Prolactin-Producing Adenoma. Clinical Presentation in Adult Sudanese Patients

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Abstract:

Objectives: To describe the clinical features of prolactin-producing pituitary adenoma (prolactinoma) in adult patients.

Methods: In a prospective hospital-based study, adult patients with prolactinoma presenting to the National Center for Neurological diseases and the National Center for cancer in Khartoum, Sudan were enrolled in the period from January 2001 to February 2005. The diagnosis was based on finding a pituitary adenoma on cranial MRI and an associated elevated blood prolactin level above 200 µg/L. The size of the adenoma was classified as either microadenoma (<10 mm without sellar enlargement or extrasellar extension) or macroadenoma (>10 mm). The hormone profile done on each patient included blood level of prolactin and other pituitary trophic hormones, free triiodothyronine and free thyroxine hormones.

Results: Sixteen (14 females and 2 males) were identified as having a prolactinoma. The female to male ratio was 7:1. Their mean age was 24 ± 5.1 years. The prolactinoma was macroadenoma in 9 cases and microadenoma in 7. Galactorrhea, amenorrhea and infertility (primary or secondary) were the commonest presenting symptom followed by headache. Affection of the visual pathway, either as bitemporal hemianopia (41.2%) or optic atrophy (11.8%), was the major neurological deficit. The mean prolactin level in macroadenoma was 2053 ± 442.6 µg/L and in microadenoma was 853.6 ± 77.8 µg/L.

Conclusions: Our prolactinoma patients, when reaching the appropriate medical attention, are more likely having an expanded macroadenoma that is compromising the visual pathway. Early recognition and referral to specialized clinics is necessary and that should have a favorable prognostic implication.

Introduction:

Pituitary adenomas are the most common cause of sellar masses in the adult population accounting for about 10 percent of all intracranial neoplasms (1). At autopsy, up to quarter of all pituitary glands harbor an unsuspected microadenoma. Microadenoma may also be an incidental finding discovered in 10% of brain CT or MRI done for other reasons (1). The lactotroph adenoma, prolactinoma, produces excess prolactin hormone and it is the commonest type of pituitary adenoma in men and women (2,3,4,5). Hyperprolactinemia may induce hypogonadism that results in infertility in both sexes and erectile dysfunction in men. An expanding paracellar macroadenoma may abut the optic chiasma or the adjacent cavernous sinus and result in neurological symptoms. Early recognition and therapeutic intervention in secretory prolactinomas are gratifying, particularly in microadenoma, since effective noninvasive pharmacological treatment is available. Dopamine agonists can induce reduction in hormonal level and shrinkage of tumor leading to restoration of gynecological functions and amelioration of neurological symptoms (6,7,8,9).

In this hospital-based prospective study we identified patients with prolactinoma and characterize their presenting features.

Material and Methods:

The study was conducted at two corporate hospitals in Khartoum; the National Center for Neurological diseases (Neurology and Neurosurgery) and the National Center for cancer. The centers are the only tertiary referral hospitals where such cases can receive specialized care. Enrollment of subjects during the study period was available from; (a) patients who were already enlisted in hospital registry since January 2001 and were still coming for treatment and follow-up when the study was initiated in November 2003, (b) new patients presenting to hospital from November 2003 until the end of study period in February 2005. All patients were interviewed and physically examined by one of the study collaborates (HAS).

For inclusion we identified, from among all patients of pituitary adenoma, those who were 16 years or above and had
a prolactinoma (defined as a pituitary adenoma associated with blood prolactin level > 200 μg/L). The cut-off level of 200 mcg/L was adopted because lower levels of prolactinemia can be secondary to some other causes (10). Other causes of hyperprolactinemia (e.g. phenothiazine drugs, pregnancy and lactation) were excluded.

Cranial MR imaging confirmed the presence of a pituitary adenoma. T1 and T2 weighted MRI of the brain and the sella were performed on all patients. The size of the adenoma was classified as either microadenoma (<10 mm without sellar enlargement or extrasellar extension) or macroadenoma (≥10 mm). The measurements were taken from initial MRI films done before starting any form of therapy.

The hormone profile done for each patient included blood level of prolactin, growth hormone, follicle-stimulating hormone (FSH), luteinising hormone (LH), adrenocorticotrophic hormone, thyroid-stimulating hormone, free triiodothyronine and free thyroxine hormone. Other important investigations included blood counts, chest x-ray and visual field charting.

Statistical analysis was performed with software SPSS. The mean value of variables was given as mean ± standard deviation. Comparison between the groups was done applying student t-test with a significant value of \( p < 0.05 \). The study was reviewed and ethically approved by the Graduate Medical Studies Board of the Faculty of Medicine of the University of Khartoum.

Results:

During the study period, from a total of 53 patients having a pituitary adenoma, 16 (14 females and 2 males) were identified as having a prolactinoma. The prolactinoma was macroadenoma in 9 cases and microadenoma in 7. The female to male ratio was 6:1. Their mean age was 24 ± 5.1 years. The frequency of the presenting symptoms and signs in the 17 patients are summarized in Table 1. Galactorrhea, amenorrhea and infertility (primary or secondary) were the commonest presenting symptom followed by headache. Affection of the visual pathway, either as bitemporal hemianopia (41.2%) or optic atrophy (11.8%), was the major neurological deficit encountered on physical examination and that was observed in patients having macroadenoma with parasellar extension (Figure 1). One of the males, aging 30 years, complained of impotence and loss of libido.

The hormonal profile is displayed in Table 2. The prolactin level was significantly higher in patients with macroadenoma (mean 2053 ± 442.6 μg/L, range 1009-2516) compared to that in subjects with microadenoma (mean 853.6 ± 77.8 μg/L, range 780-1000); \( p = 0.0003 \). In one female (patient no. 1) both FSH and LH levels were low, in another one (Patient No. 8) FSH level was marginally low. In the rest of patients the hormone profiles (except for prolactin) were within the normal limits of our laboratory reference values (non-ovulation phase FSH: 3.0-14 IU/L, LH: 1.1-14.7 IU/L). Blood counts, blood chemistry for renal and liver functions and chest x-ray were normal in all patients.

Discussion:

Most of the pituitary adenomas, previously described as chromophobe and classified as non-functioning on basis of their histological staining characteristics, were eventually discovered to secret prolactin hormone. The prolactin level in the blood correlates with the tumor size \(^{[11,12,13]}\). Rarely a non-functioning pituitary adenoma can be associated with hyperprolactinemia because the expanding tumor is interfering with delivery of prolactin-inhibiting factor via the hypophysial-
Table 2. Type of prolactinoma by size, level of prolactin and other hormones profile in the blood in 16 patients

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age/Sex</th>
<th>Type of Adenoma</th>
<th>Prolactin μg/L</th>
<th>FSH IU/L</th>
<th>LH IU/L</th>
<th>GH μg/L</th>
<th>ACTH pmol/L</th>
<th>TSH mU/L</th>
<th>T4 nmol/L</th>
<th>T3 nmol/L</th>
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<tr>
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<td>0.1</td>
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<td>2.2</td>
</tr>
<tr>
<td>2</td>
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<td>Ma</td>
<td>1009.0</td>
<td>8.0</td>
<td>6.0</td>
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<td>1.6</td>
<td>55.5</td>
<td>2.1</td>
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<tr>
<td>3</td>
<td>66/F</td>
<td>Mi</td>
<td>877.3</td>
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<td>6.0</td>
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<td>0.9</td>
<td>50.0</td>
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<tr>
<td>4</td>
<td>19/F</td>
<td>Ma</td>
<td>2516.0</td>
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<td>6.0</td>
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<td>4.4</td>
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<td>68.0</td>
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<tr>
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<td>30/F</td>
<td>Ma</td>
<td>2004.0</td>
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<td>6.0</td>
<td>5.0</td>
<td>3.5</td>
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<td>Ma</td>
<td>2432.0</td>
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<td>6.0</td>
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<tr>
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<td>Mi</td>
<td>805.0</td>
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<td>5.0</td>
<td>1.8</td>
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<td>6.0</td>
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<td>2.2</td>
<td>50.0</td>
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</table>

In young adults the commonest clinical presentation is endocrine dysfunction followed by visual symptoms secondary to the local mass effect. Suprasellar upward extension of the adenoma can compress the chiasma and cause optic nerve atrophy while lateral extension can involve III, IV, V and VI cranial nerves and cause extraocular muscle paresis. The high frequencies of macroprolactinoma (58.8%) and optic nerve involvement (53%) in our patients are, most likely, consequences of late presentation or delayed diagnosis. It also reflects difficulties commonly encountered with availability and accessibility of appropriate diagnostic tools.

Galactorrhea in both sexes and amenorrhea (94.1%-82.3%) were the leading presentation in our series obviously because females dominated and that the symptoms are appreciably inconvenient to women and readily brought to medical attention. As in our patients, galactorrhea and amenorrhea are recognized to be more frequent when the degree hyperprolactinemia is severe. The hypogonadism appears to be due to the inhibition of hypothalamic release of LH releasing hormone, resulting in a decrease LH and FSH secretions. The finding of unusually high prolactin levels in our series can be attributed to late presentation and delayed tumor discovery as has been discussed above. In more privileged countries a rising incidence of prolactinomas has been observed and that is thought to be due to widespread access to MRI and laboratory techniques. Moreover, patients are more likely than before to seek early medical attention for symptoms of sexual dysfunction and infertility.

Male patients with prolactinoma tend to have higher prolactin level and larger adenoma size because the tumor often goes unrecognized in the early stage of hyperprolactinemia and the symptoms are underestimated by the patient. At the time of diagnosis male prolactinomas, in contrast to those in females, are more often macroadenomas and tend to present more frequently with mass effect. Hyperprolactinemia also causes hypogonadotrophic hypogonadism in men manifested by decreased libido, erectile dysfunction, impaired spermatogenesis and low level of serum testosterone. The erectile and the other gonadal dysfunctions improve by correcting the hyperprolactinemia but not by estrogen replacement. Gynecomastia and galactorrhea are rare features of hyperprolactinemia in men.

Prolactinomas, similarly to other pituitary tumors, are best managed by interdisciplinary approach involving neurologist, neurosurgeon, endocrinologist and oncologist. Nevertheless, pharmacological therapy by dopamine agonists has long being established and remains to be the mainstay of treatment.
in the majority of cases in both sexes. The most commonly used dopamine agonists are bromocriptine, cabergoline and pergolide\(^6\). Bromocriptine has been extensively used for a long time when infertility is the primary indication for treatment\(^{6,7}\). Cabergoline has a better profile regarding plasma half-life, efficacy and tolerability\(^{17}\). It is especially useful when bromocriptine is ineffective or badly tolerated because of nausea, vomiting or dizziness.

Transsphenoidal surgical excision or debulking of a macroadenoma is considered when dopamine agonists have been unsuccessful in relieving symptoms and signs, lowering the hormone level or reducing the tumor size\(^{14,18,19}\). Postoperative treatment with a dopamine agonist may be necessary to control a persistent hyperprolactinemia. Radiation therapy is best reserved to prevent regrowth of residual tumor tissue after debulking of large and invasive macroadenomas. It is not advised as a primary treatment for macroprolactinoma and never for microadenomas\(^{20,21}\).

The current results indicate that our prolactinoma patients, when reaching appropriate medical attention, are more likely carrying an expanding macroadenoma that is compromising the visual pathway. Prolactinoma and hyperprolactinemia should be considered in the differential diagnosis of unexplained amenorrhea and galactorhea in women and in sexual dysfunction in men. Early recognition and referral to specialized clinics should have a favorable prognostic implication.

References: