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A single centre experience of managing a series of childhood macro/giant-prolactinoma

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Intorduction: Childhood prolactinomas often occur as aggressive macro (1-4cm) or giant (>4cm) tumours, with little consensus regarding timing of different therapies

Aim

- ✓ To highlight the phenotype and the outcome of childhood macroprolactinomas

Subjects & Method

- ✓ Collected data from 10 children (<18 years) presenting to our centre between 2009-2017 with hyperprolactinaemia due to macro/giant-prolactinomas.

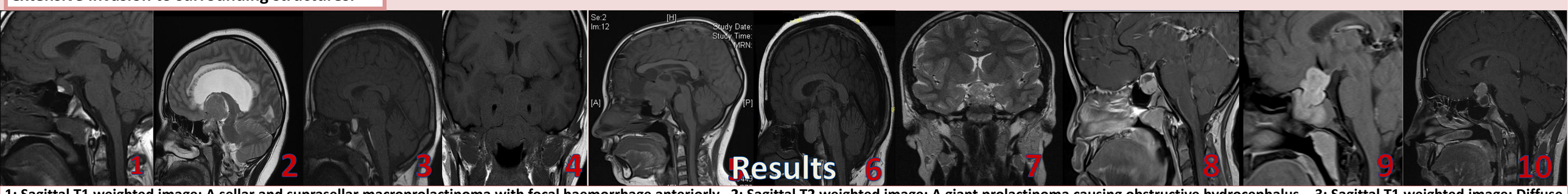
Results

- ✓ Median age at diagnosis was 13.9 years (11-16.3)
- ✓ Median duration of symptoms prior diagnosis in months was 24 (1-84)
- ✓ Presenting symptoms included headaches (10/10), visual deficit (5/10) and endocrinological signs (8/10)
- ✓ Positive family history identified in 4/10 cases. One proved heterozygous for an *MEN1* mutation. None harboured an *AIP* mutation
- ✓ At diagnosis, all children had 1-4 anterior pituitary hormone deficits

Table 1. Patient clinical, radiological, genetic characteristics at diagnosis

	Age onset symptoms/ Age diagnosis (years)	Height cm (SDS)	BMI (SDS)	Pubertal staging at diagnosis	Presenting symptoms	Length of history (Months)	FHx	Genetics	Size of tumour at diagnosis	Radiological features of tumour at diagnosis
1	8.0/15.9	180 (+0.95)	36 (+3.19)	G5, P5, A3 testes 10ml bilaterally	Dizziness, Blackouts Fatigue, Weight gain Gynaecomastia	84	Yes	Negative	Macro (14.1 x 20.6)	Suparasellar extn: L cavernous sinus. Haemorrahage
2	12.0/15.1	173 (+0.31)	27.9 (+2.314)	G3, P3, A1, testes 4ml bilaterally	Headaches Galactorrhoea Pubertal arrest Weight loss Visual disturbance	36	No	Negative	Giant (27 x 50)	Hydrocephalus, Suprasellar extension: L cavernous sinus, through foramen ovale and temporal fossa, L orbital apex.
3	14.5/15.6	166.8 (+0.6)	53.38 (+4.43)	B4, P3, A3, M1 2^{o} amenorrhea	Morning headaches Vomiting Visual disturbance	12	No	Negative	Macro (6.3 x 10.3)	Suprasellar extn: R cavernous sinus: optic chiasm abutted, Haemorrhage
4	15.8/16.3	158.5 (-2.12)	20.2 (+0.03)	G2, P3, A3, testes 6ml bilaterally	Headaches Short stature Pubertal delay	5	No	Negative	Giant (48.5 x 26.1)	Inferior extn: sphenoid sinuses; skull base;parasellar regions, anterior and suprasellar extn: orbital apices: cavernous sinuses; optic chiasm
5	8.0/11.9	139.6 (-1.2)	20.2 (+1.15)	G2, P2, A1, testes 4ml bilaterally	Headaches, visual disturbance	48	Yes	MEN1 positive	Giant (34 x 39)	Suprasellar extn: cavernous sinus; optic chiasm; Inferior extn:skull base
6	9.0/11.0	138 (-3.87)	17.5 (-1.8)	B1,P1,A1,M0	Headaches, visual disturbance		No	Negative	Macro (32 x 42)	Suprasellar extn: cavernous sinuses,cerebral arteries, optic nerves and chiasm
7	12.25/12.5	141.9 (-1.89)	27.6 (+1.9)	B2, P1, A1, M0	Visual disturbance, headaches, poor growth, pubertal arrest, weight gain	0.25	Yes	Negative	Macro (24 x 22)	Suprasellar extn: cavernous sinus; optic chiasm; Inferior extn: skull base
8	9.2/11.2	136.3 (-1.09)	20.5 (+1.05)	B1, P1, A1, M0	Headaches	24	Yes	Negative	Macro (27.8 x 27.7)	Suprasellar extn: R cavernous sinus; Inferior extn: R floor of the sella; stalk deviated on the left; haemorrhage
9	12.5/13.9	145.5 (-2.07)	29.52 (+2.56)	B5, P5, A3, M1 with 2^{o} amenorrhoea	Secondary amenorrhea Headaches	16	No	Negative	Macro (27.9 x 23.5)	Suprasellar extn: cavernous sinuses; optic chiasm and nerves; Inferior extn: skull base(body of the sphenoid bone)
10	13.8/13.9	151.5 (-1.04)	22.43 (+1.38)	G3, P3, A1, testes 5ml bilaterally	Galactorrhoea, Headaches	1	No	Negative	Macro (18.6 x 26.8)	Suprasellar extn: cavernous sinus; optic chiasm and nerves; haemorrhage

Figure 1. MRI slices for each case demonstrating extensive invasion to surrounding structures.



1: Sagittal T1 weighted image: A sellar and suprasellar macroprolactinoma with focal haemorrhage anteriorly., 2: Sagittal T2 weighted image: A giant prolactinoma causing obstructive hydrocephalus. , 3: Sagittal T1 weighted image: Diffuse haemorrhage in a macroprolactinoma., 4: Coronal T1 weighted image: A giant prolactinoma involving the cavernous sinuses, optic pathways and skull base foramina., 5: Post contrast coronal T1 weighted image: A giant prolactinoma distorting the anterior circulation and optic pathways with cavernous sinus encroachment, notably on the left., 6: Sagittal T1 weighted image: A macroprolactinoma distorting the optic chiasm and tuber cenereum. Note expansion of the sella., 7: Coronal T2 weighted image: A macroprolactinoma distorting the optic chiasm., 8: Sagittal T1 weighted image: A marcoadenoma with bleeding, invading the right cavernous sinus, scalloping of the floor of the sella on the right, deviating neurohyposphisis and stalk., 9: Sagittal T1 weighted image: A macroadenoma invading the sphenoid bone, rising out of the sella, elevate the chiasm and splay the optic nerves apart., 10: Sagittal T1 weighted image: A cystic macroadnoma extending into the suprasellar region and slay the optic nerves and the chiasm.

Results

- ✓ All children had first-line CAB treatment apart from one misdiagnosed as craniopharyngioma.
- ✓ Five cases required surgery and two radiotherapy, due to: CAB side effects (1), visual compromise (2) or tumour regrowth (2). Two patients required urgent TSS for pituitary apoplexy at initial presentation and for CSF leak post CAB.
- ✓ Seven cases continue on dose-escalating CAB treatment (1-7.5mg/week).
- ✓ Four patients experienced CAB side effects (headaches, aggressive behaviour, impulse control disorder, CSF leak).
- ✓ Median duration of follow-up in months was 24 (16-96).
- ✓ The initial median PRL levels were 61,173mIU/L (9,176- 1,238,960) and the final median levels were 4,294 mIU/L (358-44,944). 9/10 decreased median PRL levels by 93% (83-99.6%) and 1/10 (MEN1 positive patient) increased PRL by 62.7%. Two patients achieved PRL normalization.
- ✓ All patients had initially suprasellar extension with tumour infiltration of cavernous sinus (10/10), optic chiasm (8/10), skull base (5/10) and 4/10 had haemorrhage. Tumour shrinkage was achieved in 9 cases with a median percentage decrease of the tumour volume by 41.8% (24%-90%), while the MEN1 positive patient's tumour volume increased by 70%.
- ✓ At diagnosis four children had normal vision and six had visual disturbances, while at the last follow-up two were registered blind, four had visual disturbances and four maintained normal vision

Table 2. Effects of treatment on 10 patients with macro-/giant prolactinomas

	Therapy	CBG mg/week initial/max	Pituitary hormone deficiencies at diagnosis/post treatment (bold)	Vision at diagnosis	Vision post Rx	PRL basal mIU/L	PRL nadir mIU/L	% Tumour size change post Rx (Duration Rx)	Genetics
1	1. CAB	0.5/7.5	GnRH, TSH, GH, ACTH	Normal fields and VA	Normal fields and VA	44,782	7,756	24.3 ⇓ (37)	Negative
2	1. CAB 2. TSSx2	0.5/3.5	TSH, ACTH, GnRH, GH*, AVP*	Left homonymous hemianopia (worse in R eye). Bilateral papilloedema. VA L 6/19, R 6/30	Registered blind with VA R HM L 6/60	321,498	14,535	36⇓ (24)	Negative
3	1. CAB 2. TSS	1/1	GnRH, ACTH^, GH^	Bi-temporal upper quadrantanopia	Patchy field loss on R: VA 6/18 bilaterally	9,176	572	70⇓ (16)	Negative
4	1. CAB	0.5/1	GH, GnRH	Subtle bi-temporal hemianopia. Mild red desaturation	Small L supra field defect: VA normal bilaterally	1,238,960	5,747	>90⇓ (30)	Negative
5	1.CAB 2.TCSx2 3. PBRT	0.25/7	TSH, GH	Bi-temporal hemianopia. VA: counting fingers R eye, perceiving light L eye	Registered blind	27,624	2,268	70 ⇑ (24)	MEN1
6	1. 1. TCS 2. 2. CAB 3. 3. TSS 4. RT	0.5/3	ACTH, TSH^, GnRH^, GH^, AVP*	Temporal hemianopia on R. NPL on L. VA R 6/19, L NPL	Registered partially sighted R supra temporal quadrantanopia. L nasal hemi-field only. VA R 1/60. L 69/5	82,957	6,898	69⇓ (96)	Negative
7	1. CAB	1/4.5	TSH, ACTH	Bilateral superior temporal quadrantanopia (R>L). Papilloedema, VA R 6/24,L 6/7.5	No remaining field defect- Acuities 0.14 R, -0.1 L. Optic discs slight titling-mild temporal pallor	37,152	1,785	28⇓ (56)	Negative
8	1. CAB	1/1.5	TSH, GH	Normal fields and VA	Normal fields and VA	77,563	1,172	41.8⇓ (18)	Negative
9	1. CAB 2.Surgery due to CSF leak	1/1	GH, GnRH	Normal fields and VA	Normal fields and VA	106,064	358	46.9⇓ (17)	Negative
10	1.CAB 2. Candidate for surgery due psychosis by CAB	1/4	GH, GnRH, TSH, ACTH	Normal fields. Myopia	Normal fields. Myopia	39,453	2,841	30.5⇓ (19)	Negative

^Occurred following 1st surgical intervention, * occurred following second surgical intervention; PRL, prolactin; CAB, Cabergoline; TSS, Trans-sphenoidal surgery; TCS, Transcranial surgery; RT, radiotherapy; PBRT, Proton Beam Radiotherapy; Gn, Gonadotrophin; TSH, Thyroid Stimulating Hormone; GH, Growth Hormone; AVP, arginine vasopressin; VA, visual acuity; L, left; R right; HH, homonymous hemianopia; BT, bitemporal; CF, counting fingers; NPL, No Perception of Light.

Conclusions

- ✓ Cabergoline should be the first-line treatment in childhood-onset macroprolactinomas
- ✓ Dose-escalation along with prolonged administration may be necessary for achieving a delayed response and controlling disease, but needs monitoring for side effects
- ✓ In resistant disease, surgery increases endocrine deficits and radiotherapy may be necessary
- ✓ *MEN1* and *AIP* analysis is strongly recommended to inform about pathogenesis, allow screening for other manifestations and to identify at-risk relatives