

THE EVALUATION OF CLONIDINE, INSULIN, L-DOPA, EXERCISE TESTS ON GROWTH HORMONE IN SHORT CHILDREN

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Abstract - Growth hormone stimulation tests have been used to assess the growth hormone reserve of the pituitary gland in both children and adults. We have assessed the effect of clonidine, insulin, L-Dopa and exercise on growth hormone secretion in 261 short children. The results found in this study revealed that there are no significant differences in these stimulation tests (P=0.28)
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Key words: Short stature, growth hormone deficiency, growth hormone stimulation tests

criteria for GH deficiency are currently being reexamined, classic GH deficiency is defined as a GH response of less than 7ng per ml (polyclonal antibody) following two standard GH stimulation tests. All of these tests can be performed in an out patient setting after at least four hours of fasting(7).

MATERIALS AND METHODS

We studied at random 261 short children (153 boys, 108 girls) ages 9 months to 17 years (mean $9.12 \text{ y} \pm 3.65$) who were growing below the third percentile in height. After an overnight fast and 15 minutes of complete rest, a single oral dose of clonidine, $150 \mu\text{g}/\text{m}^2$ was administered. Blood sample for determination of growth hormone was drawn at 0, 30, 60, 90 and 120 minutes and blood pressure was measured every half an hour.

Oral L-Dopa 125 mg<13.5 kg, 250 mg=13.5-35 kg, 500 mg>35 kg and intravenous regular 0.1 unit /kg were administered separately and blood sample for growth hormone was obtained at 0, 30, 60, 90, 120, minutes. Although severe insulin reactions are rarely a problem, an intravenous line must be in place for glucose infusion when performing the insulin stimulation test.

Serum and plasma samples were stored at -20°c until assayed. Specific immunoradiometric assay (IRMA) techniques were used for determination of growth hormone.

RESULTS

We studied 108 healthy short children (47

INTRODUCTION

Human growth hormone (hGH) is a single chain protein which is synthesized and released from the pituitary gland.

Growth hormone is responsible for stimulation of body growth, incorporation of aminoacids into skeletal muscle, regulation of lypolysis and inhibition of the gluconeogenic effects of the glucocorticoids (1,2).

During much of the day , plasma GH is low and spontaneous peaks are often brief and unpredictable. Therefore, measurement of GH in a random blood sample is not a satisfactory screening test for GH deficiency (3,4). Presently, the accepted method for diagnosing GH deficiency is based on eliciting a growth hormone peak in response to a pharmacologic stimulus (5,6). Before performing laboratory tests, other causes of proportionate short stature must be excluded.

The four main causes of proportionate short statue include gastrointestinal, cardiopulmonary, renal and endocrine diseases. While the diagnostic

girls, 61 boys). The age, height and weight distribution of children are shown in Table 1. Serum growth hormone values increased from a baseline value of $0.95 \text{ ng/ml} \pm 1.36$ (mean \pm SD) to a peak value of $12.63 \pm 4.64 \text{ ng/ml}$ 60 minutes after clonidine administration. 53 patients (49.1%) unable to increase their serum growth hormone values adequately after clonidine test. Growth hormone titers at different times of the test are shown in Fig. 1.

Insulin Tolerance test (group B)

The effect of insulin on growth hormone concentration in the blood of 25 healthy short children (10 girls, 15 boys) was evaluated. The age, height and weight distribution of children are shown in Table 1. Serum growth hormone values increased from a baseline value of $1.44 \pm 3.08 \text{ ng/ml}$ to a peak value of $12.21 \pm 4.60 \text{ ng/ml}$ 30 minutes after insulin injection. Eighteen children (72%) were unable to increase their serum growth hormone values adequately after this test. Growth hormone titers at different times of the test are shown in Fig. 2.

L-Dopa (group C)

The effect of L-Dopa on growth hormone concentration in the blood of 95 healthy short children (44 girls, 51 boys) was evaluated. The age, height and weight distribution of children are shown in Table 1. Following L-Dopa administration serum growth hormone values increased from a baseline value of $1.83 \text{ ng/ml} \pm 3.02$ to a peak value of $12.90 \text{ ng/ml} \pm 7.70$ (21 children in 60 minutes, 14 in 30 minutes). Growth hormone titers at different times of the test are shown in Fig 3.

Exercise test (group D)

We studied 33 healthy short children (26 boys, 7 girls). The age, height and weight distribution of children are shown in Table 1. Serum growth hormone values increased from a baseline value of $1.62 \pm 1.98 \text{ ng/ml}$ to a peak level of $10.47 \pm$

4.60 ng/ml 30 minutes after exercise. In 23 children, (69.7%) serum growth hormone values were not adequately increased after exercise. Growth hormone titers at different times of the test are shown in Fig. 4.

Comparison of these four tests have shown no significant difference in the baseline values of growth hormone among the groups ($P=0.18$). In our healthy subjects insulin, clonidine, L-Dopa and exercise were able to stimulate adequate growth hormone release and no significant differences were found between the tests ($P=0.06$). This study revealed that there are no significant differences between peak value of serum growth hormone in different stimulation test ($P=0.28$). Test responses are shown in Fig (5).

DISCUSSION

GH has profound effects on tissue growth and metabolism (8).

To test for hyposecretion of hGH, the following stimuli are used: insulin, L-Dopa, L-arginine, glucagon, exercise and sleep (9, 10, 11).

Pharmacologic stimuli such as L-Dopa produce a blood GH level above 7 ng/ml (monoclonal antibody) in over 95 percent of normal children (12, 9, 13). Measurements after physiologic stimuli such as 20 minutes of exercise or after 1 hour of sleep are not considered adequate because they produce a level of 7 ng/ml or higher in only 70 percent of normal children. One report has evaluated the effect of clonidine on growth hormone secretion in children and adolescents, and concluded that clonidine is a potent pituitary growth hormone releasing agent (14, 10).

Anden et al proved clonidine to be a selective central noradrenergic receptor agonist in the Rhesus monkey, and to have no effect on serotonin and dopaminergic receptors. Results found in this study revealed that there are no

Table 1. Distribution of age, height and weight of children

variable	Group	group A	group B	group C	group D
age (year)	mean	9.12	9.76	7.69	10.06
	SD	3.65	3.88	3.60	3.60
height (cm)	mean	111.54	111.08	104.56	115.18
	SD	18.33	20.79	20.06	18.79
weight (kg)	mean	19.56	20.32	17.01	23.28
	SD	7.34	11.26	7.09	9.15

significant differences in using different recommended tests of growth hormone secretion.

Nevertheless clonidine appears to be a reliable, sensitive and safe agent for outpatient testing of growth hormone reserve (15, 16). Its administration requires no prior preparation of the patient, making it a particularly helpful tool in the evaluation of short children. A small number of short children (4 of 33 in exercise, 3 of 95 in L-Dopa, 2 of ITT, 7 of 108 in clonidine test)

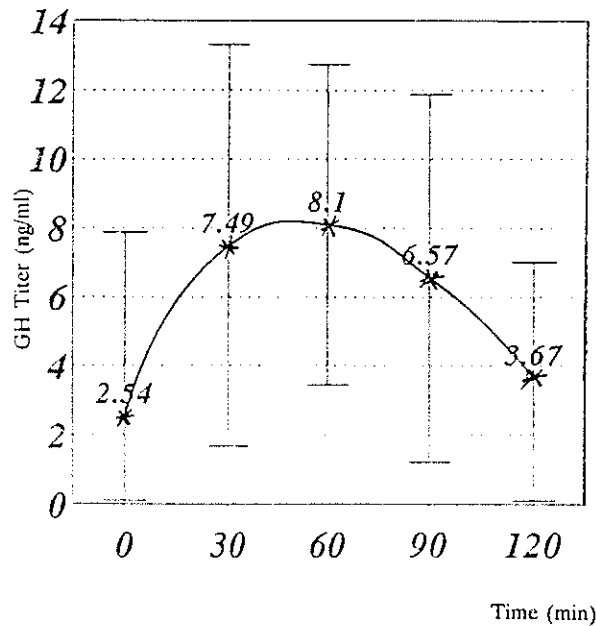


Fig. 2. Growth hormone titers in ITT test

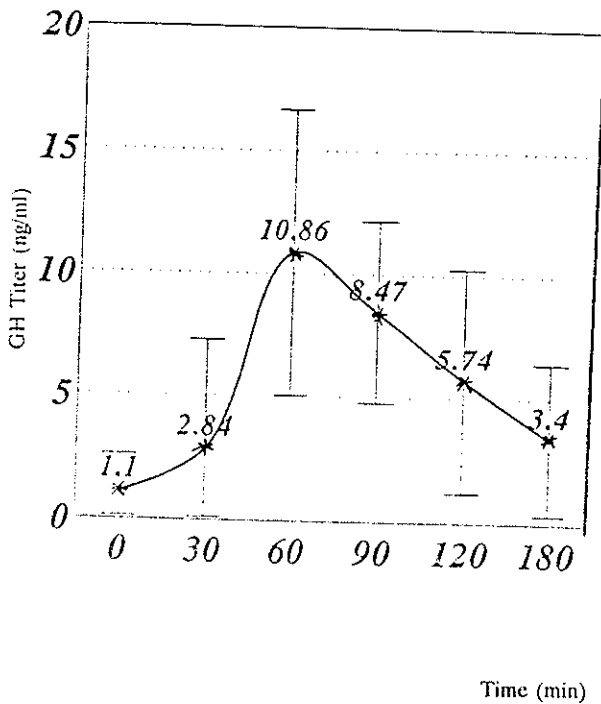


Fig. 1. Growth hormone titers in clonidine test

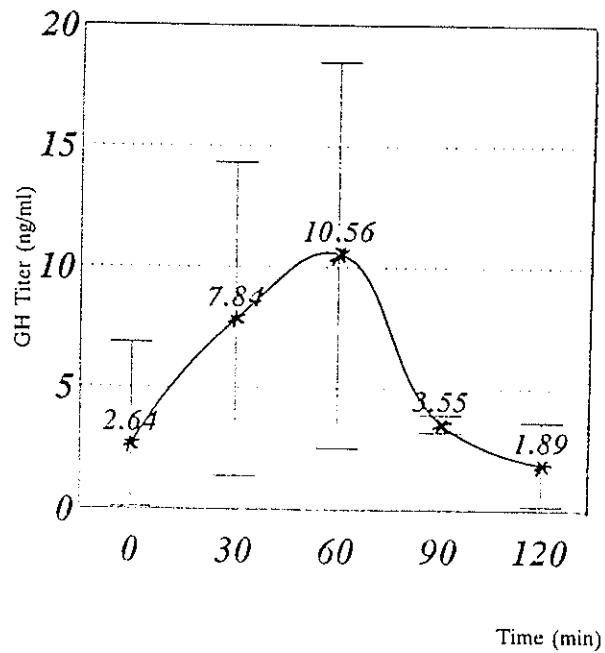


Fig. 3. Growth hormone titers in L-Dopa test

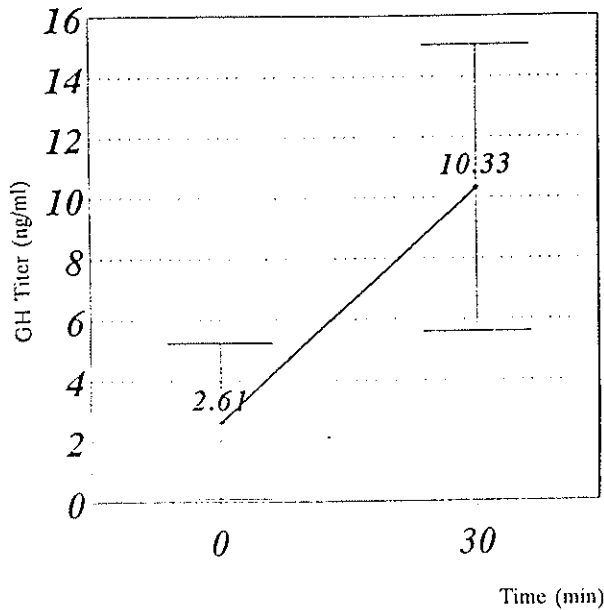


Fig. 4. Growth hormone titers in exercise test

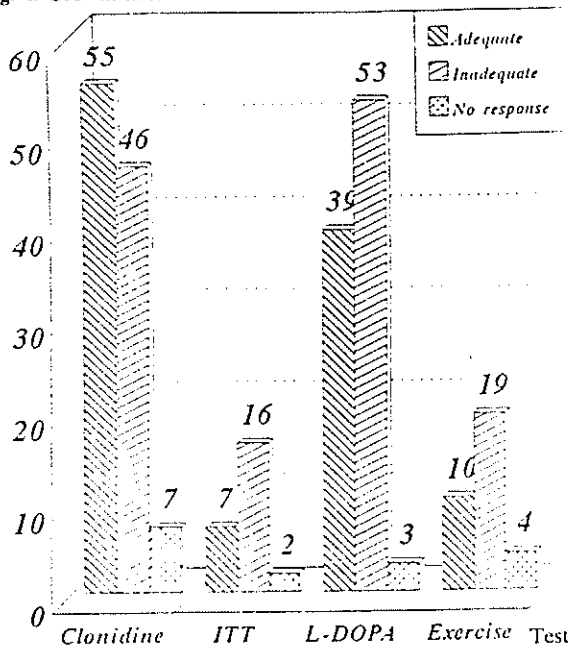


Fig. 5. Test responses

didn't respond to stimulation tests. In this study, no side effects were observed. This study support the idea that the different methods employed in diagnosing GH deficiency based on eliciting a growth hormone peak in response to a

pharmacologic stimulus are significantly different from one another.

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Eveluation Of Clonidine and ... on GH

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