PROLACTINOMAS IN CHILDREN AND YOUNG ADULTS: 10 year experience in a Tertiary Regional Paediatric – Young Adult – Neuroendocrine Surgical Centre

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Introduction

Pituitary adenomas are rare in the Paediatric and Adolescent population ~ approx. 2% of CNS tumours. Prolactinomas (PRLoma) account for < 50% of pituitary adenomas. Experience with their management in children is reported in few case-series reports (Refs1,2). We report clinical presentation and response to treatment in 9 patients in our centre (population base ~ 3.6million) in the last 10 years with age at diagnosis < 18 years.

Patients and Methods

9 patients (4 male) were diagnosed with PRLoma at 13 – 18 years of age between 2006 and 2016. 4 MicroPRLoma (Pts 1-4); 5 MacroPRLoma (Pts 5-9).

Assessment: Evaluation of puberty, growth and hypothalamic-pituitary function. Gonadotrophin, T4/TSH, and PRL secretion at baseline +/- after GnRH tests. Somatotroph function was evaluated by Glucagon test and serum IGF-1. Evaluation of pituitary-adrenal axis was assessed by glucagon +/- short Synacthen test. Patients with MacroPRLoma underwent sequential testing according to clinical progress.

Management: All patients were initially treated with oral Cabergoline (CBR).

• 5 patients responded to CBR therapy alone
• 4 were resistant or partially resistant to CBR and proceeded to trans-sphenoidal surgery (TSS)
• 1 patient required further treatment with Temozolamide and stereotactic radiotherapy (Ref 3)

Follow up: PRL levels initially monthly, then quarterly and six-monthly; with MRI and visual field examination according to clinical need.

Presentation

Microadenomas: 2/3 males, mean age 1 (0.5) yrs of no Prolactinomas associated and to ~2 yrs miU existing post-intracranial trauma. 1 patient in the other group had a median age of 14 yrs, with only 1 patient had headaches. All had normal ophthalmological examinations.

Macroadenomas: Headache, galactorrhea and hypogonadism (2/3 amenorrhea or arrest of puberty) were the presenting symptoms. 3 out of 5 patients had visual field defects and one of these also had reduced visual acuity.

Endocrinology: At presentation, serum PRL concentrations ranged from 2815-2540 mIU/L in MicroAPRLoma, and 3960-129000 mIU/L in MacroAPRLoma. Impairment of pituitary hormone secretion was found in 2 of 5 patients with MacroPRLoma at diagnosis (1 with GH and one with GH,TSH, ACTH and gonadotrophin deficiency – haemorrhagic).

Histology: 4 Specimens (TSS samples) were obtained in a selection of patients. Immunohistochemistry showed PRL expression. One had mixed GH and PRL immunopositivity (somatomammotroph adenoma). Mitotic activity Ki67 ranged: 1-4%.

Genetics: No mutations had patients in MEN1 or AIP genes, but the male microadenoma had his maternal aunt with non-functioning pituitary adenoma.

Table 1

<table>
<thead>
<tr>
<th>Microadenomas (n=3)</th>
<th>Macroadenomas (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>3</td>
</tr>
<tr>
<td>0.5 yrs</td>
<td>14</td>
</tr>
<tr>
<td>Mean age at diagnosis yrs</td>
<td>14</td>
</tr>
<tr>
<td>Range</td>
<td>14-15 yrs</td>
</tr>
<tr>
<td>Mean duration of symptoms yrs</td>
<td>1</td>
</tr>
<tr>
<td>Range</td>
<td>1 year</td>
</tr>
<tr>
<td>Max tumour diameter (mm)</td>
<td>6.5</td>
</tr>
<tr>
<td>Mean tumour diameter for group (mm)</td>
<td>5.3</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
</tr>
<tr>
<td>Galactorrhea</td>
<td>0</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>0</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>0</td>
</tr>
<tr>
<td>Potential arrest</td>
<td>0</td>
</tr>
<tr>
<td>Growth failure</td>
<td>0</td>
</tr>
<tr>
<td>Mean prolactin at diagnosis miU/L</td>
<td>3190</td>
</tr>
</tbody>
</table>

| Mean prolactin at diagnosis miU/L | 3190 | 2815-2540 |
| **Visual defects** | 2 | 1 |

Treatment and Follow up

CBR sensitive group: includes all patients with MicroPRLoma and 1 patient (#5) from the MacroPRLoma group. All had normal serum PRL levels within 6–12 months, complete resolution of symptoms and variable, but significant, tumour shrinkage. In most pts CBR was well tolerated without side effects. Pt 3 (MicroPRLoma) experienced “dizziness”, leading to poor compliance and discontinuation of CBR, later restarted in view of relapse of symptoms reflected in the swinging PRL levels (~ graph 1). In one patient (male, MicroPRLoma) treatment was stopped after involution of tumour on MRI and remains tumour free to date (3 years later).

CBR resistant group: Includes 4 of 5 patients with MacroPRLomas. CBR treatment induced PRL normalisation and significant tumour shrinkage in only 1 patient, although this was followed by tumour expansion. Three had either modest or no significant change in tumour size, modest reduction in PRL levels and ongoing symptoms eventually requiring TSS. Near complete excision was achieved in 2 pts with substantial debulking in 2 to protect optic tracts. One patient had substantial residual tumour mass and high PRL levels leading to further treatment with Temozolomide (3 yrs post-TSS.) and Radiotherapy (5 yrs post-TSS) to achieve stable clinical condition (now 9 yrs post-diagnosis). All patients are still on CBR treatment.

Disease related chronic morbidity:

Microadenoma Group: None observed.

Macroadenoma Group: 2 patients have residual hemianopia. One has isolated GH deficiency and 3 have multiple pituitary hormones impairment in different combinations and are on long term replacement. 1 Pt has co-existing Growth hormone secretary excess without symptoms. None had diabetes insipidus. One patient has chronic troublesome headaches following tumour excision the nature of which to date remains unclear. The haemorrhagic MacroPRLoma involved to leave normal pituitary function.

Conclusion

The spectrum of Prolactinomas in children and young adults requires combined expertise of a MultiDiscipline Team to provide comprehensive resources to manage these patients through a transition period.

References