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可乐定联合精氨酸激发试验在矮小儿童生长激素缺乏症中的诊断价值及生长激素峰值的影响因素分析*

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摘要 目的:探讨可乐定联合精氨酸激发试验在矮小儿童生长激素缺乏症(GHD)中的诊断价值,并分析生长激素(GH)峰值的影响因素。**方法:**选取2016年5月到2018年7月期间因身材矮小来安徽理工大学附属亳州医院就诊的矮小儿童120例,所有儿童均进行可乐定、精氨酸激发试验,比较可乐定、精氨酸、可乐定联合精氨酸激发试验的阳性率,以可乐定联合精氨酸激发试验的结果为标准,将120例矮小儿童分为GHD组(76例)和非GHD组(44例),比较两组儿童的年龄、骨龄、体质量指数(BMI)、体重指数标准差积分(BMI SDS)、胰岛素样生长因子-1(IGF-1)、胰岛素样生长因子结合蛋白-3(IGFBP-3)、GH峰值,分析可乐定联合精氨酸激发试验中GH峰值与各临床指标的相关性,并采用多因素逐步回归分析法分析可乐定联合精氨酸激发试验中GH峰值的影响因素。**结果:**可乐定联合精氨酸激发试验的阳性率高于可乐定激发试验和精氨酸激发试验的阳性率($P<0.05$),可乐定激发试验的阳性率高于精氨酸激发试验的阳性率($P<0.05$)。GHD组儿童BMI、BMI SDS高于非GHD组,IGF-1、GH峰值低于非GHD组($P<0.05$)。经Pearson相关分析显示,可乐定联合精氨酸激发试验中儿童的BMI、BMI SDS与GH峰值呈负相关,IGF-1与GH峰值呈正相关($P<0.05$)。多因素逐步回归分析结果显示,可乐定联合精氨酸激发试验中儿童的BMI SDS和IGF-1是GH峰值的影响因素($P<0.05$)。**结论:**可乐定联合精氨酸激发试验在矮小儿童GHD诊断中具有较高的阳性率,其诊断价值高于两种药物单独进行激发试验,且儿童的BMI SDS和IGF-1是激发试验GH峰值的影响因素,在进行激发试验时需考虑儿童的BMI SDS和IGF-1水平对诊断结果造成的影响。

关键词:矮小儿童;生长激素缺乏症;生长激素;影响因素;诊断价值

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Diagnostic Value of Clonidine Combined with Arginine Challenge Test in Growth Hormone Deficiency in Short Children and Analysis of Factors Affecting Growth Hormone Peak*

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ABSTRACT Objective: To investigate the diagnostic value of clonidine combined with arginine challenge test in growth hormone deficiency (GHD) in short children, and to analyze the influencing factors of growth hormone (GH) peak. **Methods:** 120 short children who came to Bozhou Hospital Affiliated to Anhui University of Technology from May 2016 to July 2018 were selected. All children were tested for clonidine and arginine challenge. The positive rates of clonidine, arginine, clonidine combined with arginine challenge test were compared. Based on the results of clonidine combined with arginine challenge test, 120 short children were divided into GHD group (76 cases) and non-GHD group (44 cases). The age, bone age, body mass index (BMI) and body mass index standard deviation scores (BMI SDS), insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3) and GH peak value of the two groups were compared. The correlation between GH peak and clinical parameters in clonidine combined with arginine challenge test were analyzed. Multivariate stepwise regression analysis was used to analyze the influencing factors of GH peak in clonidine combined with arginine challenge test. **Results:** The positive rate of clonidine combined with arginine challenge test was higher than that of clonidine challenge test and arginine challenge test ($P<0.05$). The positive rate of clonidine challenge test was higher than that of arginine challenge test ($P<0.05$). The BMI and BMI SDS in GHD group were higher than those in non-GHD group. The peak values of IGF-1 and GH in GHD group were lower than those in non-GHD group ($P<0.05$). Pearson correlation analysis showed that BMI and BMI SDS of children in clonidine combined with arginine challenge test were negatively correlated with GH peak value, and IGF-1 was positively

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correlated with GH peak ($P<0.05$). Multivariate stepwise regression analysis showed that BMI SDS and IGF-1 of children in clonidine combined with arginine challenge test were the influencing factors of GH peak ($P<0.05$). **Conclusion:** The clonidine combined with arginine challenge test has a higher positive rate in short children with GHD. Its diagnostic value is higher than that of challenge test with two drugs alone. BMI SDS and IGF-1 were the influencing factors of GH peak in challenge test. The influence of BMI SDS and IGF-1 levels on the diagnosis results should be considered in challenge test.

Key words: Short children; Growth hormone deficiency; Growth hormone; Influencing factors; Diagnostic value

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前言

生长激素缺乏症(Growth hormone deficiency, GHD)是导致儿童身材矮小的常见病因,检测血清中生长激素(Growth hormone, GH)的水平是诊断 GHD 的重要措施^[1-3],但由于人体血液中的 GH 均呈现脉冲式分泌,单次测量的血清 GH 水平不能准确地反映机体分泌 GH 的情况,因此在对 GH 进行检测时,需要行 GH 激发试验^[4-6]。由于任何一种激发试验都存在 15% 的假阳性率,因此我国的《矮身材儿童诊治指南》中建议采用作用方式不同的两种药物进行激发试验^[7],其中一种为兴奋生长激素释放的药物(可乐定、左旋多巴等),而另一种则建议使用抑制生长激素释放的药物(精氨酸、胰岛素、吡啶斯的明等)。有研究显示^[8],采用胰岛素激发试验检测 GH 峰值时,年龄和体质量指数(Body mass index, BMI)是 GH 峰值的影响因素,提示在检测 GH 峰值时需要综合考虑到年龄和 BMI 的影响,但目前关于可乐定联合精氨酸激发试验中 GH 峰值影响因素的研究较少。本研究旨在探讨可乐定联合精氨酸激发试验在矮小儿童 GHD 中的诊断价值,并进一步分析 GH 峰值的影响因素,以为临床诊断 GHD 及其治疗提供参考,现将研究结果整理如下。

1 资料与方法

1.1 一般资料

选取 2016 年 5 月到 2018 年 7 月期间因身材矮小来安徽理工大学附属亳州医院就诊的矮小儿童 120 例,纳入标准:(1)所有儿童均符合《矮身材儿童诊治指南》中关于身材矮小的标准^[7];(2)影像学、实验室检查资料完整;(3)未接受过生长激素治疗;(4)儿童家属对本研究方案知情,并在知情同意书上签字。排除标准:(1)合并遗传代谢性疾病者;(2)合并神经系统及全身系统疾病者;(3)合并染色体畸变者;(4)合并内分泌疾病者;(5)合并意识障碍或者精神疾病者。120 例矮小儿童中男 70 例,女 50 例,年龄 5-10 岁,平均年龄(7.42 ± 1.38)岁,骨龄 3-8 岁,平均骨龄(4.90 ± 1.08)岁, BMI 为 14.13-16.92 kg/m²,平均 BMI(16.24 ± 0.57)kg/m²。

1.2 方法

所有矮小儿童在入院当天抽取空腹静脉血 3 mL,以 3000 r/min 的速率离心 10 min,提取上层血清,采用免疫化学发光法检测血清中胰岛素样生长因子-1 (Insulin-like growth factor-1, IGF-1)、胰岛素样生长因子结合蛋白-3 (Insulin-like growth factor binding protein-3, IGFBP-3)的水平。同时根据文献中的中国儿童体格发育指标^[9],以公式计算体重指数标准差积分

(Body mass index SDS, BMI SDS), $BMI\ SDS = [(BMI/M) * L^{-1}] / (L * s)$,其中 M 为中位数, s 为变异系数, L 为偏度。所有矮小儿童在入院第二天清晨,在空腹、静卧状态下进行可乐定激发试验,口服盐酸可乐定片(常州制药厂有限公司,国药准字 H32021681,规格:75 μg/4 μg/kg)。所有矮小儿童在入院第三天清晨,在空腹、静卧状态下进行精氨酸激发试验,用注射用水将精氨酸(上海信谊金朱药业有限公司,国药准字 H31021692,规格:20 mL: 5 g)进行稀释,精氨酸的剂量为 0.5 g/kg,在 30 min 内完成静脉滴注,采血方式同上。采用放射免疫分析法检测血清中 GH 的水平,试剂盒为北京北方生物技术研究所生产,严格按照试剂盒说明书操作。在药物激发过程中, GH 峰值 $< 5\ \mu\text{g/L}$ 为完全缺乏,介于 5-10 μg/L 为部分缺乏, GH 峰值 $> 10\ \mu\text{g/L}$ 为不缺乏,其中完全缺乏、部分缺乏结果为阴性,不缺乏结果为阳性。

1.3 观察指标

比较可乐定、精氨酸、可乐定联合精氨酸激发试验的阳性率,以可乐定联合精氨酸激发试验的结果为标准,将 120 例矮小儿童分为 GHD 组和非 GHD 组,比较两组儿童的年龄、骨龄、BMI、BMI SDS、IGF-1、IGFBP-3、GH 峰值,分析在可乐定联合精氨酸激发试验中 GH 峰值与各临床指标的相关性,并分析在可乐定联合精氨酸激发试验中 GH 峰值的影响因素。

1.4 统计学方法

采用 SPSS19.0 软件进行统计分析,计量资料以均值±标准差表示,采用 t 检验,以率的形式表示计数资料,进行卡方检验,采用 Pearson 法分析指标间的相关性,采用多因素逐步回归法分析 GH 峰值的影响因素,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 可乐定、精氨酸、可乐定联合精氨酸激发试验的阳性率比较

可乐定联合精氨酸激发试验的阳性率为 36.67%,高于可乐定激发试验(30.00%)和精氨酸激发试验(10.83%),差异有统计学意义($\chi^2=4.620, 31.257, P=0.032, 0.000$),可乐定激发试验的阳性率高于精氨酸激发试验的阳性率($\chi^2=12.743, P=0.000$)。如表 1 所示。

2.2 GHD 组和非 GHD 组儿童临床指标、GH 峰值比较

根据可乐定联合精氨酸激发试验结果,将 120 例矮小儿童分为 GHD 组(GH 峰值 $< 5\ \mu\text{g/L}$ + GH 峰值为 5-10 μg/L 儿童)和非 GHD 组(GH 峰值 $> 10\ \mu\text{g/L}$ 儿童),其中 GHD 组 76 例儿童,非 GHD 组 44 例儿童。GHD 组和非 GHD 组儿童年龄、骨龄、IGFBP-3 比较差异无统计学意义($P>0.05$), GHD 组儿童 BMI、BMI SDS 高于非 GHD 组, IGF-1、GH 峰值低于非 GHD

组($P<0.05$)。如表 2 所示。

表 1 可乐定、精氨酸、可乐定联合精氨酸激发试验的阳性率比较[n(%)]

Table 1 Comparison of positive rates of clonidine, arginine and clonidine combined with arginine challenge test [n(%)]

GH peak value	Clonidine challenge test	Arginine challenge test	Clonidine combined with arginine challenge test
$<5\mu\text{g/L}$	35(29.17)	64(53.33)	33(27.50)
$5\sim 10\mu\text{g/L}$	49(40.83)	43(35.83)	43(35.83)
$>10\mu\text{g/L}$	36(30.00)	13(10.83)	44(36.67)

表 2 GHD 组和非 GHD 组儿童临床指标、GH 峰值比较($\bar{x}\pm s$)Table 2 Comparison of clinical indicators and GH peak values between GHD group and non-GHD group($\bar{x}\pm s$)

Groups	n	Age (years)	Bone age (years)	BMI(kg/m ²)	BMI SDS	IGF-1(ng/ml)	IGFBP-3($\mu\text{g/ml}$)	GH peak values($\mu\text{g/L}$)
Non-GHD group	44	7.18 $\pm$ 1.54	4.95 $\pm$ 1.01	15.53 $\pm$ 0.69	-0.31 $\pm$ 0.25	209.14 $\pm$ 25.31	3.73 $\pm$ 1.02	15.48 $\pm$ 4.08
GHD group	76	7.56 $\pm$ 1.31	4.87 $\pm$ 1.03	16.65 $\pm$ 0.74	0.21 $\pm$ 0.18	156.25 $\pm$ 18.32	3.57 $\pm$ 1.05	5.74 $\pm$ 3.14
t		1.374	0.415	8.343	12.092	12.134	0.819	13.657
P		0.172	0.679	0.000	0.000	0.000	0.414	0.000

2.3 可乐定联合精氨酸激发试验中 GH 峰值与各临床指标的关联性分析

经 Pearson 相关分析显示, 可乐定联合精氨酸激发试验中

儿童的年龄、骨龄、IGFBP-3 与 GH 峰值无相关性 ($P>0.05$), BMI、BMI SDS 与 GH 峰值呈负相关, IGF-1 与 GH 峰值呈正相关($P<0.05$)。如表 3 所示。

表 3 可乐定联合精氨酸激发试验中 GH 峰值与各临床指标的相关性分析

Table 3 Analysis of the correlation between GH peak values and clinical indicators in clonidine combined with arginine challenge test

Indicators	GH peak values	
	r	P
Age	-0.126	0.253
Bone age	-0.014	0.962
BMI	-0.367	0.005
BMI SDS	-0.412	0.000
IGF-1	0.354	0.008
IGFBP-3	0.012	0.970

2.4 可乐定联合精氨酸激发试验中 GH 峰值的多因素逐步回归分析

以年龄、骨龄、BMI、BMI SDS、IGF-1、IGFBP-3 为自变量,

以 GH 峰值作为应变量进行多因素逐步回归分析, 结果显示, 可乐定联合精氨酸激发试验中儿童的 BMI SDS 和 IGF-1 是 GH 峰值的影响因素($P<0.05$)。如表 4 所示。

表 4 可乐定联合精氨酸激发试验中 GH 峰值的多因素逐步回归分析

Table 4 Multivariate stepwise regression analysis of GH peak values in clonidine combined with arginine challenge test

Indicators	B	S.E	β	t	P
BMI SDS	-2.058	0.597	-0.348	-3.396	0.001
IGF-1	0.016	0.006	0.271	2.654	0.011

3 讨论

矮小儿童是指在生活环境近似的基础上, 个体身高低于同种族、同年龄、同性别儿童平均身高的 2 个标准差, 儿童身材矮小与遗传、环境、营养、宫内发育迟缓、精神心理、遗传代谢病等多种因素有关, GHD、特发性矮小、家族性矮小、体质性青春发

育期延迟、先天性甲状腺功能减低症是其常见的病因, 这五种病因中又以 GHD 最为常见^[10,11]。在正常情况下, 下丘脑脉冲式分泌促性腺激素的释放将启动丘脑-垂体系统, 从而可以促进垂体释放 GH、黄体生成素等激素, 而 GH 具有调节物质代谢、促进人体生长的作用, 进而其可以影响机体身高的增长^[12-14]。符合矮小儿童定义的儿童, 既可能是各种病因引起, 也可能是正

常生理变异,因此临床对于生长滞后的儿童必须进行相应的临床观察和实验室检查方能诊断具体的原因,GH 激发试验便是实验室检查的项目之一^[15-17]。

药物激发试验是临床检测 GH 的常用方法,可乐定、精氨酸均是我国《矮身材儿童诊治指南》中推荐的激发试验药物^[7]。本研究结果显示,可乐定在激发试验的阳性率高于精氨酸,而两种药物联合可进一步提高阳性率。其中可乐定可通过兴奋生长激素的释放来促进 GH 的分泌^[18,19],而精氨酸则可通过抑制生长抑素的释放以刺激垂体分泌 GH^[20-22],两种药物的作用机制不同,因此联合使用可提高激发试验的阳性率。此外,本研究结果还显示,GHD 组儿童 BMI、BMI SDS 高于非 GHD 组,IGF-1、GH 峰值低于非 GHD 组($P<0.05$),经 Pearson 相关分析显示,可乐定联合精氨酸激发试验中儿童的 BMI、BMI SDS 与 GH 峰值呈负相关,IGF-1 与 GH 峰值呈正相关($P<0.05$),多因素逐步回归分析结果显示,可乐定联合精氨酸激发试验中儿童的 BMI SDS 和 IGF-1 是 GH 峰值的影响因素($P<0.05$)。BMI SDS 影响 GH 分泌的具体机制尚未完全阐明,其可能涉及到两个方面,一方面肥胖患者血循环中胰岛素水平较高,而脑垂体中存在胰岛素受体,高水平的胰岛素可抑制 GH 的合成和释放^[23-25];另一方面瘦素可促进 GH 分泌,而肥胖患者体内多存在内源性瘦素抵抗,会在一定程度上降低瘦素的生物学功能,这也可能导致 GH 的分泌受到间接的影响^[26-28]。此结果提示对于 BMI 偏大的矮小儿童进行药物激发试验需要考虑到儿童的 BMI 因素,尤其是 GH 峰值处于临界点时更加需要重点考虑 BMI 的影响。IGF-1 是一种促细胞生长多肽,其分泌细胞广泛分布在人体肝、肾、肺、心、脑和肠等组织中,人体内的 IGF-1 水平主要受到 GH 的调控,而 IGF-1 对 GH 的分泌亦具有负反馈调节作用,因此二者可相互影响^[29,30]。

综上所述,可乐定联合精氨酸激发试验在矮小儿童 GHD 中有较好的诊断价值,可提高检测的阳性率,同时儿童的 BMI SDS 和 IGF-1 是 GH 峰值的影响因素,在进行 GH 激发试验时需要考虑以上因素的影响,以得到更加准确的结论。

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