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# GH Provocative Test in Diagnosis of GH deficiency in Childhood, Can We Trust on Them?

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## Article Info

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## Abstract

The most common reason for referral a Paediatric patient to the Endocrinologist is short stature. But the diagnosis of growth hormone deficiency (GHD) in childhood is a big challenge, due to the lack of gold standard tests.

The GDH can be total (the diagnosis is easy to suspect: pituitary lesions or congenital deficiency) or partial (diagnosis is more complex - cases are not accompanied by any clinic) when it will be necessary to do GH provocative tests.

Thus most common provocative tests of GH release (insulin tolerance test (hypoglycaemia), L-dopa, arginine, glucagon, propranolol, clonidine and GHRH) are used to determine GH status. But, for the definitive diagnosis not only will be necessary the provocative test results, it Will always be necessary to take into consideration also the clinical criteria together with auxological and biochemical parameters.

**Conclusion:** It would be advisable to use provocative tests of GH release with the highest percentages of sensitivity and specificity to detect subjects with GHD (insulin tolerance test "gold standar") but always excluding patients with an adequate GH response before.

**Keywords:** Provocative Test; Growth Hormone Deficiency; Arginine; Glucagon.

## Introduction

Nowadays, the most common reason for referral a Paediatric patient to the Endocrinologist is short stature. [1]. But the diagnosis of growth hormone deficiency (GHD) in childhood is a big challenge [2]. Due to the lack of gold standard tests, provocative GH tests are still considered the primary role in the diagnosis of GHD. So, the purpose of this review is to evaluate the usefulness of a variety of GH provocative test in the diagnosis of GHD in children.

The GDH can be total or partial. In the cases of total GDH (pituitary lesions or congenital deficiency), the diagnosis is easy to suspect. But in the cases of partial deficiencies, most of the cases are usually not accompanied by any clinic so the diagnosis is usually more complex and it will be necessary to do GH provocative tests. The consensus guidelines of the Growth Hormone Research Society for diagnosis and treatment of GHD in children have established that in a child with suspected isolated GHD, two stimulation tests are required [3].

## Tests to Assess GH Secretion

GH secretion is pulsatile and serum concentrations are low during many hours of the day [4]. Thus provocative tests of GH release are used to determine GH status. The most common provocative tests of GH release are: insulin tolerance test (hypoglycaemia), L-dopa, arginine, glucagon, propranolol, clonidine and GHRH. A variety of combinations

of these tests can also be used and, two provocative stimuli can be administered sequentially or in combination. Although these tests have three serious problems: the low specificity, the poor reproducibility, the great variability of the results depending on the type of stimuli [5] and provocative tests are invasive and sometimes has side effects. So, for the definitive diagnosis not only will be necessary the provocative test results, it will always be necessary to take into consideration also the clinical criteria together with auxological and biochemical parameters [6].

By way of summary, the different pharmacological stimuli to measure GH secretion are shown in table 1. But sometimes, to improve specificity of the test, pharmacological stimuli may be combined as it is shown in table 2 [7,8].

**Table 1.** GH Provocative tests**.**

| GH Provocative test | Drug administration | Blood samples | GH peak | Side effects |
|---|---|---|---|---|
| Insulin Tolerance Test (ITT), i.v | 0.05–0.01 U/kg | 0 (baseline), 15, 30, 45, 60 and 90 minutes | 15-30 minutes after the glucose nadir | Hypoglycaemia |
| L-dopa, i.v. | | | | Nausea, emesis and headache |
| Arginine HCl, i.v (over a 30-minute period) | 0.5 g/kg (max 40 g) | 0 (baseline), 30, 60, 90 and 120 minutes | 60 minutes after starting arginine infusion | Nausea and vomiting. Contraindicated in severe kidney or liver disease |
| Glucagon, i.m or s.c. | 0.03 mg/kg (max 1 mg) | 0 (baseline), 30, 60, 90, 120, 150 and 180 minutes | 2 hours after glucagon injection | Nausea and vomiting |
| Propranolol (orally)+exercise | 0,5 mg/Kg (max 40 mg) | 0, 90 (20 minutes of intense exercise), 120, 150 minutes | 120-150 minutes | Hypoglycaemia, contraindicated in asthma or cardiac pathology |
| Clonidine, i.v | 0.15 mg/m$^2$ | 0 (baseline), 30, 60 and 90 minutes | 60 minutes after clonidine administration | Decrease in blood pressure and drowsiness for several hours |
| GHRH, i.v | 1 mcg/kg | 0 (baseline), 15, 30, 45, 60, 90, and 120 minutes | 60 minutes after GHRH administration | Fainting or feeling light-headed |
| **i.v.,** intravenously | | | | |
| **i.m.,** intramuscularly | | | | |
| **s.c.,** subcutaneously | | | | |

**Table 2.** GH Provocative tests - pharmacological stimuli combined.

| GH Provocative test | Procedure | Blood samples | Side effects |
|---|---|---|---|
| Arginine i.v. + Insulin i.v. | First: Arginine dose of 0.5 g/kg (maximum of 40 g), i.v. and 60 min. later Insulin (0.05–0.01 U/kg) | 0, 15, 30, 45, 60, 80, 90, 105, 120, 150 minutes | Nausea and vomiting |
| GHRH i.v.+ArginineHCli.v. | GHRH 1 µg/kg at time 0 and Arginine, dose of 0.5 g/kg (maximum of 40 g), i.v. | 0, 15, 30, 45, 60, 90 and 120 minutes | Fainting or feeling light-headed. Contraindicated in severe kidney or liver disease |

# Results

Although in all papers reviewed, as shown in table 3, the only of the GH stimulation tests that has obtained 100% specificity and 100% sensitivity, it has been the Glucagon test in the study of Eren et al. [9], on the contrary, on the study of Kota et al. [10], the specificity was 85% and sensitivity was 73%, so it could better be considered that ITT should be one of the preferred GH stimulation tests (gold standard test) [4,11], because it has been the test that has obtained higher percentages of sensitivity and specificity: Borges et al. [12] (sensitivity 100% and specificity 96,98%), Guzzetti et al. [13] (sensitivity 94,4% and specificity 89,6%), Rhee et al. [14] (sensitivity 93,6% and specificity 78,4%), Guo et al. [15] (sensitivity 48% and specificity 76% - the lowest percentages of all papers compared), Eren et al. (sensitivity 91% and specificity 65%); Maghnie et al. [16] (sensitivity 96% and specificity 100%), Shalet et al. [4] (sensitivity 100% and specificity 97%) and Tillman et al. [17] (sensitivity 73% and specificity 85%). On the other hand, the other stimulation tests of the GH (L-dopa, Arginine HCl, Clonidine and GHRH) could hardly be considered as the gold standard test (in fact, it is not described in the last papers the sensitivity and the specificity about the Propanolol test), because they are not the most used for the detection of growth hormone defects, in addition to the percentages of sensitivity and specificity differ considerably from some studies to others [17-23]. See the values in table 3.

**Table 3.** The Sensitivity and the Specificity of the tests.

| References | | ITT | L-dopa | Arginine HCl | Glucagon | Clonidine | GHRH |
|---|---|---|---|---|---|---|---|
| Penta et al. [20] | Sensitivity (%) | – | – | 97 | – | – | – |
| Int J Environ Res Public Health (2019) | Specificity (%) | – | – | 100 | – | – | – |
| Borges et al. [13] | Sensitivity (%) | 100 | – | – | – | 86,8 | – |
| Clinics (2016) | Specificity (%) | 96,98 | – | – | – | 93,6 | – |
| Dreismann et al. [21] | Sensitivity (%) | – | – | 91 | – | – | – |
| Growth Horm IGF Res (2016) | Specificity (%) | – | – | 88 | – | – | – |
| Guzzetti et al. [14] | Sensitivity (%) | 94,4 | – | 93,9 | – | 88,5 | – |
| Euro J Endocrinology ens (2016) | Specificity (%) | 89,6 | – | 92,7 | – | 97,3 | – |
| Rhee et al. [15] | Sensitivity (%) | 93,6 | 79,2 | – | – | – | – |
| Chonnam Med J 2015 | Specificity (%) | 78,4 | 29,7 | – | – | – | – |
| Obara-Moszynska et al. [22] | Sensitivity (%) | – | – | – | – | – | 95 |
| Endokrynol Pol 2015 | Specificity (%) | – | – | – | – | – | 30 |
| Guo et al. [16] | Sensitivity (%) | 48 | – | – | – | 65 | – |
| Iran J Pediatr 2013 | Specificity (%) | 76 | – | – | – | 79 | – |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Kota et al. [10] | Sensitivity (%) | – | – | – | 73 | 70 | – |
| J Nepal Paediatr Soc 2012 | Specificity (%) | – | – | – | 85 | 85 | – |
| Eren et al. [9] | Sensitivity (%) | 91 | 94 | – | 100 | 72 | – |
| Turk Jem (2010) | Specificity (%) | 65 | 66 | – | 100 | 90 | – |
| Makimura et al. [23] | Sensitivity (%) | – | – | 62 | – | – | – |
| J Clin Endocrinol Metab (2008) | Specificity (%) | – | – | 77 | – | – | – |
| Maghnie et al. [17] | Sensitivity (%) | 96 | – | – | – | – | – |
| Eur J Endocrinol (2005) | Specificity (%) | 100 | – | – | – | – | – |
| Shalet et al. [11] | Sensitivity (%) | 100 | – | – | – | – | – |
| Endocrine Reviews (1998) | Specificity (%) | 97 | – | – | – | – | – |
| Tillman et al. [19] | Sensitivity (%) | 73 | – | – | – | – | – |
| J Clin Endocrinol Metab (1997) | Specificity (%) | 85 | – | – | – | – | – |

# Conclusion

It has not been possible to establish an ideal pattern against the results obtained in the various stimulation tests could be compared, thus dictating the definition of the sensitivity and specificity of the tests. Because there is a lack of homogeneity in the response of the same patient to two different stimuli: for example, while in some patients hypoglycaemia is a stronger stimulus than exercise and propranolol, in other patients occurs the opposite [18].

On the other hand, stimulation tests may be influenced by factors that must be taken into consideration, such as age, puberty, obesity, hypothyroidism, hypercortisolism, concomitant medication and stress [19].

For all of the above, it must be recognized that it is not surprising that the utility of GH provocation tests in the diagnosis of GH deficiency in children with short stature is more questionable. Even so, it would be advisable to use the tests with the highest percentages of sensitivity and specificity to detect subjects with GHD, but always bearing in mind that patients with an adequate GH response should be excluded beforehand.

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