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Diagnostic value of random serum growth hormone, IGF-I and IGFBP-3 concentrations for the diagnosis of growth hormone deficiency in patients below one year of life.

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Introduction

The diagnosis of Growth Hormone Deficiency (GHD) needs to combine clinical phenotype, imaging as well as biochemical assessment of GH-IGF-I axis[1]. The typical auxologic phenotype in neonates and early infants could be absent and therefore, a practical evidence-based approach to assess the usefulness of biomarkers of GH action is needed.

To our knowledge, this study is still lacking for current standardized GH, IGF-I and IGFBP-3 in patients below one year of life.

Objectives

1- To establish reference intervals for serum concentration of GH, IGF-I and IGFBP-3 for the whole first year of age.

2- To investigate GH, IGF-I and IGFBP-3 usefulness for GHD diagnosis in neonates and early infancy.

Subjects

Patients

Inclusion criteria: Infants <1 year of age, who were referred to the Endocrinology Division with clinical suspicion of GHD from March 2016 to June 2019.

- Clinical follow-up was the gold standard for **GHD** diagnosis: growth retardation, additional pituitary hormone deficiencies, brain MRI abnormalities and/or abnormal GH stimulation test during childhood.
- Non-GHD patients were diagnosed as having congenital hyperinsulinism **(HI)** or transient hypoglycemia **(TH).**

Exclusion criteria: Preterm newborns, critical sample under hypoglycemia

Healthy neonates and infants

Inclusion criteria: Surplus serum corresponding to healthy neonates and infants who consulted the Endocrinology Division for presumed endocrine abnormalities during 2016-2019 and were found to be normal.

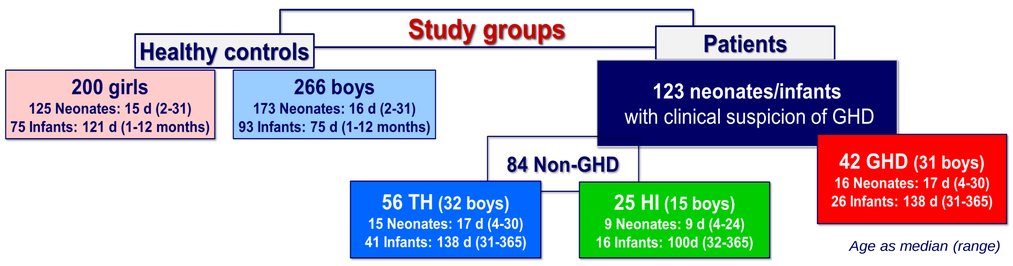
Exclusion criteria: Preterm babies, hemolysis or lipemic samples.

Methods

Design: Diagnostic validation study at a tertiary hospital.

- Random serum samples.
- GH (IRS 98/574), IGF-I (WHO 02/254) and IGFBP-3 (Siemens, IMMULITE 2000/Xpi); CV% < 5%
- IGF-I was log-transformed
- Statistics: Multiple regression analysis, Kruskal-Wallis, Fisher t Test; Receiver operating curve (ROC): **GHD** (true positive) versus **TH** (true negative)
- Primary main outcomes: GH SDS, IGF-I SDS, IGFBP-3 SDS.
- Measures by ROC: Diagnostic accuracy (DA), Area under the curve (AUC), Sensitivity (S), Specificity (Sp), Positive and Negative Predictive Value (PPV and NPV).

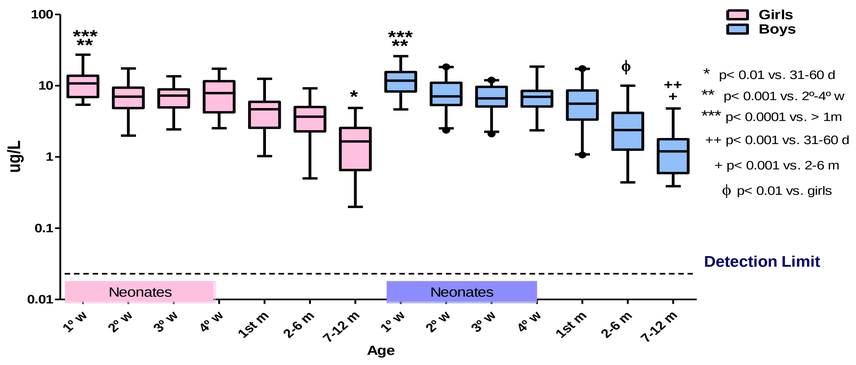
Results



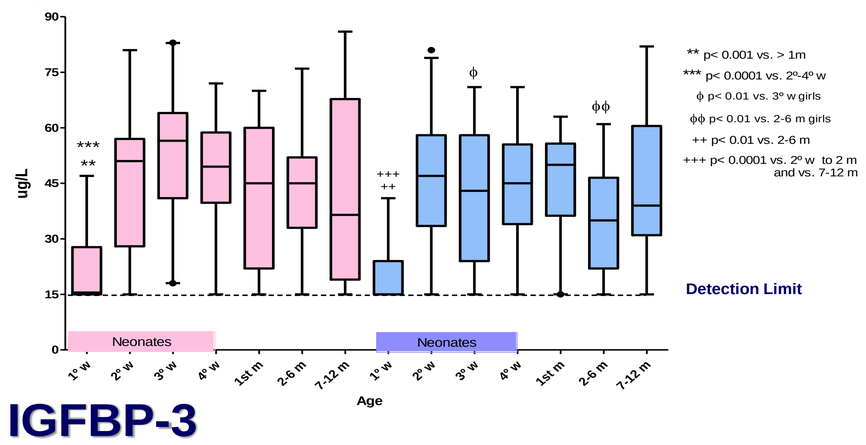
Age as median (range)

Healthy Neonates and infants

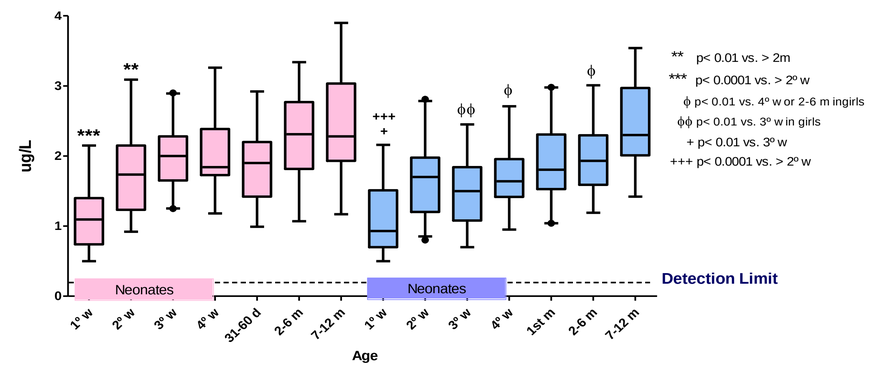
GH



IGF-I



IGFBP-3

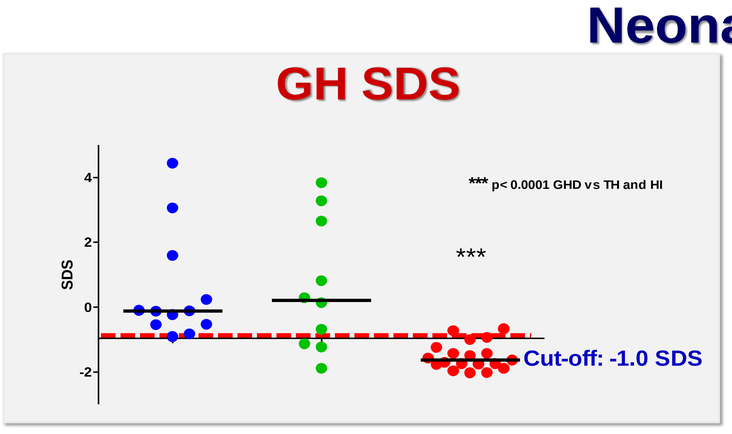


- Neonates of 1 week of age have higher GH and lower IGF-I and IGFBP-3 than other age groups. Thereafter, GH decreases and IGF-I and IGFBP-3 increase with age.
- GH is always detectable in healthy neonates and early infants. Not-detectable IGF-I are more frequently observed in neonates (18%) than in infants (9%), *p< 0.01*. Beyond the 1st week, IGFBP-3 is always detectable.
- Sexual dimorphism is observed for GH, IGF-I and IGFBP-3. Boys aged 2-6 months have lower concentration of these biomarkers than age-matched girls.

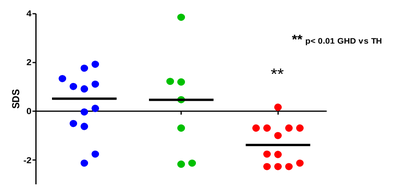
Patients

Neonates

GH SDS

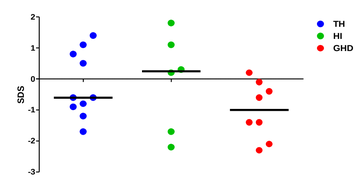


IGF-I SDS



Roc IGF-I p= 0.08 (NS)

IGFBP-3 SDS



Roc IGFBP-3 p= 0.08 (NS)

NS: not significant
(95% confidence interval)

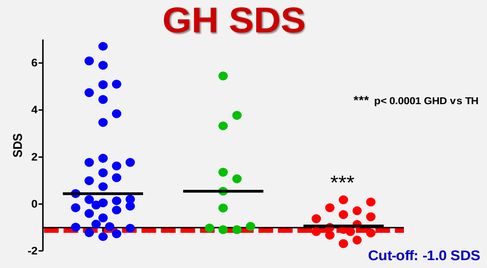
Cut-off (SDS)	AUC	S	Sp	PPV	NPV	DA (%)
GH: -1.0	**0.95** (0.87 - 1.0) p< 0.0001	**0.86** (0.57 - 0.98)	**1.0** (0.74 - 1.0)	**1.0** (0.73 - 1.0)	**0.85** (0.57 - 0.98)	**92.3**

< -1.0 GH SDS

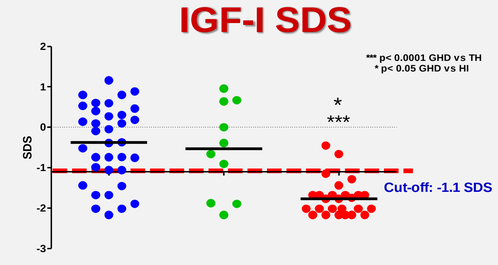
1st week	< 6.2 µg/L
2nd to 4th week	< 4.0 µg/L

Infants

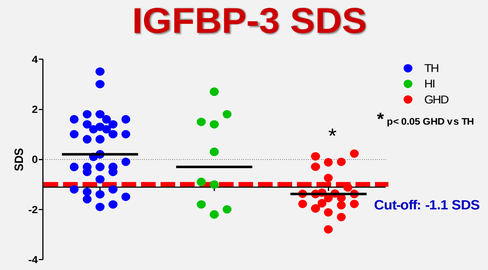
GH SDS



IGF-I SDS



IGFBP-3 SDS



Cut-off (SDS)	AUC	S	Sp	PPV	NPV	DA (%)
GH: -1.0	**0.84** (0.73 - 0.94) p< 0.01	0.50 (0.25 - 0.75)	**0.89 (0.74 - 0.97)**	0.67 (0.35 - 0.90)	0.80 (0.64 - 0.91)	75.4
IGF-I: -1.1	**0.86** (0.73 – 0.96) p< 0.0001	**0.92 (0.74 - 0.99)**	0.77 (0.60 – 0.89)	0.75 (0.57 - 0.88)	0.93 (0.77 - 0.99)	**83.3**
IGFBP-3: -1.1	**0.95** (0.87 - 1.0) p< 0.01	0.72 (0.55 - 0.83)	**0.80 (0.59 - 0.87)**	0.67 (0.45 – 0.84)	0.81 (0.64 - 0.99)	78.2

IGF-I has the highest DA in infants.

Combination of biomarkers

Cut-off (SDS)	S	Sp	PPV	NPV	DA (%)
GH < -1.0 & IGF-I < -1.1	0.50 (0.25 - 0.75)	**0.97 (0.84 - 0.99)**	**0.89 (0.51 - 0.99)**	0.76 (0.60 - 0.89)	**79.2**
GH < -1.0 & IGFBP-3 < -1.1	0.42 (0.20 - 0.66)	**1.0 (0.88 - 1.0)**	**1.0 (0.63 – 1.0)**	0.73 (0.57 - 0.85)	**77.6**

GH and IGF-I or IGFBP-3 below the cut-offs improved Sp and PPV

Conclusions

- Reference data on GH, IGF-I and IGFBP-3 obtained in a large cohort of healthy controls allowed us to calculate SDS for these biomarkers using current standardized assays.
- GH constitutes the biomarker of choice in the diagnostic work-out of GHD in neonates.
- In infants, the presence of GH and IGF-I or IGFBP-3 values below the cut-offs confirms GHD diagnosis with high specificity.
- Due to the lack of an evidence-based approach for diagnosis of GHD along the first year of life with standardized immunoassays, we conclude that the cut-offs obtained in the present study could be useful in the diagnostic work-out of neonates and early infants with clinical suspicion of GH deficiency.

Reference: [1]*Grimberg et al. Horm Res Paediatr 2016;* *Acknowledgements: Ms Ana María Montese, Ms Silvina González and Dra. Gabriela Gotta* ; Disclosure: Nothing to disclose