

·综述·

发育性髋关节发育不良发病危险因素的研究进展



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【摘要】 发育性髋关节发育不良 (developmental dysplasia of the hip, DDH) 是小儿骨科常见的下肢发育畸形, 严重危害患者及其家长身心健康。影响 DDH 发病的因素可大致分为两部分, 即遗传因素和环境因素。随着 20 世纪 80 年代高检出率髋关节超声的应用及国家二胎政策的开放, 可预见未来一段时期内 DDH 患者数量将会增加。早诊断、早治疗是该病国内外公认的诊治原则, 0~6 月龄更是其治疗的黄金时期。但目前其发病的确切病因、发病机制尚不完全清楚, 因此对婴儿进行早期筛查和及时干预, 对早期诊治意义重大。笔者通过简要综述发育性髋关节发育不良发病危险因素的研究进展, 以期为 DDH 早期筛查和诊断提供参考。

【关键词】 髋关节/生长和发育; 发育性髋关节发育不良/病因学; 危险因素

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【Abstract】 As a common developmental deformity of lower extremity in pediatric orthopedics, developmental dysplasia of the hip (DDH) seriously endangers physical and mental health of children and their families. There are many risk factors of genetic and environmental origins. With rapid developments of high-detection-rate hip ultrasound in 1980s and a new national policy of fostering a second child, it may be predicted that the number of DDH children shall spike in the future. Early diagnosis and treatment are generally established principles at both home and abroad and age of 0~6 months has been an optimal window of interventions. However, the exact etiology and pathogenesis of DDH have remained elusive. Therefore it is of great importance for the early diagnosis and treatment of DDH by early screening and timely intervention of risk factors with predictive value. Here the latest research advances of risk factors of DDH were summarized for providing practical references for its early screening and diagnosis.

【Key words】 Hip Joint/GD; Developmental Dysplasia of The Hip/ET; Risk Factors

发育性髋关节发育不良 (developmental dysplasia of the hip, DDH) 是一系列髋关节异常的总称, 可引起跛行、股骨头坏死甚至残疾, 严重影响患者及其家长的生活质量^[1]。其发病率与国家、民族、地区存在关联性^[2~6]。现将近年来对 DDH 发病危险因素的研究进行综述。

一、遗传因素

19 世纪前有研究发现 DDH 发病可能与遗传相关^[7]。后来有研究发现 DDH 可影响近 1/3 的家庭成员, Stevenson 等^[8]研究发现受该病影响的一级亲属患病率增加约 12 倍。近年 Ömeroglu 等^[9]将 192 名 DDH 婴儿和 760 名健康婴儿进行对照研究发现 DDH 患者群体中 16% 有家族史, 健康婴儿仅 7% 有家族史, 再次证实遗传因素是 DDH 发病的危险因素 ($P < 0.001$)。Manoukian 等^[10]也得到了类似的研究结果, 发现 25% 的 DDH 患者有家族史, 认为相关机制与遗传基因有关, 近年通过全基因组连锁和关联研究确定了许多候选基因, 如 WISP3、PAPPA2、

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HOXB9、*HOXD9*、*GDF5*、*TGF Beta1*、*CX3CR1*、*UQCC*、*COL1A1*、*COL2A1*、*Tbx4*、*ASPN* 基因及相关位点^[11,12]。

二、性别因素

女性 DDH 发病率普遍高于男性, 可达 2 倍以上。Salut 等^[13]研究发现在不考虑其他危险因素的情况下, 女性发病率较男性高。近年来 Tan 等^[14]再次证实了此观点, 在为期 12 年的队列研究中他们发现, 女性是预测 DDH 似然比为正值的独立危险因素 ($PLR = 1.26$)。Kural 等^[15]发现女婴患 DDH 的概率是男婴的 2.27 倍。美国儿科学会 2000 年的临床实践指南将女性发病归因于女性胎儿对母体松弛素较男性敏感, 可能造成关节韧带松弛而发病^[16]。也有人认为与雌激素的异常分泌有关, 高水平的雌激素可能导致韧带或关节囊松弛而发病^[17]。Desteli 等^[18]也发现 DDH 患者的圆韧带和关节囊内的雌激素都呈高表达。近年齐秀玉等^[19]认为孕晚期雌激素生理性的迅速升高可能有助于松弛盆腔分娩, 同时导致胎儿的韧带和关节囊松弛而发病。

三、环境因素

(一) 胎位

20 世纪有学者研究发现 DDH 发病可能与臀位产有关, 后来诸多研究均证实了此观点, 如 Suzuki 等^[20]研究发现胎儿臀位 DDH 发生率(20%)远高于足位(2%)和头位(0.7%)。近年 Ömeroğlu 等^[9]将 192 名 DDH 婴儿和 760 名健康婴儿进行对照研究发现, DDH 患者 13% 为臀位产, 健康婴儿 7% 为臀位产, 再次证实臀位产是 DDH 发病的危险因素 ($P = 0.015$)。Kural 等^[15]研究发现臀位产婴儿患 DDH 的概率是非臀位产的 2.96 倍 ($P < 0.05$), 早前研究认为相关机制可能与产伤和臀位有关^[21]。Luterkort 等^[22]和 Fox 等^[23]研究发现 DDH 是臀位本身造成的。近年有研究认为, 妊娠后期胎儿位置和姿势基本固定, 羊水较前减少, 限制了臀位儿下肢活动, 呈伸直位, 进而影响了髋关节发育; 此外胎儿入骨盆时伸髋伸膝, 也增加了脱位的可能性^[24]。也有研究认为可能是胎儿髋关节稳定性较差, 臀位儿双下肢长期处于伸直位, 头位位置不佳, 缺乏相互的生物力学刺激而导致发育不良^[25]。

(二) 分娩方式

上世纪末有研究发现, 剖宫产婴儿患 DDH 风险增加, 但剖宫产是否为 DDH 发病的危险因素一直饱受争议^[26]。近年翟大明等^[27]回顾性研究 5 227 例婴儿发现, 剖宫产婴儿 DDH 检出率(5.33%)高于

顺产(3.14%), 遂认为剖宫产是 DDH 发病的危险因素 ($P < 0.01$)。相关机制可能是采用剖宫产的大部分是臀位儿、巨大儿、羊水过少儿, 而这些都是导致 DDH 的危险因素, 所以剖宫产婴儿检出率较高。此外, 剖宫产对下肢的机械牵拉也可能使髋关节过度伸展和不稳定, 导致 DDH。而 D'Alessandro 等^[28]研究认为 DDH 发病与分娩方式没有明显关系 ($P = 0.59$)。

(三) 孕周

早产可能是 DDH 的保护因素^[29]。近年 Lange 等^[30]研究也证实了此观点, 他们对 376 名早产儿和 2 534 名足月儿进行对照研究发现, 孕周 < 36 周者未发现 DDH, 遂认为早产不是 DDH 的保护因素 ($P = 0.065$)。

(四) 羊水过少

1976 年 Dunn^[31]研究发现羊水过少可能与 DDH 发病相关, 其确切性在后来的研究中得以证实, 如 Leibovitch 等^[32]对单胎足月产的羊水过少婴儿与非羊水过少婴儿进行回顾分析发现, 羊水过少婴儿的发病率较高 ($P < 0.001$)。近年 Manoukian 等^[10]研究发现, 确诊者中 16% 羊水过少, 再次证实羊水过少为 DDH 发病的危险因素 ($P < 0.05$)。该研究认为羊水过少可能会限制胎儿髋关节活动, 继而导致发育不良^[2]。

(五) 第一胎

上世纪中期有研究发现 DDH 在第一胎中更常见, 后来有研究证实第一胎是 DDH 发病的危险因素^[7,33]。近年翟大明等^[27]再次证实了该观点, 他们回顾性研究 5 227 名婴儿资料发现第一胎检出率(4.47%)高于第二胎(3.05%), 并认为相关机制可能是孕期女性宫腔渐渐增大以满足胎儿生长需要, 而初产妇宫腔不如经产妇易于扩张, 对胎儿髋关节活动和发育不如后者有利。

(六) 出生体重

20 世纪初有研究发现 24% 的 DDH 婴儿出生体重较正常婴儿低, 后来有研究认为可能是早产所致^[7]。近年梁馨月等^[34]对 2 124 例髋关节异常的婴儿与 2 335 例双髋均正常的婴儿进行对照研究发现, 出生体重与 DDH 发病相关, 低体重和高体重都是 DDH 的保护因素 ($P < 0.05$)。

(七) 传统襁褓

1975 年日本一场变革传统襁褓(用尿布包裹婴儿, 使其下肢强制处于伸直位)的全国行动使 DDH 发病率降低为原来的 1/5, 后有研究证实传统襁褓

是 DDH 发病的危险因素 ($P < 0.05$)^[35,36]。近年 Ömeroğlu 等^[9]将 192 名 DDH 婴儿和 760 名健康婴儿进行对照研究发现,DDH 患者中 16% 有襁褓史,健康婴儿中 6% 有襁褓史,再次证实了此观点 ($P < 0.001$),相关机制可能是襁褓产生的机械力量使股骨头偏离了与髋臼形成的同心圆位置,不利于髋关节发育。

(八)出生季节

1958 年 Record 等^[7]研究发现,冬季 DDH 发病率较其他季节高。后来 Chen 等^[37]对 30 956 名新生儿进行研究证实,冬季是导致 DDH 发病的危险因素 ($P < 0.05$)。近年 Hattori 等^[38]在日本进行的一项多中心研究中再次证实了此观点,国内林莉妃等^[39]研究也支持该观点。有研究认为相关机制可能是冬季家长给孩子包裹的尿布或穿着的衣物太紧,使髋关节处于伸直位不利于其发育所致^[40]。也有研究认为可能是冬季家长对婴儿多采用直筒包裹,不利于髋关节自然复位而致^[41]。

(九)多胎妊娠、孕期喝奶少或不喝奶、非母乳喂养、海拔高

近年来 Kural 等^[15]对 9 758 名婴儿进行了研究,发现多胎妊娠可能是 DDH 发病的危险因素,多胎妊娠患 DDH 的概率是非多胎妊娠的 3.83 倍。梁馨月等^[34]对 2 124 例髋关节异常的婴儿与 2 335 例双髋均正常的婴儿进行对照研究,发现母亲孕期喝奶少或不喝奶、非母乳喂养可能是 DDH 发病的危险因素 ($P < 0.05$)。Zhao 等^[42]对 606 名西藏日喀则地区(平均海拔 3 500 m)的婴儿进行研究发现,高海拔可能是 DDH 发病的危险因素 ($P = 0.004$)。

四、特殊临床体征

(一)髋关节外展受限

20 世纪 30 年代有研究发现,DDH 发病可能与髋关节外展受限有关^[43]。后来有研究证实了此观点,如 Stoffelen 等^[44]研究发现 42.5% 的 DDH 患者存在髋关节外展受限。Choudry 等^[45]研究发现外展受限婴儿的平均年龄高于无外展受限婴儿,单侧外展受限的阳性预测值为 40% (双侧为 0.3%),认为 8 周后出现单侧外展受限是 DDH 发病的高危因素。近年 Ćustović 等^[46]研究发现 14.7% 的 DDH 患者外展受限,其阳性预测值为 40.3%,再次证实髋关节外展受限(尤其是单侧)是 DDH 发病的重要表现之一。有研究认为髋关节外展受限与内收肌群紧张有关,也有研究认为可能是宫内母体骶棘与胎儿髋部相抵,使其活动受限不利发育所致^[47,48]。

(二)臀纹不对称

20 世纪 30 年代后臀纹不对称常被作为 DDH 转诊和筛查的指征之一,有研究证实其为 DDH 发病的危险因素 ($P = 0.00006$),发现 24% 的 DDH 婴儿臀纹不对称,且臀纹不对称婴儿发病风险高出正常者近 4 倍^[49]。近年研究发现其阳性价值并不大。Touzopoulos 等^[50]研究发现仅考虑是否出现臀纹不对称对 DDH 的阳性预测值较低(4.55%)。Kang 等^[51]研究发现仅有臀纹不对称表现者 DDH 检出率为 0%,遂认为对其进行筛查的意义不大。

(三)髋关节弹响

20 世纪 30 年代后髋关节是否发生弹响是 DDH 转诊和筛查的常见判定依据之一,但其是否可作为 DDH 的危险因素一直存在争议。近年 Nie 等^[52]在为期 20 年的前瞻性研究中发现,弹响髋婴儿中仅 3% 为 DDH,且这 3% 中有 1/5 与单侧髋关节外展受限有关,认为大多髋关节弹响是生理性的,而非 DDH 的危险因素。而 Humphry 等^[53]研究发现,28% 的弹响髋婴儿被确诊,其中 15.9% 需治疗,在没有超声普查的情况下髋关节弹响作为筛查项目之一很有必要。

五、伴发畸形

(一)马蹄内翻足

上世纪后期有研究发现,DDH 发病可能与马蹄内翻足有关,后来有研究发现其为 DDH 发病的危险因素^[54]。也有研究发现两者间相关性不大,如 Carney 等^[55]研究发现 16% 的马蹄足婴儿患有 DDH。Westberry 等^[56]研究发现马蹄足儿 DDH 发病率仅 0.8%。近年 Ibrahim 等^[57]研究 2 549 名马蹄足儿发现约 4.1% 患 DDH,认为马蹄足儿的总体发病率与正常人群相似。Pollet 等^[58]对 258 499 例新生儿进行研究发现,马蹄足与 DDH 患病风险显著相关 ($P < 0.05$),并认为该现象可能与胎儿在宫内位置不佳导致髋关节活动受限有关^[31,59]。

(二)肌性斜颈

1976 年 Weiner^[60]发现 49 例 DDH 患者中有 4 例同时患有肌性斜颈,认为两者可能存在相关性。后来有研究证实了这一观点,如 von Heideken 等^[61]研究发现 DDH 患者中肌性斜颈并存率为 7.9%,肌性斜颈患者中 DDH 并存率为 12.5%。患 DDH 的男孩同时患肌性斜颈的可能性是女孩的 4.97 倍。近年 Wang 等^[62]对 5 060 名婴儿进行研究也发现 DDH 发病与肌性斜颈密切相关($P < 0.001$)。

六、小结

综上所述,关于DDH发病危险因素的研究已经取得了瞩目成绩,遗传、女性、臀位、第一胎、冬季出生、传统襁褓、髋关节外展受限等因素已被国内外专家公认,并就相关的致病机制展开了探讨,但对于遗传基因的调控通路、激素引起髋关节囊和韧带松弛的途径、婴儿体位与宫内压力的具体关系及头臼的生物力学关系等内容仍有待进一步研究。目前国内外专家针对已被证实的危险因素如遗传、女性、臀位、第一胎、冬季出生、传统襁褓、髋关节外展受限等具体致病机制,存在争议。危险因素如分娩方式、臀纹不对称、髋关节弹响、马蹄足等的确切性及其他新危险因素的发现正在进行进一步研究探索。目前已筛选出许多候选基因及相关位点,并发现雌激素和松弛素会引起髋关节囊和韧带松弛,髋关节发育和稳定与生物力学相关。未来希望通过更多研究排除有争议的危险因素,进一步阐释已证实危险因素的致病机制。

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