Diagnostic Value of Growth Hormone Stimulation Test for Growth Hormone Deficiency in Short Children

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Background

It is important to find and manage the cause of short stature in children. Growth hormone (GH) stimulation test is considered as a 'gold standard' for the diagnosis of GH deficiency (GHD), and several pharmacologic agents including insulin, glucagon, L-dopa, or clonidine are used for GH stimulation test (GHST). However, diagnostic value, sensitivity or specificity of each GHST is not clear. This study was designed to evaluate the diagnostic value of GHST by insulin, glucagon, L-dopa, or clonidine for GHD during childhood.

Subjects and Methods

Subjects who visited the pediatric endocrine clinic of Dankook University Hospital and underwent GHST using 2 or 3 combinations out of insulin, glucagon, L-dopa, or clonidine for the evaluation of short stature between 2001 and 2016 were enrolled in the study. GH deficiency was defined when serum peak GH concentration was less than 10 ng/mL during at least two provocation tests. Medical records were reviewed about clinical and laboratory characteristics. For statistics, Chi square test, Student *t*-test, Fisher's exact test, and McNemar test were done. Sensitivity, specificity, positive predictive value, negative predictive value, and ROC curve were calculated. It was considered significant if *P* value was less than 0.05.

Results

Initially 89 subjects with short stature were enrolled, but subjects who had underlying structural brain lesions or chromosomal anomaly were excluded. A total of 62 children were analyzed, and 43 subjects (69.4%) were diagnosed with idiopathic short stature. Average height z score was -2.53 in GHD. Mean IGF-1 and IGFBP3 z scores were -0.64 and –0.88 in GHD, respectively. There was no significant difference in height, IGF-1, and IGFBP3 Z scores between GHD and non GHD groups. Insulin test, glucagon test, L-dopa teat, and clonidine test were done in 62, 51, 51, and 10 subjects, respectively. In each test, sensitivity for GHD was 95.4%, 65.6%, 74.2%, and 90%, respectively. Specificity of insulin, glucagon, and L-dopa was 52.6%, 89.5%, 93.3%, respectively. Positive predictive value for GHD was highest in L-dopa test (96.2%), and negative predictive value was highest in insulin test (83.3%). There was no serious adverse event during GHST, except for mild hypoglycemic symptoms or transient vomiting.

Table 1. Clinical and laboratory characteristics of the study subjects

	Total (n=62)	GHD (n=43)	Non GHD (n=19)	*P*
Age(year)	9.04 ±3.42 (3.75~17.24)	9.42 ±3.60 (3.75~17.24)	8.18 ±2.89 (4.12~13.88)	0.157
Gender(M:F)				1.000
Male(n, %)	43 (69.4)	30 (69.8)	13 (68.4)	
Female (n, %)	19 (30.6)	13 (30.2)	6 (31.6)	
Height Z score	-2.48 ±0.53 (-4.69~-1.88)	-2.53 ±0.58 (-4.69~-1.88)	-2.35 ±0.39 (-3.21~-1.93)	0.142
Male	-2.53 ±0.59 (-4.69~-1.88)	-2.60 ±0.64 (-4.69 ~-1.88)	-2.36 ±0.42 (-3.21~-1.93)	0.162
Female	-2.37 ±0.37 (-3.29~-1.97)	-2.39 ±0.39 (-3.29~-2.06)	-2.32 ±0.34 (-2.85~-1.97)	0.702
Weight Z score	-2.02 ±0.89 (-3.84~0.62)	-1.97 ±0.88 (-3.84~0.35)	-2.13 ±0.83 (-3.83~0.62)	0.533
Male	-2.10 ±0.95 (-3.84 ~0.62)	-2.11 ±0.90 (-2.85~0.89)	-2.07 ±1.10 (-3.83~0.53)	0.900
Female	-1.82 ±0.73 (-2.91~0.35)	-1.63 ±0.75 (-2.34~0.35)	-2.25 ±0.47 (-2.91~-1.68)	0.045
BMI Z score	-0.62 ±1.03 (-3.18~2.28)	-0.51 ±0.96 (-2.85~1.85)	-0.86 ±1.18 (-3.18~2.28)	0.272
Male	-0.62 ±1.05 (-3.18~2.28)	-0.63 ±0.94 (-2.85~0.89)	-0.70 ±1.32 (-3.18~2.28)	0.865
Female	-0.55 ±1.01 (-2.51~1.85)	-0.25 ±0.97 (-1.48~1.85)	-1.21 ±0.81 (-2.51~-0.09)	0.046
IGF1 Z score	-0.58 ±0.79 (-2.53~1.39)	-0.64 ±0.70 (-2.04~1.39)	-0.45 ±0.97 (-2.53~1.18)	0.447
Male	-0.49 ±0.70 (-1.81~1.39)	-0.58 ±0.69 (-1.81~1.39)	-0.28 ±0.69 (-1.74~0.83)	0.219
Female	-0.80 ±0.94 (-2.53~1.18)	-0.80 ±0.71 (-2.04~0.38)	-0.82 ±1.41 (-2.53~1.18)	0.975
IGFBP3 Z score	-0.80 ±0.83 (-2.53~1.35)	-0.88 ±0.76 (-2.34~0.77)	-0.60 ±0.97 (-2.53~1.35)	0.265
Male	-0.78 ±0.90 (-2.53~1.35)	-0.90 ±0.80 (-2.30~0.77)	-0.51 ±1.10 (-2.53~1.35)	0.277
Female	-0.83 ±0.66 (-2.34~0.55)	-0.86 ±0.69 (-2.34~0.55)	-0.78 ±0.62 (-1.51~0.26)	0.814

Table 2. Diagnostic value of each provocation test

	Insulin (n=62)	Glucagon (n=51)	L-dopa (n=51)	Clonidine (n=10)
Sensitivity	95.35	65.63	69.44	90.00
Specificity	52.63	89.47	93.33	Can not be calculated*
Positive predictive value	82.00	91.30	96.15	100.0
Negative predictive value	83.33	60.71	56.00	0.00
Accuracy†	82.26	74.51	76.47	90.0

*** All children tested with clonidine were diagnosed as having GHD.**

† Accuracy = (True positive + True negative)/Total population.

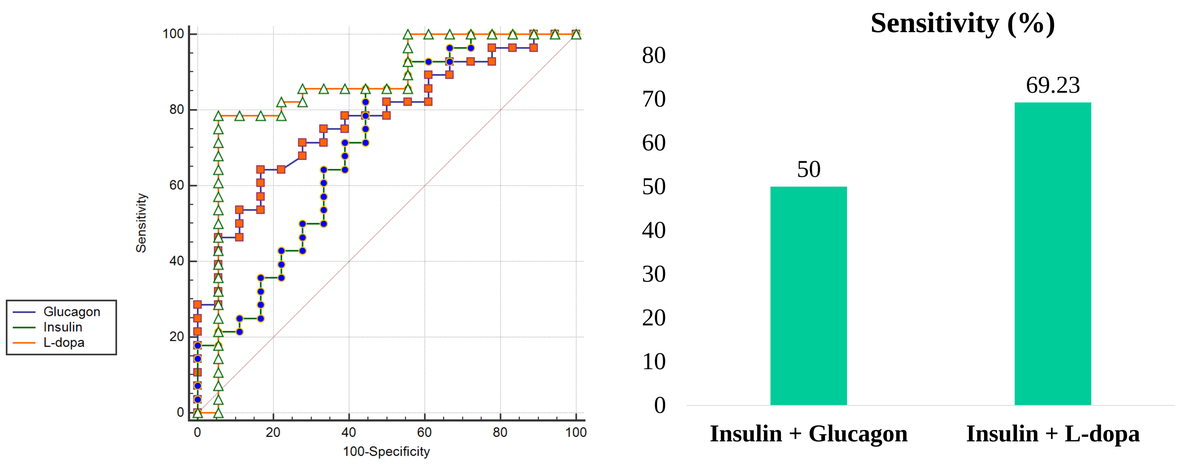

Fig. 1. ROC curves of each provocation test (lt) and sensitivity of combined tests.

Table 3. Subgroup analysis by number of positive tests

	3 positive (n=10)	2 positive (n=25)	*P*
Age (year)	11.13 ±3.01 (6.27~15.13)	8.93 ±3.25 (3.75~13.53)	0.072
Gender (M:F)			0.706
Male (n, %)	6 (60%)	17 (68%)	
Female (n, %)	4 (40%)	8 (32%)	
MPH (cm)	161.41 ±8.14 (148.10~174.35)	162.41 ±7.14 (152.15~174.75)	0.742
Height (Z score)	-2.70 ±0.59 (-3.96~-2.06)	-2.38 ±0.40 (-3.50~-1.88)	0.141
Body weight (Z score)	-1.56 ±1.22 (-3.84~0.35)	-1.94 ±0.65 (-3.40~-0.59)	0.235
Body mass index (Z score)	0.06 ±0.92 (-1.98~1.85)	-0.65 ±0.90 (-2.85~1.20)	0.050
IGF1 (Z score)	-0.57 ±0.68 (-1.48~0.37)	-0.64 ±0.62 (-2.04~0.83)	0.772
IGFBP3 (Z score)	-0.30 ±0.85 (-1.45~0.77)	-1.08 ±0.61 (-2.34~-0.05)	0.022
Prepubertal state (n, %)	6 (60%)	21 (84%)	0.186

Table 4. Subgroup analysis by peak GH levels in GHD patients

	All peaks < 5 ng/mL (n=12)	One or more peaks ≥ 5 ng/mL (n=31)	*p*
Age (year)	10.26 ±3.55 (4.89~15.13)	9.09 ±3.62 (3.75~17.24)	0.347
Gender (M:F)			0.290
Male (n, %)	10 (83.3)	20 (64.5)	
Female (n, %)	2 (16.7)	11 (35.5)	
MPH (cm)	164.47 ±8.57 (148.10~174.35)	163.17 ±6.94 (152.15~174.75)	0.646
Height Z score	-2.59 ±0.58 (-3.96~-2.04)	-2.51 ±0.59 (-4.69~-1.88)	0.706
Body weight Z score	-2.15 ±1.29 (-3.84~0.35)	-1.89 ±0.68 (-3.46~-0.59)	0.396
Body mass index Z score	-0.72 ±1.36 (-2.85~1.85)	-0.43 ±0.77 (-1.83~1.20)	0.386
IGF1 Z score	-0.82 ±0.83 (-1.60~1.39)	-0.57 ±0.64 (-2.04~0.83)	0.363
IGFBP3 Z score	-1.18 ±0.57 (-2.12~-0.04)	-0.77 ±0.80 (-2.34~0.77)	0.071
Prepubertal state (n, %)	9 (75.0)	25 (80.6)	0.692

Conclusion

Any GHST was relatively safe to perform in short children. Insulin had the highest sensitivity and L-dopa test had the highest specificity. Considering the GHST results, we could conclude that combination test using insulin and L-dopa is more useful to detect idiopathic GHD in short children.

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