A REAPPRAISAL OF THE CUT-OFF LIMITS OF THE PEAK GH RESPONSE TO STIMULATION TESTS FOR THE DIAGNOSIS OF GH DEFICIENCY IN CHILDREN AND ADOLESCENTS

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Background.

The diagnosis of GH Deficiency (GHD) in children and adolescents is classically established when GH concentrations fail to reach a cut-off level (usually between 7 and 10 µg/L) after at least two provocative tests. These limits are arbitrary and do not consider the type of test, nor the age and sex of the patient or the type of assay used to measure GH.

Objective.

The aim of this study was to define the optimal GH cut-offs to different provocative tests in children and adolescent.

	Patients (n=128)	Controls (n=310)
Sex (M/F)	76/52	195/115
Prepubertal/Pubertal	66/59	159/151
Age (years)	11.2±3.6	9.7±4.3
Peak GH to arginine (µg/L)	2.6±2.4	13.1±7.1
Peak GH to ITT (µg/L)	2.7±2.3	11.9±6.5
Peak GH to clonidine (µg/L)	2.5±2.1	15.4±6.8
H-SDS	-1.4±1.2	-2.3±0.9
BMI-SDS	0.3±1.3	-0.6±1.2
IGF-I SDS	-3±1.7	-0.9±1.1

Table 1. Main clinical characteristics of the subjects studied.

- ♦ 103 CNS tumors:
  - medulloblastoma (n=33),
  - craniopharyngioma (n=30),
  - germinoma (n=16),
  - others (n=24);
- ♦ 19 malformations:
  - ectopic neurohypophysis (n=6),
  - pituitary hypoplasia (n=4),
  - empty sella (n=3),
  - others (n=6);
- ♦ 3 leukemias;
- ♦ 2 neurofibromatosis;
- ♦ 1 PROP1 mutation.

Table 2. Clinical diagnosis of GHD patients studied.

Patients and methods.

This was a retrospective study in 438 subjects (Tables 1 and 2) who underwent evaluation of GH secretion. The patient group (P) consisted of 128 patients with organic GHD. The control group (C) consisted of 310 subjects with a GH response >10 µg/L to at least one test. IGF-I was also measured in 371 subjects at baseline. GH and IGF-I were measured by the same chemiluminescence assay in all samples (Immulite, Siemens). The provocative tests used (Table 3) were arginine (154 C, 97 P), Insulin Tolerance Test (ITT; 79 C, 90 P) and clonidine (173 C, 27 P). All provocative tests were performed between 8.00 and 9.00 am after fasting overnight.
Receiver operating characteristic (ROC) analysis and Likelihood Ratio (LR) were used to evaluate the optimal GH cut-offs and the diagnostic accuracy of the provocative tests.

Results.

The results of ROC analysis indicated that the optimal GH cut-off for the arginine test is 7.9 µg/L, for ITT is 5.3 µg/L and for the clonidine test is 6.8 µg/L. IGF-I SDS showed low accuracy in diagnosing GHD (Table 4 and Figure).
Combining the results of the provocative tests with IGF-I levels improves the specificity of the tests but does not improve the efficiency (Table 5).

Arginine
0.5 g/kg IV (max 30 g) in 30'

ITT
0.05-0.1 U/kg IV
(nadir glucose <40 mg/dL (2.2 mmol/L))

Clonidine
0.15 mg/m^2 orally

Table 3. Stimulation tests performed.

	Arginine	ITT	Clonidine	IGF-I SDS
Cut-off	7.9 µg/L	5.3 µg/L	6.8µg/L	-1.8 SDS
Sensitivity (%; 95% CI)	95.8 (89.7-98.8)	87.7 (79.1-93.7)	100 (87.2-100)	80.6 (71.3-87.9)
Specificity (%; 95% CI)	81.7 (74.6-87.4)	87.8 (78.1-94.2)	98.8 (95.8-99.8)	75.8 (70.3-80.7)
Efficiency (%)	87.2	86.5	99	77
LR+	5.2	7.2	86.5	3.3
Cut-off for sensitivity at 95%	7.9 µg/L	7.3 µg/L	6.8 µg/L	-0.9 SDS
Cut-off for specificity at 95%	2.3 µg/L	3.6 µg/L	6.8 µg/L	-2.9 SDS

Table 4. Optimal cut-off points of peak GH response to arginine, ITT, clonidine and IGF-I SDS evaluated with ROC analysis.

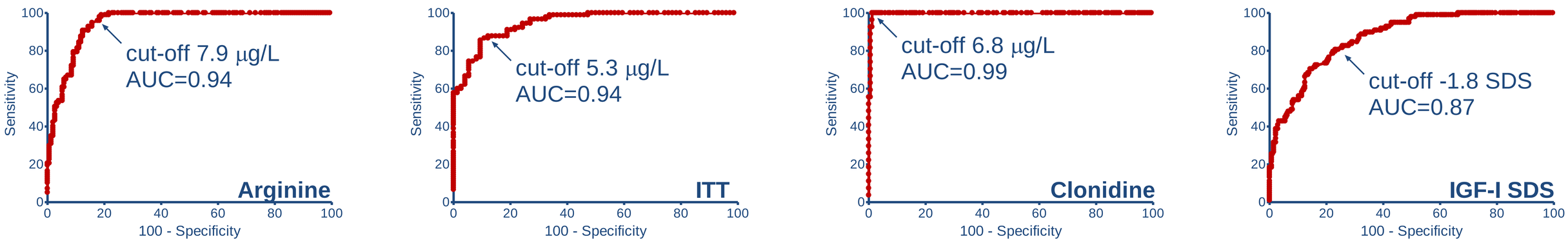

Figure. ROC curves for peak GH responses to provocative tests and IGF-I SDS.

	n	Sensitivity	Specificity	PPV	NPV	LR+	Efficiency	χ^2	P
Arginine	203	94.5	85.3	78.4	96.5	6.4	88.6	121.5	<0.0001
Arginine + IGF-I SDS		73.9	92.3	84.3	86.3	9.6	85.7	95.1	<0.0001
ITT	122	87.1	84.6	88.4	83	5.6	86.1	62.5	<0.0001
ITT + IGF-I SDS		72.8	94.2	94.4	72	12.6	81.9	54.4	<0.0001
Clonidine	196	100	98.8	93.1	100	84.5	98.9	180.3	<0.0001
Clonidine + IGF-I SDS		74	99.4	95.2	96	125.2	95.9	131.4	<0.0001

Table 5. Diagnostic accuracy of the tests alone and associated with IGF-I SDS (subnormal GH response to the test and subnormal IGF-I concentration). Only patients with available IGF-I SDS measurement were included.

Conclusions.

The results of ROC analysis showed that the cut-off limits which best discriminate between normal and GHD patients are lower than those commonly employed, and differ according to the stimulation test. IGF-I is characterized by low diagnostic accuracy.

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