The role of IGF-1 as a screening tool in radiation-induced growth hormone deficiency in childhood cancer survivors

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Background and Objectives

Conflicting outcomes have been reported about the role of low IGF-1 levels in predicting radiation-induced growth hormone deficiency (GHD) in childhood cancer survivors (CCS). IGF-1 <-2 SDS was found to have a sensitivity between 28 and 95% in different studies on CCS, but these results were drawn from small samples of irradiated patients or from mixed cohorts including patients with GHD due to different aetiologies.

Our aim was to analyse the screening role of low IGF-1 levels in CCS at risk of developing GHD after cranial radiotherapy (RT) involving the hypothalamic-pituitary (HP) area.

Patients and Methods

Design:
Observational, single centre, retrospective study.

Inclusion criteria:
Any CCS diagnosed with GHD in our centre between 2003 and 2017. Age < 16 years at GHD diagnosis.

Data Source:
- Patient's medical records and growth charts for demographical, auxological or clinical data
- Pituitary radiation doses were estimated from each RT plan.

Patients:
158 CCS:
- 123 brain tumours
- 29 leukaemias
- 6 irradiated cranial rhabdomyosarcomas

In order to describe the specific detrimental role of irradiation on GH secretion, we finally selected a cohort of 117 patients with tumours not involving the HP area (RT-NHP cohort).

Diagnosis of GHD:
GH peak <7 μg/L after a single stimulation test

Results

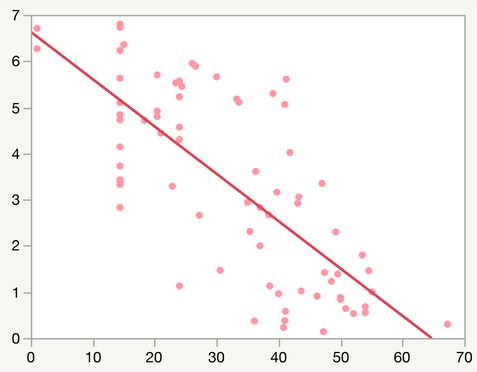
Sensitivity of IGF-1 and IGFBP-3 levels <-2 SDS in the RT-NHP cohort:
- IGF-1: 31.86%.
- IGFBP-3: 7.37%

Both results were remarkably lower than the sensitivity reported in non-irradiated GH deficient patients.

IGF-1 <-2 SDS at diagnosis of GHD in childhood showed:
- Statistically significant association with **GH peaks** < 3 μg/L in childhood (χ^2=8.65, p 0.003)
- Statistically significant association (χ^2= 9.1, p 0.003) and correlation (r: 0.47, p 0.004) with GH peaks at final height reassessment

IGF-1 <-2 SDS at final height reassessment:
Sens: 35% **Spec: 100%**
PPV: 100% NPV 58%

Correlation pituitary dose (Gy, X) – GH peaks (μg/L, Y)

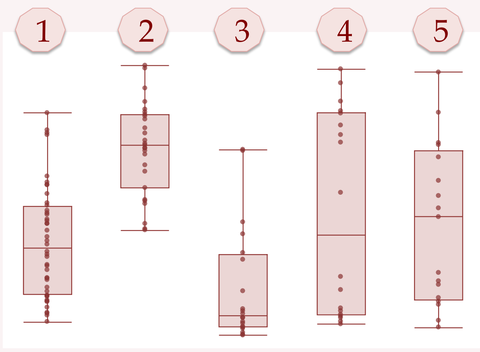


r: -0.75; p 0.00001

GH peak drops by an average value of 0.1 μg/L for each additional Gy.

The number of deficient pituitary hormones showed no correlation with IGF-1 SDS:
- at diagnosis of GHD in childhood (r 0.10)
- at final height re-testing (r 0.12)

GH peaks and IGF-1 in oncological sub-groups

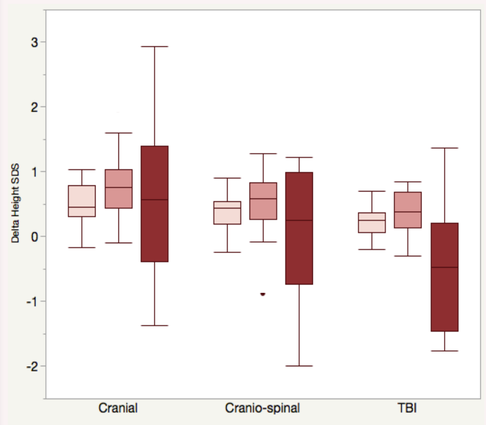


1. Medulloblastomas (MB)
2. Leukaemias (LK)
3. Craniopharyngiomas (CR)
4. Extra-optic gliomas
5. Optic-pathway gliomas

GH peaks were statistically higher in LK than MB and CR.

Sensitivity of IGF-1 <-2 SDS in LK after TBI was only 7.1%, statistically lower than in MB (43.9%, p 0.009) and CR (52.9%, p 0.014) with Fisher's exact test

Δ Height SDS 1, 2 years after start of rhGH therapy and at final height



1 year *2 years* ***Final height***

Improvement in height SDS after treatment was statistically lower in patients treated with TBI than with cranial or craniospinal RT at all time-points.

We found a weak negative correlation between IGF-1 SDS levels and Δheight SDS at final height (Pearson's r: -0.36, p 0.04)

Conclusions

IGF-1 and IGFBP-3 levels <-2 SDS had a **poor sensitivity** in predicting radiation-induced GHD.

However, a child with IGF-1 < -2 SDS had an higher risk of **severe GHD** (peak<3 μg/L) both in childhood and at final height retesting.

IGF-1 <-2 SDS at final height reassessment had a **PPV of 100%** in our study: this result suggests that dynamic re-testing in young adults with a previous history of GHD in childhood could be virtually not performed when IGF-1 levels are persistently low at the end of growth.

Normal IGF-1 levels despite overt radiation-induced GHD were particularly frequent in leukaemic patients treated with only TBI (**low pituitary radiation doses**). In this cohort, IGF-1 <-2 SDS had a sensitivity of only 7.1%

We found a negative statistical correlation between **pituitary radiation dose administered and GH peaks** achieved after stimulation test; GH dropped by an average value of 0.1 μg/L for each additional pituitary Gy.

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