POSTER NUMBER: 935 ; 5-RFC-3

# PROSPECTIVE DYNAMIC EVALUATION OF HYPOTHALAMO-PITUITARY FUNCTION IN PAEDIATRIC CRANIOPHARYNGIOMA, BY HYPOTHALAMIC INJURY AND TREATMENT; A SINGLE CENTRE SERIES.

Chiara Guzzetti[1], Laura Losa[1], Nicola Improda[1], Gloria Pang[1], Voraluck Phatarakijnirund[1], Hoong-Wei Gan[1], Richard Hayward[2], Kristian Aquilina[3], Ash Ederies[1], Helen A. Spoudeas[1].

[1]Departments of Paediatric NeuroEndocrinology, [2]Neurosurgery and [3]Neuroradiology, Great Ormond Street Hospital (GOSH) for Children, London. UK

## BACKGROUND

Craniopharyngiomas are the commonest suprasellar tumours of childhood.
Though benign histologically, their localization and invasive tendency can cause significant neuroendocrine morbidity even before treatment is imposed, but this has not been studied prospectively.

## OBJECTIVE

To prospectively determine risk factors for neuro-endocrine morbidity by longitudinal survival analysis.

## METHODS AND PATIENTS

- All (n=30, *Table 1*) new cases (01.08.2008 to 09.05.2015) of craniopharyngioma presenting to GOSH.
- Assessments of presenting auxology, basal and dynamic pituitary function, tumour volume (calculated using the software "ITK-SNAP version 3.2.0"), tumour appearance (evaluated by the neuroradiologist at MRI), degree of hypothalamic invasion by tumour according to Paris grade (PG)[1] at diagnosis and after treatment.
- Subsequent 3-6 monthly longitudinal review (*Tables 2 and 3*).
- Kaplan-Meier and Cox-regression analysis of patient, tumour and treatment effects on progression free survival (PFS[2]), endocrine event-free survival (EEFS[2]) and total endocrine morbidity score (EMS[2])

*Table 1. Patient demographics (n=30) . Data presented as Median (Range) or Proportions.*

| Patient Characteristics | |
|---|---|
| **Ethnicity** (White / Not white / unknown) | 11 (36.7%) / 17 (56.7%) / 2 (6.6%) |
| **Sex** (Male / Female) | 22 (73.3%) / 8 (26.7%) |
| **Age at diagnosis** (years) | 7.6 (1.1-17.2) |
| **Duration of symptoms before diagnosis** (≤1 months / ≤1 year / > 1year / unknown) | 11 (36.7%) / 12 (40%) / 4 (13.3%) /3 (10%) |
| **Hydrocephalus at diagnosis** | 13 (43.3%) |
| **Follow Up** (years) | 4 (0.3-7.4) |
| **Tumour Characteristics** | |
| **Diagnostic tumour volume** ($cm^3$) | 16.1 (1.8-193.3) |
| **Position** | |
| • Suprasellar | 15 (50%) |
| • Suprasellar, intrasellar | 9 (30%) |
| • Suprasellar, intrasellar and retrochiasmatic | 6 (20%) |
| **Appearance pre-treatment** (cystic / solid + cystic) | 11 (36.7%) / 19 (63.3%) |

*Table 2 A. Definition of Paris Grade[1] 0, 1 and 2; at Diagnosis and Post Operatively*

***Preoperative Paris Grade[1]:***
**PG 0** → No hypothalamic involvt.
**PG 1** → Tumour displaces hypothalamus
**PG 2** → Hypothalamus no longer identifiable

***Postoperative Paris Grade[1]:***
**PG 0** → No hypothalamic damage
**PG 1** → Negligible hypothalamic damage or displacement by tumour
**PG 2** → Significant hypothalamic damage

*Table 2 B. Number of patients with Paris Grade 0, 1 ,2 subdivided by treatment.*

| Paris Grade | 0 | 1 | 2 | Missing MRIs |
|---|---|---|---|---|
| **At diagnosis** | 3 | 7 | 19 | 1 |
| **After decompression** | 1 | 9 | 9 | - |
| **After resection** | 1 | 8 | 8 | - |
| **After radiotherapy** | 1 | 10 | 7 | 2 |
| **At last Follow-up** | 2 | 12 | 13 | 3 |

*Table 3. Proportion of Patients Developing Endocrinopathies at Diagnosis and by Each Treatment Phase.*

| * % refers to the number of tested patients<br>** only M>14ys and F>13ys at last follow up included in the analysis | At diagnosis (n=30)* | After surgery (n=29) | After radiotherapy (n=20) | At last Follow-up (n=30) |
|---|---|---|---|---|
| **GHD** | 17 (74%) | 11 (36.7%) | 2 (6.7%) | 30 (100%) |
| **GnD**** | 3 (13,6%) | 5 (16.7%) | - | 8 (26.7%) |
| **ACTHD** | 5 (19,2%) | 10 (33.4%) | 2 (6.7%) | 17 (56.7%) |
| **TSH** | 7 (46,7%) | 15 (50%) | 5 (16.7%) | 27 (90%) |
| **DI** | 5 (16.7%) | 11 (36.7%) | 1 (3.4%) | 17 (56.7%) |
| **Obesity** | 2 (6.7%) | 1 (3.4%) | 6 (20%) | 9 (30%) |

At diagnosis, 17/23 assessed (74%) already had GHD and 4/30 (13%) (all intra- and suprasellar tumours) had panhypopituitarism (3 with additional diabetes insipidus (DI)). At last FU 13 (43.3%) had panhypopit., 10 with DI.

## RESULTS

**Treatment Strategy** *(Figure 1)*
- Cyst decompression + radiotherapy (RT)
- Resection (Debulking + RT vs complete resection)
- Watch and Wait

**Paris Grade**:
- At diagnosis 7 (23,3%) were PG 1, 3 (10%) were PG 0; no change with treatment (*Tables 1-2, Figure 1*).
- 13 (43,3%) presenting with hydrocephalus & 11 (36,7%) with cysts required decompression. 6/22 graded PG 2 at diagnosis downgraded to PG 1 after decompression.

**Surgical strategy**: Decompression only (n=12), or with interval resection (n=7, complete(CR) in 3), primary resection (n=10, CR in 5), or watch/wait (n1).
**Radiation (RT):** 20 received upfront (n=18) or delayed (n=2) Intensity Modulated (n=7) or Proton (n=13) RT.
**Relapse:** 5 patients (16,7%) relapsed 5 (1.4-5.5) years later (*Figure 1*).

*Figure 1. Treatment Strategy in 30 Patients. In ovals: Numbers of Patients and Median (Range) Age.*

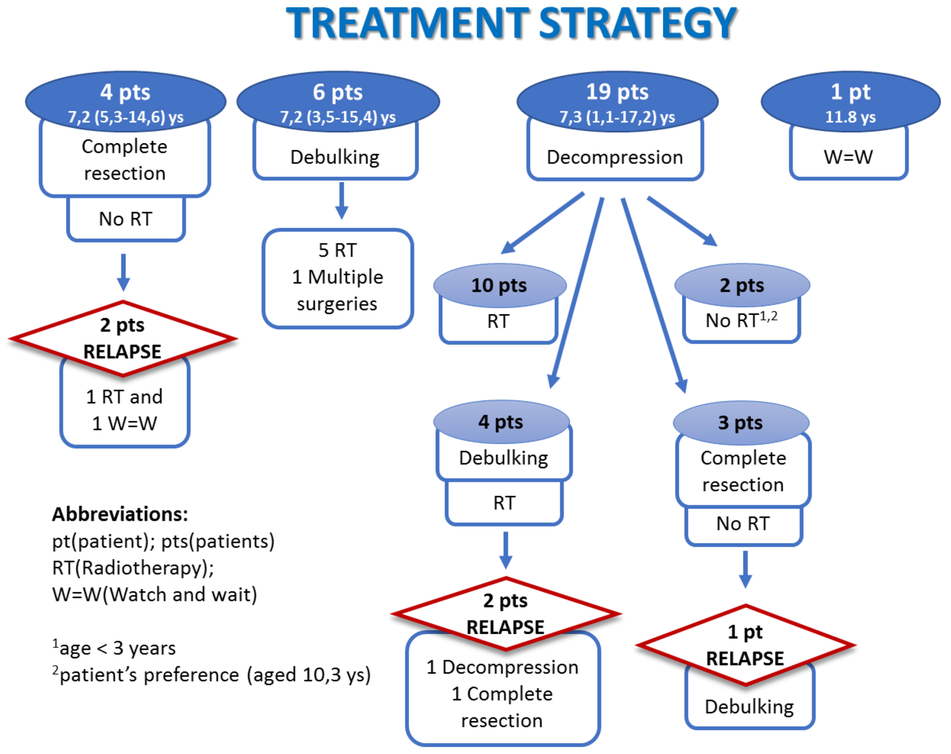
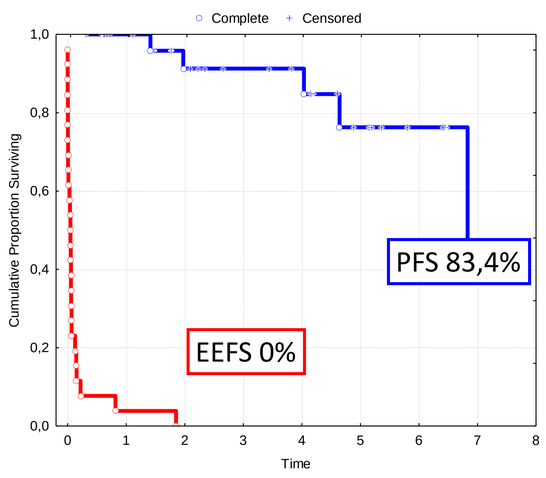
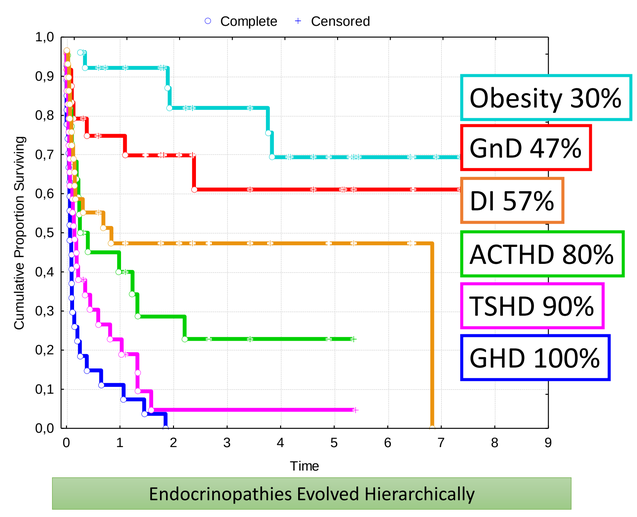



*Figure 2. Kaplan-Meier Survival Curves of PFS and EEFS.*




Despite 100% Survival and 5y PFS of 83.4%, no patients was free of endocrinopathy (EEFS was 0%) .

*Figure 3. Kaplan-Meier Survival Curves of Endocrinopathies*




Endocrinopathies Evolved Hierarchically

*Table 4. Evaluation of Influence of Independent Variables on Endocrine Status; shown as: univariate Cox regression for GHD, GnD, ACTHD, TSHD, DI, Obesity; Spearman Correlation, Mann-Whitney U test or Kruskall Wallis for Initial and Final EMS*

| Indipendent Variables | PFS | | EEFS | | GHD | | GnD* | | ACTHD | | TSHD | | DI | | Obesity | | Initial EMS | Final EMS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HR | P | HR | P | HR | P | HR | P | HR | P | HR | P | HR | P | HR | P | P | P |
| **Age at diagnosis** | 0.97 | 0.8 | 1.03 | 0.44 | 1.08 | 0.08 | **1.35** | **0.006** | 0.96 | 0.46 | 0.98 | 0.73 | 0.97 | 0.51 | 0.97 | 0.7 | 0.3 | 0.59 |
| **Duration of symptoms** | 0.88 | 0.87 | 0.9 | 0.73 | 1.09 | 0.79 | 1.58 | 0.37 | 1.84 | 0.09 | 1.15 | 0.62 | 1.06 | 0.87 | 0.94 | 0.9 | 0.61 | 0.78 |
| **Hydrocephalus at diagnosis** | 1.31 | 0.77 | 0.56 | 0.16 | 0.43 | 0.053 | 0.64 | 0.54 | **0.29** | **0.02** | **0.32** | **0.007** | **0.31** | **0.04** | 0.96 | 0.95 | 0.13 | 0.09 |
| **Tumour position** | 1.66 | 0.4 | 1.61 | 0.08 | **1.91** | **0.02** | 1.01 | 0.98 | 0.97 | 0.92 | 1.02 | 0.93 | 0.8 | 0.45 | 1.11 | 0.81 | 0.63 | 0.72 |
| **Tumour volume** | 0.98 | 0.37 | 1.00 | 0.62 | 1.00 | 0.82 | 0.97 | 0.28 | 1.00 | 0.82 | 1.00 | 0.96 | 1.00 | 0.43 | 0.99 | 0.34 | 0.1 | 0.83 |
| **Tumour appareance** | - | - | 0.85 | 0.69 | 1.03 | 0.93 | 0.68 | 0.6 | 0.51 | 0.17 | 0.81 | 0.6 | 1.08 | 0.88 | 1.24 | 0.76 | 0.58 | 0.39 |
| **Paris Grading at diagnosis** | 1.21 | 0.83 | 0.82 | 0.47 | 0.87 | 0.62 | 1.17 | 0.77 | 0.71 | 0.25 | 0.77 | 0.62 | 1.49 | 0.35 | 1.65 | 0.47 | 0.56 | 0.16 |
| **Paris Grading at follow-up** | 2.71 | 0.28 | 0.9 | 0.74 | 0.96 | 0.88 | 0.88 | 0.81 | 0.65 | 0.17 | 0.62 | 0.08 | 1.19 | 0.67 | 2.92 | 0.13 | - | 0.3 |
| **Surgery strategy** | 2.99 | 0.09 | 1.23 | 0.43 | 1.47 | 0.15 | 1.68 | 0.21 | **2.31** | **0.04** | 1.7 | 0.07 | **2.58** | **0.005** | 1.06 | 0.91 | - | 0.17 |
| **N. decompression** | 0.43 | 0.2 | 1.01 | 0.95 | 0.83 | 0.28 | 0.49 | 0.15 | 1.22 | 0.43 | 1.18 | 0.42 | 0.82 | 0.45 | 0.84 | 0.63 | - | 0.88 |
| **N. debulking** | 0.62 | 0.46 | 0.88 | 0.59 | 0.91 | 0.71 | 0.96 | 0.95 | 1.21 | 0.49 | 1.13 | 0.65 | 1.28 | 0.37 | 0.67 | 0.36 | - | **0.03** |
| **N. complete resection** | 9.05 | 0.052 | 0.94 | 0.87 | 0.74 | 0.45 | 0.77 | 0.75 | 2.53 | 0.07 | **3.71** | **0.007** | **4.28** | **0.005** | 0.69 | 0.65 | - | 0.052 |
| **N. resection (debulk.+complete res.)** | 1.21 | 0.68 | 0.89 | 0.58 | 0.87 | 0.49 | 0.9 | 0.82 | 1.4 | 0.16 | 1.43 | 0.1 | **1.57** | **0.04** | 0.65 | 0.29 | - | **0.0001** |
| **N. transphenoidal surgeries** | 1.08 | 0.9 | 1.26 | 0.31 | 1.2 | 0.44 | **5.6** | **0.008** | **1.99** | **0.048** | 1.32 | 0.24 | 1.71 | 0.051 | 1.1 | 0.82 | - | **0.02** |
| **N. craniotmy** | 1.37 | 0.46 | 0.78 | 0.25 | 0.74 | 0.18 | 0.3 | 0.17 | 1.37 | 0.21 | 1.16 | 0.49 | 1.42 | 0.14 | 1.06 | 0.86 | - | 0.24 |
| **Total n. surgeries** | 0.95 | 0.82 | 0.93 | 0.46 | 0.92 | 0.39 | 0.75 | 0.33 | 1.19 | 0.16 | 1.12 | 0.24 | 1.18 | 0.16 | 0.88 | 0.48 | - | **0.02** |
| **Radiotherapy binary** | 0.69 | 0.69 | 1.09 | 0.83 | 0.08 | 0.78 | 3.76 | 0.22 | 0.82 | 0.71 | **0.31** | **0.02** | 0.51 | 0.2 | 3.29 | 0.26 | - | 0.82 |
| **Radiotherapy** | 1.1 | 0.88 | 1.25 | 0.34 | 1.27 | 0.3 | 1.25 | 0.6 | 0.95 | 0.85 | **0.56** | **0.03** | 0.72 | 0.28 | **3.27** | **0.04** | - | 0.95 |
| **Relapse** | - | - | 0.93 | 0.88 | 0.79 | 0.64 | 0.66 | 0.7 | 1.63 | 0.44 | 1.84 | 0.24 | **3.58** | **0.03** | - | - | - | 0.14 |

- **Presenting hydrocephalus reduced ACTHD and TSHD but increased the prevalence of DI,**
- **Number of transphenoidal surgeries increased rates of ACTHD and GnD, and complete resection increased TSHD and DI**
- **Final EMS was directly related to total numbers of transphenoidal or resective surgeries but not to Paris Grade, radiation or tumour volume**

*only M>14ys and F>13ys at last follow up included in the analysis

## CONCLUSION

The evolving endocrinopathy, typical of suprasellar tumours is:
- Hierarchical and present from diagnosis,
- Worse in small intrasellar tumours without mass effect,
- Aggravated by surgical resection,
- But unaffected by hypothalamic invasion, tumour volume or imposed radiation.

[1]Puget S. et al. J Neurosurg 106:3–12,2007. [2]Gan H.W. et al. JCEM 100(10):3787-99,2015.

55ESPE 3--5-RFC
Pituitary
Chiara Guzzetti
DOI: 10.3252/pso.eu.55ESPE.2016
Poster presented at: ESPE 2016 PARIS
PosterSessionOnline.com