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Original Article

Prolactinomas in Adolescents: A Long-term Follow-up Study

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Abstract ***Introduction:*** Prolactinoma occurs most frequently in females between 20 and 50 years of age. In the paediatric population, the estimated incidence of prolactinomas is <0.1 case per million population per year. ***Methods:*** A retrospective analysis was performed on all patients below 19 years diagnosed to have prolactinomas in a paediatric department between 2002 and 2020. The clinical features and treatment response of five girls and a boy were analysed. ***Results:*** The estimated incidence of paediatric prolactinomas was 0.29 case per million population per year in our catchment area. Pubertal delay and galactorrhoea were the most frequent presentation. All subjects were initially treated with bromocriptine. A patient required cabergoline. Another did not comply with medications and required trans-sphenoidal surgery. Three female patients required hormonal replacement therapy due to associated hypogonadotropic hypogonadism. Galactorrhoea in two patients subsided before normoprolactinaemia was achieved. ***Conclusion:*** Dopamine agonist is a safe and effective first-line treatment for both micro- and macroadenomas in adolescent patients.

Key words *Adolescent; Dopamine agonists; Galactorrhoea; Prolactinoma, Pubertal delay*

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Introduction

Prolactinoma, a benign prolactin-secreting pituitary adenoma, occurs most frequently in females between the age of 20 and 50 years.[1,2] In the paediatric age population, the estimated incidence of prolactinomas is less than 0.1 case per million population per year, representing fewer than 2% of all paediatric intracranial tumours.[2,3] Prolactinomas are more frequent in girls than in boys.[4] However, boys tend to have a higher proportion of macroprolactinomas.[4] The clinical features of prolactinomas vary with the age of presentation and sex.[5] Headache, visual field defect, amenorrhoea, galactorrhoea and pubertal delay are some common clinical manifestations of prolactinomas resulting from mass effect and hormonal disturbance.[6-9] Dopamine agonists are first-line treatment, while trans-sphenoidal surgery and radiotherapy are second-line therapies for prolactinomas.[10]

Given the rarity of paediatric prolactinomas, studies on the condition are scarce. In this retrospective study, the clinical presentation, treatment response and long-term outcomes of six patients with adolescent-onset prolactinomas seen in our department between 2002 and 2020 were reviewed.

Methods

A retrospective analysis was performed on all patients who were diagnosed to have prolactinomas below the age of 19 years in a paediatric department in Hong Kong between 2002 and 2020.

The following clinical data were collected: sex, chronological age at presentation, current age, height, weight, bone age, menstrual history, presence of galactorrhoea, presence of gynecomastia, presence of pressure symptoms and signs including headache, nausea and vomiting, focal neurological deficits, and pubertal stage according to Tanner staging.[11] Side effects of treatment with dopamine agonists were evaluated.

Baseline serum concentrations of prolactin and anterior pituitary hormones, i.e. thyroid-stimulating hormone, luteinising hormone, follicle-stimulating hormone, cortisol, estradiol in female and testosterone in male were measured. Poly-ethylene-glycol precipitation was performed to rule out macroprolactinaemia.[12] Computed tomography or magnetic resonance imaging (MRI) of the pituitary were done for all patients at diagnosis and during follow-ups. Pituitary macroadenoma is defined by a maximal tumour diameter ≥10 mm and pituitary microadenoma <10 mm on pituitary imaging. The tumour volume is calculated using maximal tumour diameters (A, B, C) in three dimensions (½ x A x B x C) based on imaging results. Tumour property was described as solid, cystic or mixed solid-cystic.

Results

A male and five female paediatric patients with prolactinomas who presented between 2002 and 2020 were analysed. Subjects 1, 4 and 5 had pituitary microadenomas, while subjects 2, 3 and 6 had macroadenomas. The main clinical, hormonal and radiological findings are summarised in Table 1.

Clinical Findings

The median chronological age at diagnosis was 16 years (14-18 years). The bone age was available for subjects 2 and 4 only, which corresponded to the chronological age. All five female patients presented with menstrual problems. Subjects 1-4 presented with primary amenorrhoea and subject 5 with secondary amenorrhoea. A girl (subject 5) and a boy (subject 6) had galactorrhoea. Subject 6 also had gynaecomastia. Subject 2 with macroadenoma had headache and delayed thelarche, while subject 4 had short stature. The duration of symptoms before presentation was recorded in three patients. Subject 5 had two weeks of galactorrhoea, subject 2 had two years of headache and subject 5 had six months of secondary amenorrhoea and galactorrhoea. Focal neurological

Table 1 Baseline clinical, hormonal and radiological findings of the six patients with adolescent-onset prolactinomas and the treatments received

Case	Sex	Age at diagnosis (years)	Current age (years)	Presenting complaints	Serum prolactin level at presentation (mIU/L)	Associated hormone deficiency	Classification	Maximum tumour dimension at presentation (mm)	Tumour volume at presentation (mm^3)	Tumour invasion	Tumour property	Tumour received
1	F	16	34	A1	9630	FSH/LH	ma	4	n/m	no	Solid	BCT, CAB, OP
2	F	14	29	A1, T, H	154350	FSH/LH	MA	46	46552	yes	Solid	BCT
3	F	17	30	A1	14690	FSH/LH	MA	15	750	yes	Solid-cystic	BCT
4	F	14	24	A1, SS	3534	–	ma	6	108	no	Solid	BCT
5	F	18	19	A2, Gal, Gy	2159	TSH	ma	6	n/m	no	Solid	BCT
6	M	18	25	Gal	40460	–	MA	16	1056	yes	Solid-cystic	BCT, CAB

F, female; M, male; A1, primary amenorrhoea; A2, secondary amenorrhoea; T, delayed thelarche; H, headache; SS, short stature; Gal, galactorrhoea; Gy, gynaecomastia; FSH, follicle-stimulating hormone; LH, luteinising hormone; TSH, thyroid-stimulating hormone; MA, macroadenoma; ma, microadenoma; n/m, not measured; BCT, bromocriptine; CAB, cabergoline; OP, operation

deficits, including visual field defect and extra-ocular movement palsy, were absent in all subjects.

Hormonal and Radiological Findings

The serum prolactin concentrations at diagnosis ranged from 2159-9630 mIU/L in patients with microadenomas and 14690-154350 mIU/L in macroadenomas. Associated anterior pituitary hormone deficiencies, which were present in four patients, occurred in both micro- and macroadenomas. Subjects 1-3 had hypogonadotropic hypogonadism and subject 5 had central hypothyroidism.

The median of the maximal tumour diameters was 15 mm (4-46 mm). The tumour volume of the four patients with 3-dimensional measurement available ranged from 108 mm^3 to 46552 mm^3. The serum prolactin level at diagnosis was proportional to the tumour volume.

Two out of the three patients with macroadenoma had a mixed solid-cystic tumour, while other patients had solid tumours. Tumour invasion occurred in all three patients with macroadenoma. Subject 2, who complaint of headache, had tumour encasement of the left internal carotid artery (ICA), invasion of the left cavernous sinus and extension into the left middle cranial fossa causing mild hydrocephalus. Suprasellar and right cavernous sinus invasion was noted in subject 3. Encasement of the left ICA, invasion of the left cavernous sinus and suprasellar cistern in proximity with the optic chiasma occurred in subject 6.

Treatment and Follow-up

As all six subjects had clinical, biochemical and imaging findings highly suggestive of prolactinoma, all were initially treated with bromocriptine ranging from 1.25 mg daily to 2.5 mg twice daily. Bromocriptine was well tolerated and effective in four patients (subjects 2-5), who were on maintenance dose ranging from 1.25 mg to 2.5 mg daily. Subject 6 did not respond to bromocriptine despite a maximal dose of 10 mg twice daily. He was successfully treated with cabergoline 0.25 mg twice weekly and was maintained at 0.25 mg once weekly. Subject 1 did not comply to bromocriptine or subsequent cabergoline treatment due to severe dizziness. She underwent trans-sphenoidal surgery, which failed to normalise the serum prolactin level. She was restarted on cabergoline, but the compliance was suboptimal. Her latest serum prolactin level was 3028 mIU/L (79-493 mIU/L), yet she remained asymptomatic. None of the patient underwent radiotherapy.

The median duration to achieve normoprolactinaemia was 19.5 weeks (1-112 weeks) excluding subject 1. Galactorrhoea resolved at a serum prolactin level of 609 mIU/L (Ref: 44-484 mIU/L) and 636 mIU/L (Ref: 86-324 mIU/L) in subjects 5 and 6 respectively. Follow-up MRI pituitary scans showed tumour shrinkage in all our patients.

Menarche occurred 27 weeks after bromocriptine treatment in subject 4 and menstruation returned after 17 weeks in subject 5. In view of persistent primary amenorrhoea despite normoprolactinaemia in subjects 1-3, which was likely due to associated hypogonadotropic hypogonadism, hormonal replacement therapy was initiated.

The median duration of follow up was 11.5 years (1-18 years). All patients were referred to adult endocrine clinic and have been followed up from diagnosis to now. Subject 4 discontinued bromocriptine after six years of treatment and had been in remission for three years. Subjects 2, 3 and 6 have been maintained on low dose dopamine agonist because of the invasiveness of the tumours.

Discussion

In this retrospective study, we described the clinical features, response to treatment and long-term outcomes of a cohort of six paediatric patients diagnosed with prolactinomas.

Paediatric prolactinomas are rare in children and adolescents, with an incidence of less than 0.1 case per million population per year.[3] Being a regional hospital with a paediatric department serving a population of 1.15 million in the catchment area in 2017,[13] we diagnosed six adolescent patients with prolactinomas between 2002 and 2020. The estimated incidence of paediatric prolactinomas was 0.29 case per million population per year in our catchment area. Previous studies showed that paediatric prolactinomas were more common in girls than boys with a sex ratio of 2:1. However, more aggressive tumours in terms of disease onset, serum prolactin level and tumour volume were noted in boys[3,4,14] We observed higher incidence in girls and the only boy in our study had an invasive macroadenoma with a serum prolactin level of >40000 mIU/L at diagnosis.

The clinical presentation of prolactinoma varies by age and sex. All our patients presented at pubertal age, with pubertal delay and galactorrhoea being the most frequent presentations. It could be explained by the suppression of gonadotropin secretion or destruction of the pituitary.[9] We

noted that our findings were slightly different from those of two recent German studies on 12 and 27 paediatric patients with prolactinomas, which reported headache and pubertal delay as the most common symptoms.[7,14] After ruling out non-compliance, all subjects responded to dopamine agonist. In view of absence of dopamine agonist resistance in invasive macroadenoma, tumour biopsy was not indicated and not performed in our subjects.[15]

Menarche and return of menses occurred respectively when normoprolactinaemia was achieved in two of the female patients, while the other three required hormonal replacement therapy due to persistent hypogonadotropic hypogonadism. Notably, it was observed that galactorrhoea subsided before the serum prolactin level was normalised, at a level of 609 mIU/L (Ref: 44-484 mIU/L) and 636 mIU/L (Ref: 86-324 mIU/L) in the two patients respectively.

Having one to 18 years of follow-up with interval serum prolactin measurement and MRI scans in our patients, our results concur with previous suggestions that dopamine agonist is a safe and effective first-line treatment for both micro- and macroadenomas in adolescent patients.[4,14,16,17] However, there is no consensus yet on the optimal medical treatment strategy and duration for adult prolactinomas,[18] and no relevant studies were done for the paediatric population. In a meta-analysis with 743 adult patients, normoprolactinaemia was maintained after dopamine agonist withdrawal in only 21% patients (95% CI, 10-37%) for microprolactinomas and 16% (95% CI, 6-36%) for macroprolactinomas.[19] In view of tumour invasion in all three patients with macroprolactinomas and well drug tolerance and safety, the majority of our patients preferred to maintain a low dose of dopamine agonist.

Retrospective single-centre analysis and the variability of documentation, especially on bone age and imaging reports, are limitations of our study. The disease incidence in our population may have been over-estimated due to the single-centre experience and referral bias. To our best knowledge, this is the first clinical study on adolescent-onset prolactinomas in Hong Kong. In order to have a more comprehensive understanding of the disease including an accurate incidence estimation in the local paediatric population, a territory-wide multi-centre study is necessary.

Author Contributions

The authors confirm contribution to the paper as follows: concept or design: all authors; acquisition of data: LM Wong, MY Ng; analysis of data: TY Li, LM Wong; drafting of the manuscript: TY Li, LM Wong; critical revision of the manuscript for important intellectual content: all authors. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Declaration of Interest

All authors have no conflicts of interest to disclose.

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Ethics Approval

The study was approved by the New Territories West Cluster Research Ethics Committee, Hong Kong, China (REC Ref. No: NTWC/REC/21005).

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