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Original Article

Comparative analysis of clonidine and L-DOPA stimulation tests in diagnosing growth hormone deficiency in children and adolescents

Fatih Kilci[1], Emre Sarıkaya[1]

[1]Department of Pediatric Endocrinology, Kocaeli City Hospital, Kocaeli, Türkiye

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ABSTRACT

Background: Growth hormone deficiency (GHD) is a significant cause of growth failure in children and is diagnosed through growth hormone (GH) stimulation tests. However, the sensitivity and specificity of these tests vary, leading to different protocols across centers. Clonidine and Levodopa (L-DOPA) are two commonly used GH-stimulating agents in pediatric endocrinology, yet data on their diagnostic performance and comparative effectiveness remain limited. This study aimed to evaluate the results of L-DOPA and clonidine stimulation tests in patients undergoing evaluation for suspected GHD at our clinic.

Methods: A retrospective analysis was conducted on patients who underwent both L-DOPA and clonidine stimulation tests between January 2020 and January 2025. Demographic, anthropometric, and biochemical parameters, including Insulin-like growth factor-1 (IGF-1) and Insulin-like growth factor-binding protein-3 (IGFBP-3) levels, were recorded. Tests were performed after an overnight fast, with oral administration of L-DOPA (10 mg/kg) and clonidine (150 mg/m²) at 08:00–09:00 AM, followed by GH measurements at 0, 30, 60, 90, and 120 minutes. A peak GH level <7 ng/mL in both tests was used to define GHD.

Results: A total of 133 patients (median age: 10 years, range: 1.3–16.1; 62.4% male) were included. There were 67 patients diagnosed with GHD and 66 patients without GHD. The median peak GH response was significantly higher with clonidine (6.9 ng/mL) than with L-DOPA (3.2 ng/mL) ($p<0.001$). In 95.5% of cases, the L-DOPA test yielded lower peak GH responses than the clonidine test. There were no significant differences between the GHD and non-GHD groups in terms of age, sex, height standard deviations (SD), body mass index (BMI) SD, or IGF-1 SD. However, the GHD group had a significantly higher proportion of pubertal cases, along with significantly lower IGFBP-3 SD levels and peak GH responses on both the L-DOPA and clonidine tests compared to the non-GHD group.

IGFBP-3 SD showed a weak positive correlation with peak GH responses in both the L-DOPA ($r=0.261$, $p=0.044$) and clonidine ($r=0.294$, $p=0.033$) tests in the GHD group. Additionally, in the GHD group, a weak negative correlation was observed between BMI SD and peak GH responses in the clonidine test ($r = -0.279$, $p = 0.032$), whereas no correlation was observed between BMI SD and peak GH responses in the L-DOPA test ($p = 0.358$).

Conclusions: Our findings indicate that clonidine stimulation results in significantly higher GH peaks compared to L-DOPA and demonstrates greater specificity. Using clonidine as the first-line stimulation test may reduce the number of unnecessary tests and associated costs in the diagnostic process. Furthermore, IGFBP-3 levels appeared to be more closely associated with GHD than IGF-1 levels, suggesting that IGFBP-3 could serve as an additional diagnostic marker. Larger-scale studies are warranted to validate these findings and optimize GHD screening strategies.

Keywords: body mass index, clonidine, growth hormone deficiency, insulin-like growth factor 1, insulin-like growth factor binding protein 3, levodopa

✉ Fatih Kilci ▪ fatihkilci@gmail.com

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INTRODUCTION

Growth hormone deficiency (GHD) is a significant cause of short stature and impaired growth in children.[1] The diagnosis of GHD relies on growth hormone (GH) stimulation tests, which assess the ability of the pituitary gland to secrete GH in response to pharmacological stimuli.[2] However, the sensitivity and specificity of these tests vary depending on the agents used, the test protocols, and the diagnostic thresholds applied.[3,4] Due to these variations, there is ongoing debate regarding the most reliable and accurate GH stimulation test for diagnosing GHD in pediatric patients.

Among the various GH stimulation agents, clonidine and Levodopa (L-DOPA) are two of the most commonly used in pediatric endocrinology.[5,6] Clonidine, an α2-adrenergic agonist, stimulates GH release by reducing hypothalamic somatostatin tone, whereas L-DOPA, a dopamine precursor, exerts its effect by increasing dopaminergic stimulation of GH secretion.[7] Despite their widespread use, the diagnostic efficacy and relative superiority of these agents remain uncertain. Previous studies have reported conflicting findings regarding GH peak responses to clonidine and L-DOPA, and the optimal cut-off values for GHD diagnosis remain a topic of debate.[8-10]

Given the variability in GH responses and the limited data comparing the diagnostic utility of these two agents, further investigation is warranted to determine their effectiveness in clinical practice. Understanding the performance of these tests in different populations and settings is essential for refining diagnostic algorithms and improving the accuracy of GHD diagnosis.

In this study, we aimed to evaluate the results of GH stimulation tests with clonidine and L-DOPA in pediatric patients with suspected GHD evaluated at our clinic. By analyzing the GH peak responses to these agents, we sought to compare their diagnostic efficacy and assess their clinical utility in distinguishing children with GHD from those with normal GH secretion.

METHODS

Study design and setting

This retrospective study reviewed patients' medical records who underwent both L-DOPA and clonidine GH stimulation tests for suspected GHD at our clinic between January 2020 and January 2025. Patients with systemic or endocrine disorders affecting GH secretion, or with syndromic short stature, were excluded. Growth hormone stimulation tests were performed in children with a height below −2 standard deviations (SD) for chronological age and/or a subnormal height velocity (below the 25th percentile). In addition, other clinical indications such as delayed bone age, height more than 1.5 SD below the mid-parental target height, physical features suggestive of growth hormone deficiency, and low serum insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-binding protein-3 (IGFBP-3) levels were also considered in accordance with current clinical guidelines.[11] The study protocol received approval from the local institutional review board (approval number: 2024/127).

Data collection and diagnostic procedures

Anthropometric data, including height, weight, and body mass index (BMI), were collected at the time of testing by a single experienced nurse. Measurements were taken without shoes and in light clothing, using a device with an accuracy of ±0.1 cm for height and ±0.05 kg for weight. The anthropometric measurements of the patients were evaluated according to the national auxological references.[12] Participants' pubertal stages were determined according to the Tanner classification system.[13] For analytical purposes, patients were classified as prepubertal if at Tanner stage 1 and as pubertal if at Tanner stage 2 or above, in line with the physiological onset of puberty.

All tests were conducted in the morning between 08:00 and 09:00 following an overnight fast of at least eight hours, while patients were in a euthyroid and eucortisolemic state. An intravenous catheter was placed before the test initiation. As per departmental protocol, the L-DOPA test was conducted first, with a second test using clonidine for those who did not pass the L-DOPA test, and sex-steroid priming was not performed in peripubertal children.

For the L-DOPA stimulation test, L-DOPA was administered orally at a dose of 10 mg/kg, with a maximum dose not exceeding 500 mg. For the clonidine stimulation test, clonidine was administered orally at a dose of 150 mcg/m² of body surface area, with a maximum dose not exceeding 250 mcg.

Blood samples for GH measurement were collected at baseline and at 30, 60, 90, and 120 minutes for both tests. The highest GH value obtained during either test was recorded as the peak GH level. A peak GH concentration below 7 ng/mL in both tests was considered diagnostic of GHD.[14] Those with a peak GH response below 7 ng/mL in both tests formed the GHD group, while those with a peak

GH response greater than or equal 7 ng/mL in the second test formed the non-GHD group.

Serum IGF-1 and IGFBP-3 levels were also measured at baseline, and their SD's were calculated according to national standards based on chronological age and sex.[15] GH levels were measured using the electrochemiluminescence immunoassay method with the Roche Diagnostics Cobas® e801 system (Roche Diagnostics, Mannheim, Germany). Serum IGF-1 and IGFBP-3 concentrations were determined using the chemiluminescence immunoassay technique with the Maglumi SNIBE X3® analyzer (Snibe Diagnostics, Shenzhen, China).

Statistical analysis

Statistical analysis was performed using SPSS, version 23.0 (IBM Inc., Armonk, NY, USA). Categorical variables were presented as frequencies and percentages, while normality was assessed using the Kolmogorov-Smirnov test. Depending on the data distribution, parametric data were described as mean ± standard deviation, and nonparametric data were presented as median and range (minimum-maximum). The chi-square test or Fisher's exact test was used to compare the differences of categorical variables presented as counts (percentages). The Student's t-test was used to compare parametric variables between the two groups, while the Mann-Whitney U test was applied for nonparametric data. Correlation analyses between GH peak responses (to L-DOPA and clonidine separately) and auxological/laboratory parameters were performed using the Spearman correlation test, as the data did not show normal distribution. A value of $p < 0.05$ was considered statistically significant.

RESULTS

A total of 133 patients, with a median age of 10 years (range: 1.3–16.1), were included in the study, of which 62.4% were male. There were 67 patients diagnosed with GHD and 66 patients without GHD. Forty-five patients (33.8%) were in the pubertal stage. The median peak GH response to the clonidine test for all cases was 6.9 ng/mL (range: 0.3–18), which was significantly higher than the median peak GH response to the L-DOPA test, with 3.2 ng/mL (range: 0.1–6.7) ($p<0.001$). Except for six patients, all others (95.5%) exhibited lower peak GH responses on the L-DOPA test compared to the clonidine test.

There were no significant differences between the two groups in bone age, chronological age, gender, height SD, BMI-SD, or IGF-1 SD. However, the GHD group had a significantly higher proportion of pubertal cases, along with significantly lower IGFBP-3 SD levels and peak GH responses on both the L-DOPA and clonidine tests compared to the non-GHD group (Table 1).

When analyzed by pubertal status, no significant difference in L-DOPA-stimulated peak GH responses was observed between prepubertal and pubertal patients within the GHD

Table 1. Clinical and Laboratory Characteristics of the Study Population

	Total (n=133)	GHD Group (n=67)	Non-GHD Group (n=66)	P-Value
CA, years, median (range)	10 (1.3 to 16.1)	9.95 (1.3 to 15)	8.85 (1.6 to 16.1)	0.117
BA, years median (range)	7.8 (0.5 to 14)	7.8 (0.5 to 13)	6.75 (0.75 to 14)	0.272
Male, n (%)	83 (62.4)	45 (67.2)	38 (57.6)	0.286
Weight SD, median (range)	-1.77 (-4.6 to 0.75)	-1,7 (-4.6 to 0.75)	-1,8 (-3,05 to 0,52)	0.333
Height SD, median (range)	-2.47 (-4.7 to -1.45)	-2.54 (-4.7 to -2)	-2.44 (-4 to -1.45)	0.204
BMI SD, median (range)	-0.4 (-2.5 to 1.6)	-0.39 (-2.5 to 1.6)	-0.42 (-2.24 to 1.3)	0.208
IGF1 SD, median (range)	-1.69 (-4.29 to 0.45)	-2.09 (-3.7 to -0.23)	-1.88 (-4.29 to 0.45)	0.164
IGFBP3 SD, median (range)	-0.89 (-3.84 to 1.7)	-1.25 (-3.84 to 1.3)	-0.62 (-2.34 to 1.7)	0.008
Proportion of Pubertal Patients (%)	33.8	43.3	24.2	0.028
Peak GH Response to L-DOPA (ng/mL), median (range)	3.2 (0.1 to 6.7)	2.55 (0.17 to 5.9)	4.34 (0.17 to 6.7)	<0.001
Peak GH Response to Clonidine (ng/mL), median (range)	6.9 (0.3 to 18)	4.2 (0.39 to 6.9)	11.1 (7.24 to 18)	<0.001

CA: Chronological age, BA: Bone age, BMI: Body mass index, IGF1: Insulin-like growth factor-1, IGFBP3: Insulin-like growth factor-binding protein-3, GH: Growth hormone, GHD: Growth hormone deficiency, SD: Standard deviation.

group. However, a statistically significant difference was observed in clonidine-stimulated peak GH responses, with higher responses in prepubertal patients than in pubertal patients (Table 2). In contrast, in the non-GHD group, no significant differences were observed between prepubertal and pubertal participants in either the L-DOPA or the clonidine stimulation tests (Table 3).

In the GHD group, no significant correlations were observed between GH peak responses (to both L-DOPA and clonidine) and age, weight, height, or IGF-1 SD. However, a weak positive correlation was found between IGFBP-3 SD and GH peak responses to the L-DOPA test (r = 0.261, p = 0.044). Similarly, a weak positive correlation was also identified between IGFBP-3 SD and GH peak responses to the clonidine test (r=0.294, p=0.033). Additionally, a weak negative correlation was observed between BMI SD and GH peak responses to the clonidine test (r = –0.279, p = 0.032) in the GHD group. These findings are summarized in Table 4.

DISCUSSION

In patients with suspected GHD, random serum GH measurements are not useful for diagnosis. Therefore, two different GH stimulation tests are required, and both tests must yield abnormal results to confirm GHD.[11,16] In the diagnosis of GHD in children, various stimulation agents such as the insulin tolerance test (ITT), clonidine, glucagon, L-DOPA, arginine, and GH-releasing peptide-2 are used.[5] Although ITT is considered the gold standard, its use in pediatric GHD diagnosis is limited due to the need for close medical supervision, poor reproducibility, and the unpleasant symptoms associated with hypoglycemia. [7] Additionally, the low specificity and sensitivity of traditional GH stimulation tests significantly reduce their diagnostic reliability, as no single test is sufficiently sensitive and specific to confirm the diagnosis.[3,17] Moreover, these tests have poor reproducibility, and their results can be influenced by factors such as age, sex, puberty, nutritional status, and body weight.[6]

In this study, we demonstrated that the clonidine test elicited significantly higher peak GH responses compared to the L-DOPA test in children and adolescents with suspected GHD. Notably, while the majority of patients showed this pattern, a small subset exhibited discordant responses between the two tests, emphasizing the variability inherent in GH stimulation testing and the need for careful interpretation of results in clinical practice. In addition, we observed a negative correlation between BMI-SD and GH peak levels in the clonidine test.

Some studies suggest that L-DOPA is a more sensitive test for stimulating GH secretion, particularly in pediatric populations.[8] In contrast, others have shown that this test has lower sensitivity than the clonidine test but similar specificity and has been shown to increase accuracy when combined with arginine.[18-20] The findings of the present investigation, in which all subjects first underwent the L-DOPA stimulation test, and those who failed to meet the 7 ng/mL GH threshold were subsequently evaluated using the clonidine test, suggest that clonidine is a more robust and efficacious GH secretagogue than L-DOPA. Based on

Table 2. Comparison of Peak GH Responses to L-DOPA and Clonidine Tests According to Pubertal Status in the GHD Group

Stimulation Test	Pubertal Status (n)	Peak GH (ng/mL), median (range)	P-Value
L-DOPA	Pubertal (29)	2.8 (0.1 to 5.9)	0.728
	Prepubertal (38)	2.4 (0.18 to 5.1)	
Clonidine	Pubertal (29)	3.7 (0.4 to 6.9)	0.035
	Prepubertal (38)	5.54 (0.3 to 6.9)	

GH: Growth hormone.

Table 3. Comparison of Peak GH Responses to L-DOPA and Clonidine Tests According to Pubertal Status in the Non-GHD Group

Stimulation Test	Pubertal Status (n)	Peak GH (ng/mL), median (range)	P-Value
L-DOPA	Pubertal (16)	3.45 (0.17 to 6.4)	0.151
	Prepubertal (50)	4.45 (1.32 to 6.76)	
Clonidine	Pubertal (16)	10.2 (7.6 to 18)	0.976
	Prepubertal (50)	11.1 (7.2 to 18)	

GH: Growth hormone.

Table 4. Correlation of Clinical and Biochemical Parameters with Peak GH Responses in L-DOPA and Clonidine Stimulation Tests

Variable	L-DOPA– GHD Group	L-DOPA – Non-GHD Group	Clonidine– GHD Group	Clonidine– Non-GHD Group
Age (years)				
r	0.034	-0.108	-0.209	-0.024
p	0.783	0.387	0.089	0.109
Height-SD				
r	0.056	0.031	0.145	0.190
p	0.650	0.804	0.240	0.127
Weight-SD				
r	-0.0069	-0.0021	-0.104	-0.053
p	0.578	0.976	0.402	0.672
BMI-SD				
r	-0.114	-0.005	-0.279	-0.107
p	0.358	0.978	0.032	0.391
IGF-1 SD				
r	0.043	0.020	0.025	0.031
p	0.733	0.875	0.844	0.804
IGFBP-3 SD				
r	0.261	0.070	0.294	0.047
p	0.044	0.595	0.033	0.720

BMI: Body mass index, IGF1: Insulin-like growth factor-1, IGFBP3: Insulin-like growth factor-binding protein-3, GHD: Growth hormone deficiency, r: Spearman Rho correlation coefficient, SD: Standard deviation.

our findings, we recommend using the clonidine test as the primary diagnostic approach for GHD, as this strategy could reduce unnecessary tests and improve diagnostic efficiency. Additionally, our study suggests that adopting lower cut-off values for diagnosing GHD on the L-DOPA test may be warranted, which could further refine diagnostic criteria and facilitate earlier detection of the condition.

It is well known that malnutrition and chronic undernutrition can blunt GH responses during stimulation tests, despite normal or even elevated endogenous GH secretion.[6] In our study, although some patients had low weight and BMI SD values, these parameters did not differ significantly between the GHD and non-GHD groups. Therefore, we believe the comparison of GH responses between the groups remained valid. Nevertheless, the potential influence of nutritional status should be kept in mind, particularly when interpreting borderline test results.

Body mass index significantly affects GH secretion, leading to reduced spontaneous and stimulated GH release in obese individuals. Furthermore, the GH response to various stimuli, including clonidine, shows a negative correlation with BMI.[21-23] In line with the literature, our study revealed a weak negative correlation between BMI SD and GH peak responses to the clonidine stimulation test in patients diagnosed with GHD. However, no such correlation was found with the L-DOPA stimulation test. This discrepancy may be due to the differing mechanisms of action of the two agents and the generally lower GH peaks elicited by L-DOPA, which could limit the detection of BMI-related effects. Therefore, the clonidine test appears to be a more reliable and superior diagnostic tool than L-DOPA when evaluating GH response in relation to BMI.

During puberty, sex steroids influence the GH/IGF-I axis, resulting in enhanced GH secretion and responsiveness to diverse stimuli, including the administration of testosterone or estrogen.[24,25] However, there is no consensus regarding the role of sex steroids in priming for GH stimulation tests. Some studies suggest that prepubertal children may fail GH stimulation tests due to the influence of sex steroids[26,27], while other studies have found that puberty itself does not significantly impact the GH response to stimuli.[17,28] A recent study by Ibba et al.[9] evaluating the reliability of clonidine in diagnosing GHD in children and adolescents, as well as the effect of puberty on the GH response to clonidine, suggested that clonidine is effective and reliable in both prepubertal and pubertal children, without the need for sex steroid priming. Interestingly, in our study, GH responses to the

clonidine test were lower in pubertal than in prepubertal cases within the GHD group. This finding suggests that, despite hormonal fluctuations during puberty, clonidine remains a reliable diagnostic tool for GHD across different pubertal stages, reinforcing the argument that sex steroid priming may not be necessary for the accurate assessment of GH response in this population.

Serum IGF-1 and IGFBP-3 levels indicate endogenous GH secretion in healthy children, making them potential screening tools for GHD.[29] However, the diagnostic utility of IGF-1 and IGFBP-3 in distinguishing GHD from non-GHD remains a matter of debate. Previous studies have reported conflicting results regarding their predictive value. For instance, Jensen et al. found that the sensitivity of IGF-1 and IGFBP-3 for diagnosing GHD was 90% and 81%, respectively.[30] In contrast, Boquete et al.[31] reported that IGF-1 was superior to IGFBP-3 in identifying GHD. On the other hand, Iwayama et al. demonstrated that IGF-1 had poor diagnostic accuracy as a screening test for GHD and concluded that IGF-1 alone should not be used for screening purposes.[32] In our cohort, IGF-1 SD did not differ significantly between GHD and non-GHD groups, whereas IGFBP-3 SD was significantly lower in the GHD group, consistent with its closer association with GH status. These findings suggest that IGFBP-3 may provide additional insight into GH deficiency, but, due to modest differences, it cannot reliably serve as a standalone diagnostic marker, underscoring the continued necessity of GH stimulation testing for accurate diagnosis.

Limitations

Our study has several limitations. First, its retrospective design may introduce selection bias and limit the generalizability of our findings. Second, the diagnosis of GHD was based on GH stimulation tests, which are known to have variability in reproducibility and specificity. Third, the lack of ITT data, which is considered the gold standard for GHD diagnosis, may limit the diagnostic accuracy of our findings. Additionally, we did not assess other potential biomarkers or dynamic testing methods that could further refine GHD diagnosis. Future prospective studies with larger cohorts and alternative biomarkers are needed to validate our findings.

Conclusion

The current study confirms that clonidine induces a higher GH response than L-DOPA and that BMI SD negatively correlates with GH levels during the clonidine test. Additionally, IGFBP-3 SD was significantly lower in the GHD group, indicating an association with GH deficiency, whereas IGF-1 SD did not differ between groups. Given its superior GH response, using clonidine as the initial GH stimulation test may reduce the number of unnecessary tests and lower diagnostic costs. These findings underscore the need for novel biomarkers to enhance the accuracy of GHD diagnosis and screening.

Ethical approval

This study has been approved by the Kocaeli City Hospital Ethics Committee (approval date 31.10.2024, number 2024-127). Written informed consent was obtained from the participants.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: FK, ES; data collection: FK, ES; analysis and interpretation of results: FK; draft manuscript preparation: FK. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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