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Serum IGFBP-2 concentration in neonates with potential diagnosis of growth hormone deficiency (GHD)

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Background

- Diagnostic criteria for GHD diagnosis in the neonatal period remain controversial due to the absence of the typical auxologic phenotype and the lack of specific cut-off references for basal GH & IGFs biomarkers whereas provocative GH are not recommended in early life.
- In a retrospective study on neonates with clinical suspicion of GHD, we found that using an adequate cut-off for GH in serum, GHD diagnosis was excluded with high diagnostic accuracy while IGF-I and IGFBP-3 were less informative[1].
- IGFBP-2 is negatively regulated by GH and its measurement in serum was proposed to reflect GH status in the diagnostic work-out of GHD in children and adults[2,3]. To our knowledge, the accuracy of IGFBP-2 has not been investigated for neonates.

Objectives

- To prospectively validate basal GH, IGF-I and IGFBP-3 in neonates with clinical suspicion of GHD.
- To investigate the usefulness of IGFBP-2 for diagnosing GHD in neonates.

Design

- Prospective validation study

Subjects

Inclusion criteria: Full-term neonates <1 month of life with neonatal hypoglycemia that were referred to The Endocrinology Division to rule-out GHD from March 2017 to June 2018.

Gold standard for final diagnosis: Clinical follow-up

GHD
- Growth retardation
- Hypothalamic-pituitary defects (MRI)
- Deficiency of at least one additional pituitary hormone.

Non-GHD
- Congenital hyperinsulinism (HI)
- Transient hypoglycemia (TH).

Methods

- GH (IRS 98/574), uncertainty: 10%; cut-off: 6.5 ng/mL; IGF-I (WHO 02/254) and IGFBP-3 by Siemens, Immulite 2000/XPi. CV% < 5%
- IGFBP-2 by Elisa-Mybiosource.
- Kruscal-Wallis, Pearson correlation

Random serum sample

Main outcome measures by Receiver operating curve (ROC): Sensitivity (S), specificity (Sp), negative predictive value (NPV) and positive PV (PPV) of GH and IGFBP-2.

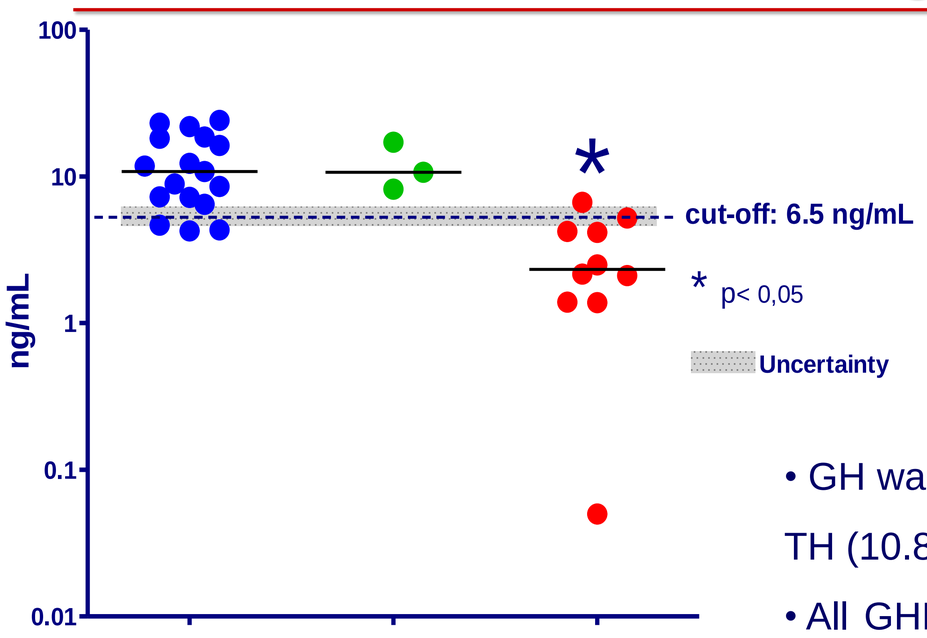
Results

Study groups

30 neonates with clinical suspicion of GHD

- 20 non-GHD — Median age: 25 days; Range: 2-31 days
  - 17 TH
  - 3 HI
- 10 GHD — Median 24 days; Range: 5-30 days

GH

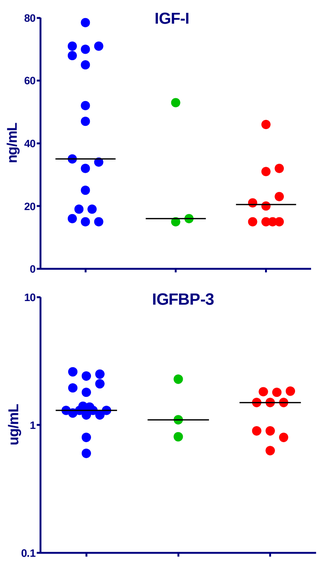


GH accuracy by ROC
Cutoff: 6.5 ng/mL *(Fisher p< 0.0001)*

S	Sp	PPV	NPV
0.90 (0.60-1.0)	0.87 (0.66-0.97)	0.75 (0.46-0.95)	0.95 (0.76-1.0)

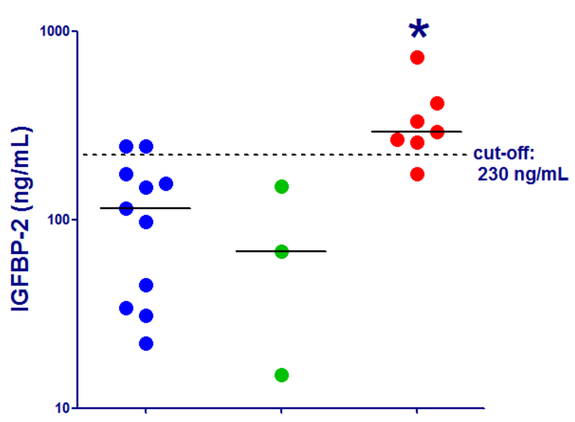
- GH was significantly lower in GHD (median: 2.3 ng/mL) than in TH (10.8 ng/mL) or HI (10.7 ng/mL), *p< 0.01.*
- All GHD presented a GH concentration below the uncertainty range (5.9 – 7.1 ng/mL),

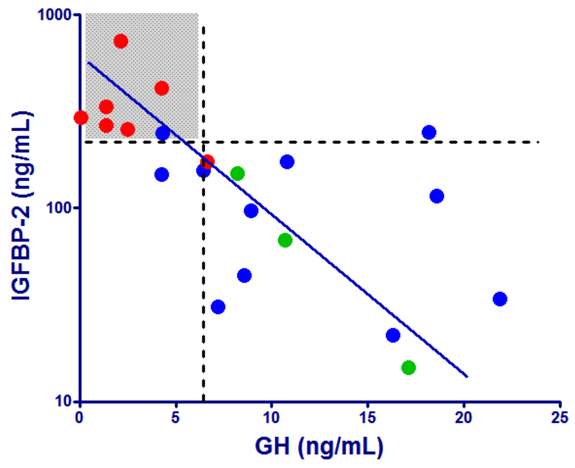
IGF-I and IGFBP-3



- No significant differences were observed among groups for IGF-I *(p= 0.06)* or IGFBP-3 *(p= 0.78)*.

IGFBP-2 (measured in 21/30 neonates: 11 TH, 3 HI and 7 GHD)





IGFBP-2 accuracy by ROC
Cutoff: 230 ng/mL *(Fisher p< 0.001)*

S	Sp	PPV	NPV
0.86 (0.42-0.99)	0.86 (0.57-0.98)	0.75 (0.35-0.97)	0.92 (0.64-1.0)

- Neonates with **GHD** presented significantly **higher IGFBP-2** than non-GHD groups, ***p< 0.01.***
- IGFBP-2 was negatively associated to GH, r= - 0.79, p< 0.0001
- Serum random GH (86.7%) and IGFBP-2 (85.7%) presented similar diagnostic accuracy for GHD in the neonatal period.

Conclusions

- This study highlights that serum GH >6.5 ng/mL excludes GHD with high diagnostic accuracy. Hence, we strongly recommend to include basal serum GH in the diagnostic work-out of GHD during the newborn period.
- Although less explored, IGFBP-2 seems to reflect GH action in neonates. A larger sample size should be necessary to further consider IGFBP-2 measurement as a reliable biomarker for diagnosing GHD on them.
- According to this study, IGF-I and IGFBP-3 were less useful in the immediate post natal life.

[1] Ballerini MG. et al. Horm Res in Paediatrics 2017;P2-804
[2] Smith WJ. et al. Clin Endocrinol Metab 1993; 77:1294-99
[3] Ranke MB. et al. Horm Res 2000: 54:60-68