**IGF-1 assessed by pubertal status has the best positive predictive power for GH deficiency diagnosis in peripubertal children**

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# Supplemental Table 1 – Clinical and laboratory characteristics of the GHD, Non-GHD, ISS and SGA patients

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | GHD | Non-GHD | ISS\* | SGA\* |
| N | 23 | 131 | 100 | 31 |
| Gender (M:F) | 12:11 | 90:41 | 78:22 | 12:19 |
| Midparental height SDS | -1.1 ± 0.9  -1.1(-2.4 to 0.7) | -1.0 ± 0.9  -0.9 (-2.6 to 0.3) | -1.0 ± 0.9  -0.9 (-2.4 to 0.5) | -1.2 ± 0.8  -1.0 (-2.7 to -0.0) |
| Chronological age (years) | 13.1 ± 3.2 a  13.5 (8.5 to 17.3) | 12.6 ± 2.4  12.8 (8.5 to 16.2) | 13.0 ± 2.3b  13.2 (9.4 to 16.3) | 11.3 ± 2.3a,b  11.3 (8.1 to 15.7) |
| Bone age (years) | 10.1 ± 4.0  9.8 (3.7 to 17.4) | 10.5 ± 2.2  11.0 (6.1 to 13.7) | 10.8 ± 2.0  11.0 (7.0 to 13.5) | 9.8 ± 2.7  10.0 (5.9 to 14.0) |
| Bone age delay (years) | -3.4 ± 2.0a  -3.9 (-6.7 to 0.6) | -2.1 ± 1.5a  -2.1 (-4.5 to 0.6) | -2.3 ± 1.6a,b  -2.3 (-4.5 to 1.0) | -1.5 ± 1.0a,b  -1.3 (-3.3 to -0.2) |
| Height SDS | -3.8 ± 1.7  -3.5 (-6.5 to -0.9)a | -2.7 ± 0.5  -2.8 (-3.4 to -1.8)a | -2.7 ± 0.5a  -2.7 (-3.4 to -1.7)a | -2.8 ± 0.5  -2.9 (-3.6 to -2.0) |
| BMI SDS | -0.1 ± 1.5a  -0.1 (-2.5 to 2.3) | -1.0 ± 1.5  -0.8 (-3.8 to 1.1) | -1.0 ± 1.6a  -0.8 (-4.3 to 1.1) | -0.8 ± 1.2  -0.7 (-3.1 to 0.9) |
| Pubertal stages I  II  III  IV | 65%  4%  22%  9% | 50%  35%  10%  7% | 49%  33%  10%  7% | 52%  41%  7%  0% |
| Maximum GH peak (µg/L) | 1.3 ± 1.5  0.9 (0.1 to 4.9)a | 9.4 ± 5.3  8.1 (3.2 to 21.2)a | 9.2 ± 5.2  8.1 (3.2 to 21.9)a | 10.4 ± 5.6  8.5 (3.0 to 20.1)a |
| IGF1-SDS-CA | -3.1 ± 0.8  -3.2 (-4.1 to -0.9)a | -1.2 ± 1.4  -1.3 (-3.1 to 1.1)a | -1.4 ± 1.3  -1.6 (-3.0 to 1.0)a,b | -0.6 ± 1.4  -0.3 (-3.2 to 1.2)a,b |
| IGF1-SDS-BA | -2.4 ± 1.2a  -2.6 (-3.7 to 0.0) | -0.5 ± 1.1a  -0.5 (-2.2 to 1.4) | -0.5 ± 1.1a  -0.6 (-2.1 to 1.2) | -0.2 ± 1.3a  0.2 (-2.8 to 1.7) |
| IGF1-SDS-PS | -1.7 ± 0.8  -2.1 (-2.4 to -0.1)a | -0.1 ± 0.8  -0.1 (-1.0 to 1.0)a | -0.1 ± 0.9  -0.1 (-1.0 to 0.9)a | 0.0 ± 0.8  -0.1 (-1.0 to 1.1)a |

\* ISS and SGA groups compose the Non-GHD group. Data are shown as mean ± SD and median (5th and 95th centile range) for numerical variables and absolute number or percentage for categorical variables; a – significant difference between the GHD and Non-GHD groups (p < 0.001) or between GHD group and ISS or SGA groups (p < 0.05) when noted; b – significant difference between the ISS and SGA groups (p < 0.05) when noted; GHD: Growth hormone deficiency; ISS: idiopathic short stature; SGA: patients born small for gestational age; SDS: standard deviation score; IGF-1-SDS-CA: IGF-1 SDS according to chronological age; IGF-1-SDS-BA: IGF-1 SDS according to bone age; IGF-1-SDS-PS: IGF-1 SDS according to pubertal status.

# Supplemental Table 2 – Clinical and laboratorial characteristics of GHD patients with normal IGF-1-SDS and Non-GHD patients with abnormal IGF-1-SDS according to chronological age, bone age and pubertal status

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **GHD group with normal IGF-1-SDS** | | |  | **Non-GHD group with abnormal IGF-1-SDS** | | |
|  | **IGF-1-SDS-CA** | **IGF-1-SDS-BA** | **IGF-1-SDS-PS** |  | **IGF-1-SDS-CA** | **IGF-1-SDS-BA** | **IGF-1-SDS-PS** |
| **N** | 2 | 5 | 9 |  | 46 | 11 | 2 |
| **Gender (M:F)** | 2:0 | 4:1 | 6:3 |  | 40:6 | 7:4 | 0:2 |
| **Chronological age (years)** | 10.8 and 10.9 | 10.9 (9.8 to 15.5) | 12.2 (8.9 to 17.3) |  | 14.0 (10.1 to 16.3) | 14.5 (9.9 to 16.5) | 11.2 and 13.2 |
| **Bone age delay (years)** | -4.9 and -2.8 | -4.4 (-6.8 to -3.1) | -4.3 (-6.3 to -1.4) |  | -2.7 (-4.47 to -0.7) | -2.0 (-3.0 to -0.4) | 2.2 and 2.4 |
| **Height SDS** | -2.2 and -2.5 | -3.1 (-4.9 to -2.3) | -4.4 (-5.5 to -2.3) |  | -3.0 (-3.6 to -2.4) | -3.4 (-3.7 to -2.6) | -2.3 and -3.4 |
| **BMI SDS** | 0.8 and 2.0 | 0.6 (-2.6 to 1.8) | -0.3 (-2.3 to 2.0) |  | -1.7 (-4.9 to 0.2) | -1.0 (-5.6 to 0.2) | -1.0 and 0.4 |
| **Pubertal stages (n)** |  |  |  |  |  |  |  |
| **I** | 2 | 5 | 8 | 22 | 6 | 0 |
| **II** | 0 | 0 | 1 | 20 | 5 | 2 |
| **III** | 0 | 0 | 0 | 4 | 0 | 0 |
| **Maximum GH peak (µg/L)** | 1.6 and 2.9 | 1.7 (0.8 to 2.8) | 1.8 (0.5 to 4.9) |  | 8.1 (4.0 to 22.1) | 9.0 (5.1 to 22.6) | 5.7 and 6.3 |
| **Normal IGF1-SDS-CA (n)** | - | 2 | 2 |  | - | 11 | 2 |
| **Normal IGF1-SDS-BA (n)** | 0 | - | 4 |  | 11 | - | 1 |
| **Normal IGF1-SDS-PS (n)** | 0 | 4 | - |  | 2 | 1 | - |
| **Abnormal MRI** | 1 | 2 | 7 |  | 0 | 0 | 0 |

Data are shown as median (5th and 95th centile range) for numerical variables and absolute number for categorical variables; IGF-1-SDS: IGF-1 Standard deviation score; IGF-1-SDS-CA: IGF-1 SDS according to chronological age; IGF-1-SDS-BA: IGF-1 SDS according to bone age; IGF-1-SDS-PS: IGF-1 SDS according to pubertal status.

# Supplemental Table 3 – Estimative of performance of a GH stimulation test (with an sensitivity of 88.5% and specificity of 97.4% (6)) according to the pre-test probability

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Pre-Test Probability  (estimated disease prevalence) | GH Stimulation Test | Sensitivity | Specificity | PPV | NPV |
| Height SDS < -2: 2.0%\* | Clonidine | 88.5 | 97.4 | 41.0% | 99.8% |
| + IGF-1-SDS-CA < -2: 5.1% | Clonidine | 88.5 | 97.4 | 64.8% | 99.4% |
| + IGF-1-SDS-BA <-2: 16.8% | Clonidine | 88.5 | 97.4 | 87.3% | 99.4% |
| + IGF-1-SDS-PS <-2: 44.8% | Clonidine | 88.5 | 97.4 | 96.5% | 99.4% |
|  |  |  |  |  |  |
| Height SDS < -2: 2.0%\* | ITT | 94.4 | 89.6 | 15.6% | 99.9% |
| + IGF-1-SDS-CA < -2: 5.1% | ITT | 94.4 | 89.6 | 33.0% | 99.7% |
| + IGF-1-SDS-BA <-2: 16.8% | ITT | 94.4 | 89.6 | 64.7% | 98.8% |
| + IGF-1-SDS-PS <-2: 44.8% | ITT | 94.4 | 89.6 | 88.0% | 95.2% |

PPV: positive predictive value; NPV: negative predictive value; IGF-1-SDS-CA: IGF-1 SDS according to chronological age; IGF-1-SDS-BA: IGF-1 SDS according to bone age; IGF-1-SDS-PS: IGF-1 SDS according to pubertal status. \* for the assessment of the PPV and NPV we considered a maximum prevalence of GHD of 2% in peripubertal children with short stature