赶生长,改善认知结局,提高健康水平和生活质量。

关键词: 小于胎龄儿; 追赶生长; 认知发育

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Catch-up growth and cognitive development in small for gestational age infants

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Abstract: Small for gestational age (SGA) infants often experience poor cognitive development outcomes, particularly those who fail to achieve catch-up growth. Research has demonstrated an association between catch-up growth in SGA infants and their cognitive development outcomes. Understanding the patterns of catch-up growth in SGA infants and its relationship with cognitive outcomes is crucial for timely identification of abnormal growth trajectories and early intervention to improve their cognitive development. This article elucidates the relationship between catch-up growth and cognitive development in SGA infants from three dimensions of weight, length (height), and head circumference, in order to provide reference for postnatal physical growth in these infants and facilitate optimal catch-up growth, thereby ultimately improving their overall health and quality of life.

Keywords: small for gestational age; catch-up growth; cognitive development

国内标准将小于胎龄(small for gestational age, SGA)儿定义为出生体重低于同胎龄同性别新生儿出生体重的第10百分位数(P_{10})或低于平均体重2个s的新生儿。SGA患病率的地区差异大,大部分地区不到10%,中国SGA患病率约为6.5%,而南亚则高达40.9%^[1-2]。SGA儿常因宫内生长受限而导致各系统器官发育不完善,与适于胎龄(appropriate for gestational age, AGA)儿相比,SGA儿在新生儿期死亡率升高^[3],儿童期易患生长迟缓和认知发育落后^[4-5],成年后肥胖、代谢综合征等发生风险增加^[6-7]。SGA儿出生后常出现生长加速的补偿现象,即追赶生长(catch-up growth, CUG)。SGA儿国际共识指南将其定义为持续生长率大于

实足年龄和性别的中位数^[8]。健康足月SGA儿追赶生长通常在2岁前完成^[9],而早产SGA儿可能持续至4岁或更久^[10]。

SGA儿的追赶生长有利于改善发育落后,但是过快的追赶生长会导致成年后代谢综合征和心脑血管疾病的风险增加^[11]。因此在促进其追赶生长的同时,也要平衡代谢风险。本文从体重、身长/高和头围3个维度对SGA儿追赶生长与认知发育的关系进行综述,以期通过监测体格生长尽早识别认知发育落后并有效干预。

1 小于胎龄儿与认知发育

1.1 小于胎龄儿与不良认知发育结局有关 受母

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体、胎盘、胎儿、遗传代谢及环境等多重因素影响,SGA 儿在宫内大多存在氧气及营养摄入障碍,而不良的宫内环境与后代不良的神经系统结局相关。因此 SGA 是公认的神经过发育缺陷的风险因素,易导致认知障碍和神经系统后遗症。一项荟萃分析发现,与同胎龄 AGA 儿相比,SGA 儿在出生后 12 年内的认知功能均较差,早产 SGA 儿患边缘性智力障碍(认知评分 $<1s$)和智力障碍(认知评分 $<2s$)的可能性分别是早产 AGA 儿的 1.57 倍和 2.77 倍,说明 SGA 与儿童不良认知结局相关,并且增加早产儿患神经系统后遗症的风险^[6]。SGA 对认知功能的负面影响可能持续至成年期。Eves 等^[12]研究发现,相比于 AGA 儿,SGA 儿从婴儿期到成年期的认知表现更差。

1.2 小于胎龄影响认知发育的机制 SGA 影响认知发育的机制还未完全明确,但是 SGA 已经被证实与脑发育轨迹的改变有关,并且这种改变可能起始于宫内。不良的宫内环境导致 SGA 胎儿慢性低氧血症、胎儿营养摄入障碍,最终导致胎儿生长减速。此外,脑血流会发生改变,大部分 SGA 胎儿通过重新分配血流以有利于重要器官如大脑、心脏的生长发育。然而,这种方式也并不能确保正常的脑发育。胎儿期是人类大脑发育的关键时期^[13],该时期的生长发育受限可能永久性地影响大脑的结构和功能。在 SGA 儿中,已经发现包括皮质、海马、小脑等多个脑区的灰质和白质体积减少^[14],导致 SGA 儿的出生头围比同胎龄 AGA 儿相对减小^[15],而婴儿期头部较小是神经发育结局较差的强预测因子^[16]。SGA 儿还会出现髓鞘含量减少、髓鞘形成延迟和/或连接性降低^[17],这也是白质体积减少的原因。足月 SGA 儿生后 1 周内的脑弥散张量成像结果显示,相比于足月 AGA 儿,胼胝体、壳核、皮质脊髓束等多个区域各向异性分数减低^[18],此外,Leponmäki 等^[19]也发现 SGA 儿在丘脑前放射、皮质脊髓束、枕部和额部胼胝体辐射线、下额枕束、钩束等区域的各向异性分数低于 AGA 儿,SGA 儿的运动及认知功能落后可能与这些区域发育异常有关。

2 追赶生长与认知发育

SGA 儿追赶生长失败是导致不良认知结局的重要原因^[20]。Lindström 等^[21]对瑞典青少年的研究则发现,SGA 儿学习表现不佳的风险随着足够的追赶增长而减少。因此,追赶生长是 SGA 儿认知发育的重要预测因素,也是影响其神经发育结局的关键因素,如何有效监测和促进 SGA 儿的追赶生长显

得尤为重要。

2.1 体重追赶与认知发育 体重是衡量健康和营养状况的重要指标,可反映近期的生长发育情况。一项纵向队列研究发现,足月 SGA 儿出生后 3 个月内体重的适度追赶可能有利于以后的神经发育^[22]。在一项针对足月小于胎龄儿的系统性综述中,31 项观察性研究发现出生后体重增加改善神经认知表现,但是同时也发现体重与肥胖,胰岛素抵抗和血压呈正相关^[23],说明体重增长对认知发育有益,但是其对肥胖和代谢的不良影响不容忽视。也有研究发现体重的增长和认知结局评分存在非线性关系,即“体重追赶”只在一定程度和范围内促进认知发育,两者之间可能存在“高原效应”。Pylypow 等^[24]探究了 463 名宫内生长发育迟缓(intrauterine growth retardation,IUGR)婴儿在出生后 16 周时的体重增长与 7 岁时的智商之间的关联,发现其呈现“倒 J”形的关系,即体重增长最大和最小的两个极端的儿童认知测试评分较低,表明体重增长过多或过少对认知发育都存在负面影响。可见,过度“体重追赶”对认知发育的益处有限,而与超重或肥胖的风险显著相关,需要谨慎权衡。

2.2 身高/高追赶与认知发育 身高/高是体格生长监测中最重要的指标之一,可反映一段时间内的生长发育情况,监测身高有助于保护身高的正常生长和促进身高生长潜能的发挥。SGA 儿身高/高的追赶生长与认知发育呈显著正相关^[25]。基于日本全国人口的纵向研究发现,与 AGA 儿相比,在 2 岁半时未实现身高追赶生长的足月 SGA 儿爬楼梯和说 2 字词语的能力较差,并且更容易发生攻击性行为^[26],在 2 岁时未实现身高追赶生长的早产 SGA 儿在 8 岁时注意力不集中的风险更大^[27]。由此可见,SGA 儿的身高/高追赶不良对智商、语言发展、运动发展和注意力等认知结局存在负面影响。但是也有研究发现,SGA 与儿童中期和青春期认知发育的关系仅在较小程度上由年龄别身高/高 Z 评分介导^[28]。目前尚无研究发现 SGA 儿身高/高与认知结局评分之间的具体关系,但是身高/高的监测对促进 SGA 儿的体格生长、改善其认知发育具有非常重要的意义,需要密切观察和早期干预,以避免矮小和认知发育不良等后果。

2.3 头围追赶与认知发育 儿童头围的增长直接关系到脑和颅骨的生长发育,关注 0~6 岁尤其是 2 岁以前 SGA 儿的头围,对早期识别和干预神经行为发育迟缓具有重要意义。在未区分 SGA 类型的研究中发现 SGA 儿头围的完全性追赶生长与更好

的认知结局相关。Cho 等^[29]的一项回顾性队列研究纳入了 90 例出生体重 $<1\ 500\text{g}$ 或胎龄 <32 周的早产 SGA 儿童,发现从出生到矫正年龄 35 周的头围 Z 评分变化与 Bayley-III 量表的评分显著相关,矫正年龄为 4 月时头围追赶生长失败 ($<P_{10}$) 的早产 SGA 儿童认知发育结果更差。不仅是早产 SGA 儿,既往研究在足月 SGA 儿童中也得出类似的结论。在一项有关足月 SGA 儿出生后生长和神经认知结局的系统性综述中,发现出生后头围的快速增长与更好的远期认知结局相关^[23]。

SGA 儿依据体型可划分为两类:匀称型 SGA 儿和非匀称型 SGA 儿。匀称型 SGA 儿生长受限主要发生于孕早期,出生时其头围、身高及体重常成比例减低。非匀称型 SGA 儿生长受限多发生于孕晚期,出生时其体重减低较头围、身高减低更为明显^[30]。在区分 SGA 类型的研究中也发现,无论是匀称型 SGA 儿还是非匀称型 SGA 儿,头围的追赶生长对认知发育都是有利的,且非匀称型 SGA 儿的头围生长优于匀称型 SGA 儿^[31]。以体重及头围是否同时小于第 5 百分位 (P_5) 来区分匀称型和非匀称型 SGA 儿,并在 9 月龄时进行 Brunet-Lezine 评估,结果发现非匀称型 SGA 儿追赶生长的概率更高,头围更大,且两种类型 SGA 儿中无追赶生长的婴儿神经发育迟缓的风险均更高^[32]。

对于遗传因素导致的伴有小头畸形的矮小 SGA 儿,头围的生长和认知发育则不容乐观。其病因包括单基因疾病(双等位基因 IGF1 突变、原发性侏儒症)、印记基因疾病(Prader-Willi 综合征)和甲基化障碍(Silver-Russell 综合征),多伴有认知发育迟缓或智力障碍^[8]。对于患有小头畸形的矮小 SGA 儿,神经发育预后主要取决于大脑发育异常的潜在病因而非头围。

2.4 追赶生长模式与认知发育 根据“成人疾病的发育起源”假说,SGA 儿童出生后的快速追赶性生长与许多代谢紊乱有关^[33],然而持续的出生后生长不良增加身材矮小、认知受损的风险。SGA 儿是否有最佳的生长轨迹,有研究对此进行了探索,但是目前还未形成共识。有研究提出,足月 SGA 婴儿的最佳体重生长轨迹可能是在最初几个月内快速追赶生长至约第 30 百分位,此后适度追赶生长至 7 岁,达到约第 50 百分位,这样的生长轨迹下疾病的总风险最低^[34],然而其数据来源较为久远,且临床实践中实现难度较大。一项系统性综述指出了改善认知发育的关键生长时间窗,对于足月 SGA 儿,出生后的前 4~6 个月可能是体重和身高追赶生长的关键时

期,对于头围追赶,出生后的前 20 个月可能都非常重要^[35],但是由于缺乏足够的证据,无法得出明确的结论。对于早产 SGA 儿,只有一项研究探索出有利于认知发育的最佳生长时间窗,在校正年龄为 4 个月时实现头围生长追赶,在校正年龄为 9 个月时实现身长和重量追赶,则预测早产 SGA 儿在校正年龄为 18 个月时具有最佳神经发育^[29],但是该研究也存在回顾偏倚,并且随访时间较短,尚难以预测远期神经发育结局。因此,SGA 儿平衡代谢风险和认知获益的最佳生长轨迹还不明确,追赶生长的最佳时间窗亦需要进一步地探索和证实。

综上所述,SGA 儿生后应对其体重、身长/高、头围等进行早期生长监测,以及时发现生长轨迹的偏离,促进生长发育。良好的追赶生长益于 SGA 儿的认知发育,但是也要避免过度喂养,以降低远期代谢紊乱的风险。因此,对于 SGA 儿应提倡健康的追赶生长,即体重和身长的均衡增加,尤其是生后前几个月。针对我国 SGA 儿最佳追赶生长模式还需要多中心长期队列研究的支持。

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