



The Epidemiology of Prolactinomas

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Abstract. Prolactin-secreting tumors (prolactinomas), the most frequently occurring pituitary tumor, have a frequency that varies with age and sex. They occur most frequently in females aged 20 to 50 years old, at which time the female-to-male ratio is approximately 10:1. In the pediatric-adolescent age group, prolactinomas have a prevalence of 100/million population, and account for less than 2% of all intracranial tumors. Prolactinomas occur in approximately 30% of patients with multiple endocrine neoplasia type 1 and in this setting, they may be more aggressive than their sporadic counterparts. Patients with Carney complex or McCune-Albright syndrome may exhibit hyperprolactinemia due to a pituitary tumor derived from somatomammotropic cells that secrete both growth hormone and prolactin. Few familial cases of prolactinoma unrelated to MEN-1 are reported in literature.

Key Words. prolactin, prolactinoma, pituitary, tumor, inherited, neoplasm, epidemiology

Introduction

Pituitary tumors appear to occur commonly in the general population based on data derived from autopsy series and radiological imaging studies [1–3]. In autopsy series, the generally accepted mean prevalence approaches 10%, although both higher and lower rates have been reported [1,2]. Hall *et al.* noted a similarly high incidence of visible pituitary tumors in a magnetic resonance image (MRI) study of a cohort of healthy individuals without previously known pituitary disease [3]. The corresponding rate of clinically-active pituitary disease is unknown, and the impact on diagnosis rates of the widespread availability of accurate laboratory tests and MRI, is currently under investigation.

Hyperprolactinemia is one of the most frequently diagnosed clinical disorders in routine endocrine practice [4,5]. The most frequent symptoms are hypogonadism and/or galactorrhea in both sexes. Microprolactinomas (<10 mm) or macroprolactinomas (>10 mm) are the most common causes of hyperprolactinemia, although the pathogenesis of the disorder is diverse (Table 1). Any process that interferes with dopamine synthesis, its transport to the pituitary gland or its action at lactotroph dopamine receptors may produce hyperprolactinemia. Hyperprolactinemia is noted in 15–20% of women with secondary amenorrhea or oligomenorrhea, in approximately 30% of those with

galactorrhea or infertility, and in 75% of those with both amenorrhea and galactorrhea [4,5]. In men, hyperprolactinemia is often present for many years without symptoms; the most important symptom in males is decreased libido and/or sexual potency. Consequently, the mean age at diagnosis is 10 years greater in men than in women [4,5].

Sporadic Prolactinoma

General

Prolactinomas are the most common pituitary adenoma and account for up to 45% of pituitary tumors in the clinical setting [6,7]. They occur with an incidence of 6–10 cases per million population per year, which translates into a prevalence of approximately 60–100 cases per million [8]. Recent research indicates, however, that the prevalence of all pituitary tumors, including prolactinomas, may be 3–5 times higher than once thought [9]. In young adults, prolactinomas occur much more frequently in women than in men, while this sex-imbalance is not apparent in the middle aged population [7]. Women present earlier than men and hence frequently exhibit microprolactinomas at diagnosis; this earlier presentation may be a function of the greater symptom burden caused by hyperprolactinemia in women. Men on the other hand may present later due to the nature of their symptomatology, in which decreased libido predominates. Thus, males with prolactinomas have a higher frequency of macroadenomas and attendant mass effects on the pituitary and visual system than women [4–6]. However, it remains uncertain if this difference between the sexes is entirely due to delayed diagnosis or whether gender-specific differences in tumor behavior exist. In support of the latter, some data appear to show that at least some men have rapidly growing prolactinomas with elevated markers of cellular proliferation [10,11].

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Table 1. Causes of hyperprolactinemia

a. Hypothalamic Disorders
<i>Tumors:</i> craniopharyngioma, germinoma, third ventricle tumor, cyst, glioma, hamartoma, metastasis
<i>Infiltrative diseases:</i> sarcoidosis, tuberculosis, Langerhans cell Histiocytosis
<i>Pseudotumor cerebri</i>
<i>Cranial irradiation</i>
b. Pituitary Disorders
<i>Micro- or Macroprolactinoma</i>
<i>Acromegaly</i>
<i>Cushing's disease</i>
<i>Pituitary stalk section</i>
<i>Empty sella syndrome</i>
<i>Pseudoprolactinomas:</i> non functioning adenoma, meningioma, intrasellar germinoma, metastasis that may produce functional stalk section
<i>Infiltrative diseases:</i> giant cell granuloma, sarcoidosis
c. Drugs
<i>Neuroleptics:</i> perphenazine, fluphenazine, thiorazine, promazine, trifluoperazine, haloperidol, chlorpromazine, dopamine
<i>Receptor blockers:</i> metoclopramide, sulpiride, domperidone, cimetidine
<i>Antidepressants:</i> amoxapine, imipramine, amitriptyline
<i>Antihypertensives:</i> α -methyldopa, reserpine
<i>Estrogens</i>
<i>Opiates</i>
<i>Phenylalkylamine class N-type channel calcium blockers:</i> verapamil
d. Primary Hypothyroidism
e. Chronic renal failure
f. Cirrhosis
g. Neurogenic
<i>chest wall or spinal cord lesions, breast stimulation</i>
h. Stress physical or psychological
i. Idiopathic

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Elderly

The diagnosis and treatment of prolactinomas in the elderly has received less attention over the years than disease characteristics in other age groups [12–16]. As suggested by Turner *et al.* [16], outcomes research may be scarce due to a lower likelihood that microprolactinomas would be diagnosed in elderly patients. In support of this, Kovacs *et al.* found that autopsy revealed the presence of prolactin-staining microadenomas in 13% of patients aged over 80 [12]; data which have been replicated elsewhere [13]. Only three clinical series of elderly patients aged 65 years or more with pituitary tumors have been reported in the literature, [14–16]. In contrast to the autopsy series, these studies showed a clear prevalence of non-functioning adenomas, while prolactinomas represented only the 4–8% of the total [14–16]. All but one tumor was a macroprolactinoma, which is not entirely surprising given that indicators of hormonal disturbance, such as, menstrual disturbance, reduced sexual function, and

infertility are not as informative in elderly subjects; indeed macroprolactinomas are often diagnosed in the elderly when they produce local mass effect symptoms.

Children

In children, pituitary adenomas comprise 2.7% of supratentorial tumors and prolactinoma is the most common of these. The female preponderance seen in adults is maintained in children. A large retrospective surgical series of 136 young patients with pituitary tumors reported that prolactinoma was the most frequent tumor type encountered; these cases presented almost exclusively during teenage years [17]. Clinical presentation with a prolactinoma in childhood varies by age and sex [18]. As noted by Lafferty and Chrousos, prepubertal children usually present with headache, visual disturbances and growth failure [19]. During puberty, females can present with hypogonadism, pubertal arrest and galactorrhea due to hormonal suppression or destruction of normal pituitary tissue by the encroaching adenoma [19]. In pubertal males symptoms relating to mass effects can accompany arrested growth and puberty, perhaps due to a higher frequency of macroadenomas in males [19].

Extremely rarely, young subjects with hyperprolactinemia may present in the setting of McCune-Albright syndrome, which is caused by a post-zygotic activating mutation of the cAMP regulating protein GNAS 1 gene product Gs α [20]. This results in the constitutive activation of adenylate cyclase and subsequent cAMP formation as a second messenger [20]. McCune-Albright syndrome is characterized by a triad of poly- or monostotic fibrous dysplasia, café-au-lait macules and endocrine hyperfunction. Hyperprolactinemia in patients with McCune-Albright syndrome is usually associated with hypersecretion of growth hormone and to date only 15 cases have been reported in the literature [21].

Malignant prolactinoma

Pituitary carcinomas are very rare with only about 100 cases reported in the literature; of these 29 malignant prolactinomas have been described [22]. The diagnosis of a pituitary carcinoma is based on the patient's medical history and the demonstration of metastases. Malignant prolactinomas do not present with distinct clinical signs that distinguish them from benign tumors and the initial radiological appearance may mimic that of an adenoma. Histological examination does not allow easy differentiation between adenomas and well differentiated carcinomas [22]. The diagnosis is usually raised because of multiple recurrences and progressive inefficacy of treatment, but in many cases the definitive diagnosis is made only after metastases have been discovered. Malignant prolactinomas usually metastasize to the central nervous system and arachnoidal tissues, while distant metastases are rare. The prognosis is poor with only 50% of patients described in the literature surviving more than one year.

Inherited Prolactinomas

Multiple Endocrine Neoplasia-I (MEN-I)

Multiple endocrine neoplasia type 1 (MEN-1) is an autosomal dominant disorder with endocrine and other tumors with an estimated prevalence of 0.02–0.2 per 1000 [23]. MEN-1 is related to mutations in *MEN1* gene on chromosome 11q13 that encodes the protein menin. Ninety percent of affected cases express parathyroid adenomas, 64% enteropancreatic endocrine tumors and 35–40% anterior pituitary tumors. Overall 22% of patients with MEN-1 develop a prolactinoma. Verges *et al.* showed specific characteristics of prolactinomas in patients with MEN-1 [24]. In fact, among the 136 patients with pituitary adenomas, 85 were prolactinomas (62% of the whole series) [24]. Macroprolactinomas were noted in 71 of 85 patients (84%), including 20 invasive tumors [24]. Macroprolactinomas were more frequent in MEN-1 patients than in sporadic cases (84% vs. 24%, respectively) and normalization of plasma prolactin levels was significantly less frequent in MEN-1 patients than in sporadic, non-MEN-1 subjects (44% vs. 90%, respectively) [24]. These data are supported by those of [25], although other groups have considered the clinical behavior and response to treatment of MEN-1 and non-MEN-1 pituitary adenomas to be similar [26,27]. Finally a MEN-1 variant with unusually high prevalence of prolactinoma was reported in four large and seemingly independent kindreds, originating around the Burin Peninsula of Newfoundland [28]. Affected members of all four Newfoundland families with MEN-1 were recently shown to share not only the same *MEN1* germline mutation but also the same 11q13 haplotype [29,30] suggesting a correlation between genotype and phenotype, although the validity of this correlation remains to be proven.

Carney complex

Carney complex is an autosomal dominant multiple endocrine neoplasia characterized by the complex of “spotty skin pigmentation, myxomas, endocrine overactivity and shwannomas” [31]. Two gene loci have been identified, one on chromosome 17q22-24 and the other on chromosome 2p16. The former is associated with the gene encoding the α regulatory subunit of protein kinase A type I (*PRKARIA*) and mutations have been identified in up to 60% of CNC patients. To date approximately 400 cases have been described in the largest case collection. Hyperprolactinemia, usually mild, occurs almost exclusively in association with clinical or subclinical acromegaly in patients with Carney complex. The disorder of prolactin and growth hormone secretion is due to multifocal hyperplasia of somatomammotropic cells within the anterior pituitary. Hence, asymptomatic hyperprolactinemia in addition to elevations in growth hormone and insulin-like growth factor-I are present in up to 75% of patients with Carney complex [31].

Familial Isolated Pituitary Adenomas (FIPAs)

Familial pituitary adenomas have been characterized in the settings of MEN-1 and Carney complex, as noted above, while isolated familial acromegaly has been reported in about 100 patients. Interestingly, Berezin *et al.* and Poncin *et al.* have reported familial prolactinomas unrelated to MEN-1 or Carney complex [32,33]. Recently we have observed other pituitary phenotypes not linked to these previous syndromes, which may represent a new entity: familial isolated pituitary adenomas (FIPAs). To obtain further clinical and genetic insight of FIPAs, a retrospective European multicenter study was undertaken [34]. A hundred and forty cases have been identified in 64 families, including prolactinomas, acromegaly, clinically non-secreting adenomas, Cushing’s disease and gonadotrophinomas. There were 54 families with two patients, 8 with three and two with four affected members. Prolactinomas were the most frequent, with 56 affected members observed in 41 families and the female predominance seen in sporadic prolactinoma was maintained.

Conclusions

Prolactinomas are the most commonly diagnosed pituitary tumors. They occurs more frequently in women than in men particularly between the second and third decades of life. Special attention is required for the diagnosis of prolactinoma in males and in the elderly, as signs and symptoms may not be as suggestive of hyperprolactinemia as in females of child-bearing age. Prolactinomas can occur in a familial setting in MEN-1, while pituitary adenomas and hyperprolactinemia can complicate other inherited conditions such as Carney complex.

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