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ENDOCRINOPATHY IN CHILDHOOD INTRACRANIAL GERM CELL TUMOURS IS PREDICTED BY DISEASE LOCATION NOT TREATMENT 32 YEAR EXPERIENCE FROM A SINGLE TERTIARY CENTRE

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INTRODUCTION

- Childhood Intracranial Germ Cell Tumours (IGCT) are rare malignant tumours of the pituitary stalk and pineal region which are generally highly curable (>90%) by neuraxial radiation alone
- International trials have aimed to decrease late radiation-induced neuroendocrine morbidity by decreasing radiation volume and/or substituting chemotherapy (CT), without compromising survival
- Tumour location, especially in the suprasellar position, is arguably more important to neuroendocrine outcomes, although these are not always routinely assessed at diagnosis with dynamic tests
- Without longitudinal studies, disease and treatment contributions to long term outcomes remain unknown

PURPOSE

- To determine long term neuroendocrine morbidity in intracranial Germ Cell Tumours and define tumour and treatment-related factors. **Is endocrinopathy disease or treatment-related?**

MATERIAL AND METHODS

- Retrospective longitudinal analysis of IGCTs registered in our joint centre (UCLH/GOSH) and confirmed by MRI and/or histopathology, between 1.1.1983 and 31.12.14 (32 years).
- Search on both our local endocrine late effects database and central electronic patient records using the terms: *"germ cell tumours"/"germinomas"/"non germinomatous germ cell tumours" and "Central Nervous System"/"intracranial".*
- Tumour 3D volume was assessed using novel software ITK-SNAPv3.2.0. Statistical analysis was done with SPSS 21st using non parametric tests (Mann-Whitney U and exact Fisher tests were used for inter group comparison of quantitative and qualitative variables respectively), and data presented as medians and quartiles. McNemar tests were used to assess evolution of endocrinopathies with time subsequently expressed as survival curves (*Figure 6*).

RESULTS

DEMOGRAPHICS

76 patients with intracranial GCTs, 5 excluded for missing data

71 patients included

- Male : Female 36:30 (54.5%:45.5%)
- Status alive : dead 64:7 (90,1%:9,9%)
- Relapsed 10/66 (15,2%) all secreting
- Age at diagnosis 10,49 years (7,91; 12,85)
- Time to diagnosis 0,26 years (0,11; 0,99)
- Age at last information 16,29 years (12,88; 20,12)
- Follow-up time since diagnosis 6,04 years (3,32; 8,95)
- Germinomas : NGGCT 35:18 (66%:34%)
- Secreting : non secreting 12:49 (19.7%:80.3%)

TREATMENT

Surgical intervention 61/71 (85,9%)	
11/59 (18,6%) Only biopsy 12/59 (20,4%) Ventriculostomy/VP shunt	39% Minimal
6/59 (10,2%) Debulking 20/59 (33,9%) Subtotal resection 10/59 (16,9%) Complete resection	61% Major
Radiotherapy 58/71 (81,7%)	
Chemotherapy 27/71 (38%)	

Biopsy 26/71 (36,6%)
Secreting/NGGCT tumours do not require a biopsy as the diagnosis can be made by tumour marker elevation in serum or CSF alone.

Treatment modalities

Only surgery	10/70 (14.3%)
Surgery+RT	27/70 (38.6%)
Surgery+CT	2/70 (2.9%)
Surgery+RT+CT	17/70 (24.3%)
RT+CT	8/70 (11.4%)
Only CSI 6/70	6/70 (8.6%)

Endocrinopathy	Yes	No	p-value
Major/minor surgery	24:23	5:2	0,431
Radiotherapy (yes:no)	46:4	6:1	0,494
Chemotherapy (yes:no)	21:29	2:5	0,689
Relapse (yes:no)	6:44	2:5	0,252

CLINICAL PRESENTATION

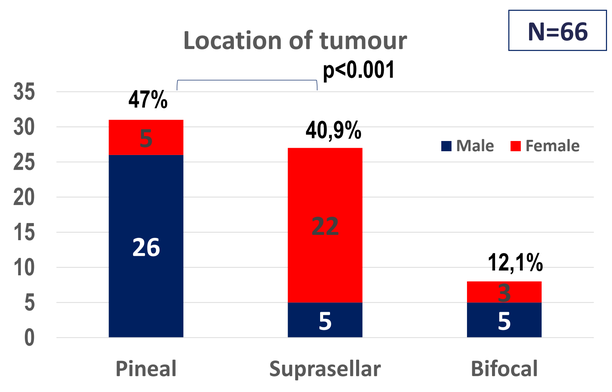

Figure 1. Overall male predominance, female predominance in suprasellar tumours and male predominance in pineal tumours

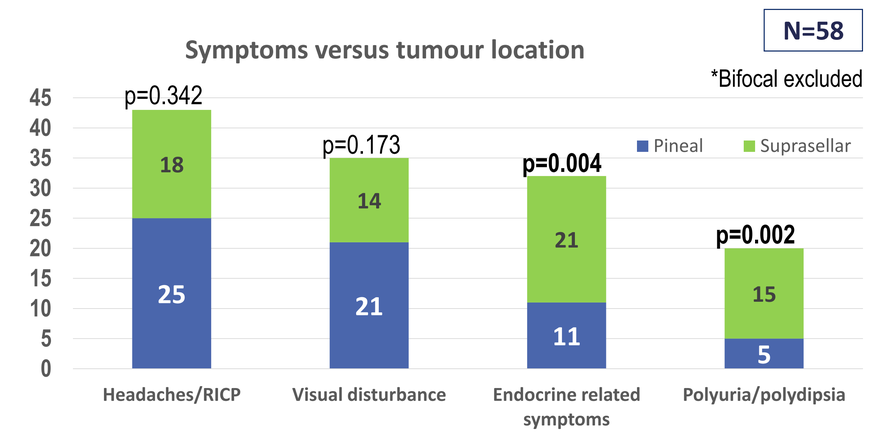

Figure 2. Endocrine related symptoms were more frequent in suprasellar tumours

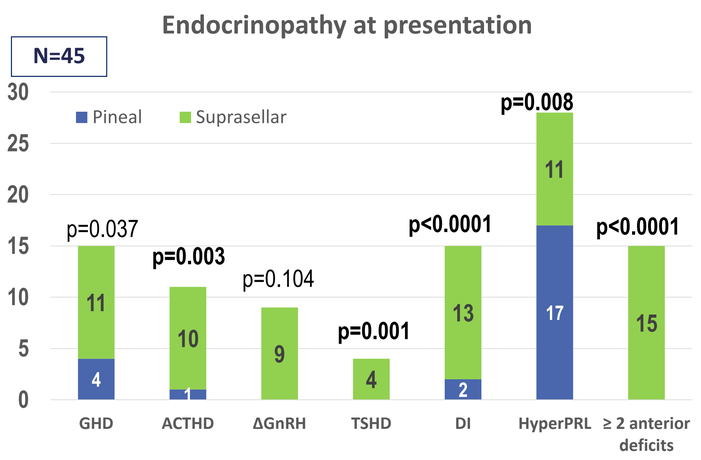

Figure 3. Suprasellar presented more endocrinopathies: 15/19 (78.9%) vs pineal 5/18 (27.8%); **p=0,003**

Headache/RICP	**48/64 (75%)**
Visual disturbance	38/63 (60,3%)
Polyuria/polydipsia	25/64 (39,1%)
Failure to shrive/Short stature	14/64 (21,9%)
Precocious/delayed puberty	11/64 (17,2%)
Others	9/64 (14,1%)

	Pineal	Suprasellar	*p*
Time to diagnosis (y)	0,16 (0,06; 0,41)	0,63 (0,16; 2,00)	**0,005**
Tumour volume (cm3)	3,90 (2,90; 7,60)	4,10 (2,70; 5,30)	0,808

Figure 4. Pineal presented earlier despite lower volume

EVOLUTION OF ENDOCRINOPATHIES

	At presentation	At last information	p
Endocrinopathy	31/49 (63,3%)	53/60 (88,3%)	**0,025**
Panhypopituitarism	17/45 (37,8%)	40/60 (66,7%)	**0,001**

Time to deficits (years)	Suprasellar	Pineal	P value
- GHD	0,33 (0,22; 0,83)	1,73 (0,50; 0,52)	**0.020**
- ACTHD	-0,20 -0,68; 0,36)	-0,40 (-0,51; 1,52)	**0.036**
- TSHD	-0,39 (-1,15; -0,08)	1,52 (-0,40; 4,44)	**0.002**
- GnRH	1,84 (-0,39; 3,51)	3,37 (2,27; 4,01)	0.132
- DI	-0,31 (-0,70; -0,08)	0,56 (-0,40; 1,52)	**0.004**

Figure 5. Suprasellar presented GHD, TSHD and DI earlier than pineal; Pineal presented ACTHD earlier than suprasellar

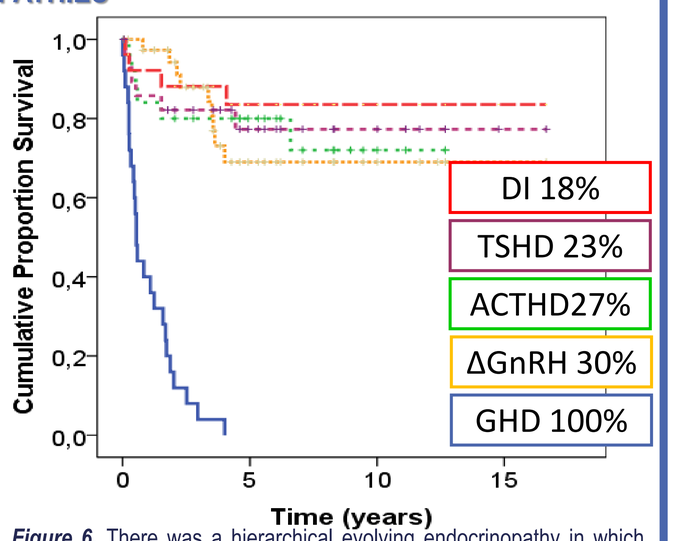

Figure 6. There was a hierarchical evolving endocrinopathy in which GHD was first and ACTH was last

SUMMARY AND CONCLUSIONS

- Pineal tumours present earlier than suprasellar despite smaller volume disease, due to raised intracranial pressure, whilst the latter developing occult endocrinopathy (often GHD) typical of the area
- Endocrinopathies are frequent at diagnosis (89%), especially in suprasellar disease, and evolve hierarchically to include multiple deficits (69%), but do not differ between treatment groups in which surgical resection is equally prevalent
- Surgical resection tends to increase endocrine deficits (without reaching significance) and needs longitudinal study
- The majority experience visual sequelae (51%) and require extra schooling support

1. Endocrinopathies are predicted by disease location rather than imposed by radiation, and possibly escalated by resective surgery;
2. All patients should be routinely assessed at diagnosis for occult endocrinopathy, especially GHD and followed prospectively
3. Substituting ventricular irradiation and adjuvant chemotherapy for neuraxial (CSI) radiotherapy does not avoid these morbidities

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