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

MG Ballerini, D Braslavsky, A Keselman, ME Rodriguez, G Gotta, MG Ropelato, I Bergadá

Centro de Investigaciones Endocrinológicas "Dr. César Bergadá" (CEDIE) CONICET–FEI–División de Endocrinología. Hospital de Niños “Ricardo Güitezm” Buenos Aires, Argentina

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-1 and IGFBP-3 were less informative.
- 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. 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.

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.
- 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.
  - Kruskal-Wallis, Pearson correlation

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
  - 10 GHD Median 24 days Range: 5-30 days
  - 17 TH
  - 3 HI

- **IGF-I and IGFBP-3**
  - No significant differences were observed among groups for IGF-I (p=0.06) or IGFBP-3 (p=0.78).
  - Neonates with GHD presented significantly higher IGFBP-2 than non-GHD groups, p<0.01.

- **IGFBP-2** (measured in 21/30 neonates: 11 TH, 3 HI and 7 GHD)
  - Cutoff: 6.5 ng/mL (Fisher p=0.0001)
  - S: 0.90, Sp: 0.87, PPV: 0.75, NPV: 0.95
  - 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).
  - 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 postnatal life.