Epidemiology and Management Challenges in Prolactinomas

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Abstract

Clinically relevant pituitary adenomas are present in about 1 per 1000 of the general population and prolactinomas are by far the most common clinical subtype of pituitary adenomas. Usually prolactinomas affect pre-menopausal women and present with typical symptoms of menstrual disturbance and/or galactorrhea. They are generally managed with dopamine agonists to restore fertility and to control symptoms and tumour size. In a subset of prolactinomas, however, management remains challenging. Studies in recent years have identified the factors related to dopamine agonist resistance, such as, male sex, genetic features, and aggressive tumor behaviour. Certain other patient groups represent particular challenges for management, such as pediatric patients and pregnant women. Treatment with dopamine agonists is usually safe and effective, and adverse effects such as clinically relevant cardiac valvular complications and impulse control disorders may occur in isolated instances.

A number of important disease characteristics of prolactinomas remain to be explained, such as the difference in sex prevalence before and after menopause, the higher prevalence of macroadenomas in older males and the biochemical mechanisms of resistance to dopaminergic agonists.

Introduction

Hyperprolactinemia is one of the most common endocrine disorders in clinical practice and usually presents with signs and symptoms that include loss of libido, menstrual/fertility disorders or galactorrhea [1]. Furthermore, recent evidence suggests that the prevalence of hyperprolactiemia in the community is rising [2]. Various factors can result in prolactin excess (pituitary stalk compression, drug side effects, estrogen, etc.), but pituitary adenomas represent the most clinically important diagnosis. Apart from the common symptoms of hyperprolactinemia, prolactinomas can also be responsible for mechanical compression of local structures leading to visual field disturbance (Figure 1). Epidemiological studies on pituitary adenomas have shown a much higher prevalence than previously thought, with prolactinomas being the most frequent tumour subtype reported [3-6]. Consequently, prolactinomas will be encountered regularly in the clinical setting. Dopamine agonists are the treatment of choice for prolactinomas. Cabergoline is widely available and allows for control of prolactin levels and decrease in tumour mass in most cases. In consequence, surgery and radiotherapy are seldom used in the management of prolactinomas, apart from rare aggressive cases or where medical therapy is ineffective or contraindicated. In this review we provide an update on the clinical presentation and epidemiology of prolactinomas and highlight some existing challenges related to their presentation and management.

Epidemiology

In 1994, an epidemiological study about the radiological evaluation of pituitary disease in a healthy subject cohort reported a 10% prevalence of pituitary adenomas [7]. A decade later, Ezzat et al conducted an in-depth meta-analysis regarding the prevalence of these tumours. In that study, 10 original studies on radiological and post mortem prevalence demonstrated a prevalence of 22.5% in radiological studies and 14.4% in autopsy series (overall prevalence: 16.7%); prolactinomas were the most common subtype (25-41%) [8]. That finding was confirmed in a subsequent autopsy series of individuals without a pre-existing pituitary adenoma diagnosis, which found that prolactin positive immunohistochemical staining was seen in 39.5% of pituitary adenomas [9]. In that series the vast majority of tumours were very small microadenomas.

Before 2006, few data were available about the prevalence of pituitary adenomas in the clinical setting. The first study about the prevalence of clinically relevant pituitary adenoma was conducted in the Liège area of Belgium in 2006 [3]. Three distinct districts (rural, periurban and urban) were studied with a total of 71.972 inhabitants and reported a pituitary adenoma prevalence of 1/1064. Of these cases, 66.2% were prolactinomas, of which 80% were microprolactinomas (<10 mm diameter) occurring in females. These results were confirmed in different geographical settings thereafter. In 2009 in Switzerland, Fontana *et al* found 44 adenomas out of 54.607 inhabitants (prevalence of

1/1241) out of which 73% affected women. Once again, prolactinomas were predominant (56%; 36% being microadenomas and 20% macroadenomas). Subsequently in the United Kingdom, Fernandez *et al* found 63 cases of pituitary adenomas in 81.149 population (prevalence 1/1289) of which 57% were prolactinomas. These were the more frequent subtype in people under 60 years of age, while non-functioning adenomas were more frequent in those aged >60 years of age. Other data from Finland [10] and Malta [6], found similar results and the same proportions of prolactinomas (Table 1). In Sweden, the prevalence was estimated at 1/2688 inhabitants [11]. Although this confirmed the increased frequency of PA in general population, these results were lower than other reports. They also found a lower proportion of prolactinomas (32%) and a higher proportion of non-functioning pituitary adenomas (54%). This imbalance may be the consequence of the criteria used for considering prolactinomas (prolactin levels >3x the upper limit of normal). The lower prevalence may be also due to a lack of data from general practitioners, as it was a registry-based study. Moreover, they reported a higher prevalence of macroadenomas (65%) in respect to microadenomas (33%). In contrast, the pituitary adenoma prevalence in Iceland evaluated in 2012 was higher (1/865) with 40% being prolactinomas, suggesting a higher prevalence of pituitary adenomas [12]. Some studies have reported incidence rates for pituitary adenomas [6,10,12,13]. Most report an increase in the incidence over the years, possibly indicating the contribution of improved access to diagnostic tools (such as MRI or hormonal assays) and improved disease recognition. Standardised incidence rates (SIR) for pituitary adenomas range between 4 and 7.39 (Table 2).

Gender differences

In a retrospective study of about 2230 patients that underwent surgery for a pituitary adenoma, Mindermann and Wilson reported that prolactinomas were the most frequent tumour subtype (39%) [14]. They highlighted an important difference in prolactinoma prevalence by sex and age. They reported a female to male sex ratio for prolactinomas of 10:1 between 18 years old and the fifth decade of life, while after this age the ration was 1:1 [15]. In 2009, Kars et al focussed their attention on hyperprolactinemic patients treated using dopamine agonists [16]. They reported a clearly higher incidence rate in women aged 25-34 compared to men, while this difference disappeared after menopause. In contrast, no specific peak in incidence rate was found in men. Similarly, evaluation of SIR in Iceland found the same discrepancy between sexes with a median peak in incidence that was significantly younger in women than in men (32 *versus* 47 years of age, respectively) [12].

To date, this sex difference has not been fully explained, although some factors have been suggested. One such factor is the expression of estrogen receptors (ER) in prolactinomas. An immunocytochemistry study performed in 42 pituitary adenomas revealed a higher prevalence of ER in prolactinomas compared with other subtypes [17]; ER are also strongly expressed in normal and adenomatous lactotroph pituitary cells [18]. However, a retrospective study failed to identify a relationship between the use of estrogen-based oral contraception and a higher incidence of

prolactinoma [19]. A prospective study in 16 hyperprolactinemic women (8 idiopathic; 8 with prolactinoma) receiving oral contraceptives did not show any significant change in prolactin levels or radiological features of pre-existing pituitary adenomas during the estrogenic therapy [20]. Moreover, although a case of a *de novo* prolactinoma developing in a transgender male receiving high doses of estrogen has been reported [21], more recent studies suggest no influence of estrogen in a large cohort of 98 subjects [22].

Genetic aspects

MEN1 gene mutations lead to multiple endocrine neoplasia type 1 (MEN1), an autosomal dominant disease characterised by parathyroid adenomas (90% of cases), enteropancreatic neuroendocrine tumours (64%) and pituitary adenomas (35-40%). The prevalence of MEN1 is 0.02-0.2/1000 and about 22% of cases have a prolactinoma [23]. Compared with non-MEN1 cases, these adenomas show more aggressive behaviour with a preponderance of macroadenomas and a higher resistance to dopamine agonist treatment [24]. Prolactinomas can also occur in an inherited or familial setting as part of familial isolated pituitary adenoma (FIPA) kindreds [25]. Among a small group of prolactinoma patients, germline mutations in the *aryl hydrocarbon receptor interacting protein* (*AIP*) gene have been identified either in FIPA families or in the sporadic setting [25]. In an international study, we evaluated the prevalence of *AIP* mutations in 163 large, aggressive sporadic macroadenomas (mean tumour size: 29.2 mm) diagnosed before the age of 30. An *AIP* mutation was found in 7/61 prolactinomas (11.5%) [26]. Pituitary adenomas, including prolactinomas, also form part of the emerging clinical condition of pheochromocytoma-paraganglioma-pituitary adenoma association (3PA) [27]. These patients can have prolactinomas in combination with pheochromocytomas/paragangliomas, and individual cases have been shown to have germline mutations in genes such as the succinate dehydrogenase complex subunits (*SDHx*) or mutations/intragenic deletions in *MAX* [27,28].

Prolactinomas in Special Populations

Pediatric patients

Pituitary adenomas account for 2% of supratentorial tumours in children, and prolactinomas are the most frequent subtype of adenoma, although they only occur with an incidence of $< 0.1/1000000$ population [29,30]. Girls are more frequently affected than boys, with the latter tending to have more macroadenomas [31,30]. Clinical presentation also varies by age and sex. During the pre-pubertal period, headache, growth failure and visual field defects are the most frequent signs, while during puberty galactorrhea, hypogonadism or pubertal arrest are more characteristic [32]. Salenave *et al* reported a large French series of 77 children and adolescents with macro-prolactinomas and found twice as many females as males affected [33]. Across the entire population, irrespective of sex, the main presenting signs/symptoms were pubertal delay/disorders, visual effects and growth problems.

As in other populations, tumor size and prolactin secretion was higher in males than in females. In a recent study, a cohort of 27 paediatric prolactinomas was described [34]. Prevalence was higher in girls (sex ratio 2:1) while earlier onset, larger tumour volume and higher prolactin levels were seen in boys. Except for cases that needed surgical decompression, cabergoline treatment was effective in controlling prolactin levels and decreasing tumour size.

Elderly patients

Prolactinomas in patients older than 65 years account for 4-8% of pituitary adenomas [29], but precise data about their exact prevalence are scarce. A study based on 17 prolactinomas diagnosed in the postmenopausal period reported a majority of macroadenomas (1 micro and 12 macroadenomas; 4 giant adenomas). In that series, only one giant prolactinoma was resistant to cabergoline (dose of 3 mg/week for 138 months without normalization of prolactin levels) and presented with cavernous sinus invasion, which is a poor prognostic factor for cabergoline responses [35]. Among 14 postmenopausal women with prolactinomas, Shimon *et* al reported most had large tumors >20 mm in diameter, but that responses to dopamine agonists were generally good [36]. The effect of menopause on the regression of hyperprolactiemia and micro-prolactinoma was studied by Karunakaran *et al* [37]. They noted that postmenopausal women had a statistically significantly higher chance of spontaneous regression of their hyperprolactinemia than non-menopausal controls.

An important limitation of studies in the elderly is that prolactinoma prevalence is likely to be underestimated in the elderly as they can have less clear clinical repercussions at that age (libido loss) and this may lead to later presentation. In an autopsy series, Kovacs et al noted the presence of prolactin-staining microadenomas in 13% of patients aged over 80 [38].

Pregnancy

During pregnancy, a physiological hyperplasia of lactotroph cells leads to pituitary hypertrophy and elevation of prolactin levels by up to 10-fold. Moreover, pregnancy is an important hyperestrogenic state that could also influence the evolution of pre-existing prolactinomas. However, the risk of size increase during pregnancy is low in micro-prolactinomas (2.7%), and previously treated macro-prolactinomas (4.8%); size increase is significantly more frequent in untreated macro-prolactinomas (22.9%) [39]. These results suggest the existence of different tumour development mechanisms among prolactinomas and it is difficult to predict which tumours will expand during pregnancy. It is recommendable to intensify clinical follow-up in macroadenomas during pregnancy, starting with a visual field evaluation followed by an unenhanced MRI in women experiencing severe headaches [15]. In case of tumour growth, bromocriptine should be considered as the first line therapy, as it has the largest safety database available and is in line with the Endocrine Society guidelines [15]. However, recent studies suggest that cabergoline has no relevant adverse effects during the first weeks of gestation, but medication choices should err on the side of caution [40]. In contrary, the use of

quinagolide is not recommended. Quinagolide use has been evaluated in 176 pregnancies; 24 (14%) ended in spontaneous abortion, nine resulted in foetal malformations and one was a premature delivery [41]. Considering the possibility of tumour growth during pregnancy [39] [42], surgery has been considered as an alternative for macro-prolactinomas in women planning pregnancy. However, the success of surgery depends on the tumour dimensions and invasion and the neurosurgical experience, so decisions on choosing surgery or relying on bromocriptine need to be made on a case by case basis.

Challenges in prolactinoma treatment

Dopamine agonist resistance

Dopamine agonists are first-line therapy for prolactinomas as they are effective in controlling clinical symptoms, prolactin levels and tumour volume, and they are well tolerated [43,44]. Cabergoline has been the treatment of choice for more than 15 years in many countries, as it allows normalisation of prolactin in 90% of patients with microadenomas and in 80% with macroadenomas at a median weekly dose of ~1.0 mg [45,46]. Data about the prevalence of resistance to cabergoline treatment are scarce, as a firm consensus on the definition of such resistance has been lacking. Considering a cabergoline dose of 2 mg per week (the upper labelled clinical dose) as the cut-off for our definition of resistance, we collected a series of 92 patients among 12 different centres [47]. All received cabergoline for at least six months at or above the cut-off dose without normalization of prolactin levels. Using this definition, the prevalence of resistance to cabergoline was 3.4% among centres. Most of these resistant prolactinomas were macro-prolactinomas or giant (>40 mm) adenomas (82.6%) and genetic or hereditary features were seen in 13%. In a cohort of 122 macroprolactinomas, Delgrange reported a low prevalence of resistance as 105 were controlled with a dose of 2.5 mg per week [48]. In that series, cavernous sinus invasion was shown to be a poor prognostic factor for control as it was associated with a 10-fold risk of resistance. In comparison to dopamine agonist responsive prolactinomas, men were overrepresented in the dopamine agonist resistant group. Among types of dopamine agonists, cabergoline has become the treatment of choice. In one large review of resistance to DA, Molitch reported a lower resistance rate for cabergoline in respect to bromocriptine. Among 1022 patients with bromocriptine, 76% achieved normal prolactin levels while this goal was obtained in 86% of cases among 612 patients with cabergoline [49]. Responses to dopamine agonists have been noted to change over time, as it is well known that some patients may, after many years of successful treatment, be able to withdraw temporarily or completely from dopamine agonist therapy [50,51]. Patients with a successful withdrawal are usually those with normalisation to low doses of therapy; among others recurrence is frequent. Interestingly, even in some cases of initially poor responders to cabergoline (needing ≥ 2 mg/week), chronic therapy followed by careful dose reduction can be associated with stable tumor size [52]. However, in patients on maximal dose cabergoline with large tumor mass or significant impingement on surrounding structures, dose reduction would not appear to be a safe option.

Neurosurgery is an important treatment option in patients with dopamine agonist resistance that persists despite dose-escalation. Before the widespread use of primary dopamine agonist therapy, surgery was the main treatment for micro and macroprolactinomas [53]. Primary dopamine agonist and surgical treatment of prolactinomas are both associated with good efficacy and safety profiles [54]. Follow-up of surgically managed prolactinomas has shown that initial postoperative control rates can be as high as 60-63%, but that the risk of recurrent hyperprolactinemia can occur in up to a third of cases [55]. Ma et al recently performed a meta-analysis comparing primary medical and surgical therapies and they concluded that significantly higher long-term disease control was achieved surgically [56]. However, the availability of experienced neurosurgical centres is not uniform globally and many prolactinoma patients will not want or be suitable for major neurosurgical intervention.

Cardiac safety of dopamine agonists

Since the reporting of cardiac valvular problems in patients treated with cabergoline for Parkinson's disease [57], the safety of its use in the treatment of prolactinomas has been evaluated by several groups. The initial studies were retrospective series, beginning in 2008 with a cohort of 102 treated prolactinomas as compared to matched controls. Despite a mean cumulative cabergoline dose of 204 mg, we found no significant valvular disease was noted on echocardiography [58]. Wakil reported similar results in a smaller cohort of 44 patients but with a mean cumulative dose of 311 mg [59]. These results were confirmed by three subsequent studies [60-62]. Only two studies found discordant results. Colao *et al* reported significant tricuspid valve regurgitation in a cohort of 50 patients (cumulative cabergoline dose of 280 mg) [63]. At the same time, Kars *et al* reported a higher prevalence of mild tricuspid regurgitation and aortic valve calcification in treated patients, which were deemed to not be clinically relevant [64].

The first prospective study on cabergoline in pituitary disease was performed in acromegaly patients. After a follow-up of at least four years, treated patients had no increased incidence of valvular disease versus controls [65]. The cohorts of Colao *et al* and Kars *et al* reported prospective data [66,67]. Both concluded that there was a non-significant evolution in valvular status. Recently, we reported a large cohort of 100 patients receiving cabergoline for endocrine disease. The vast majority of our population were, as expected, female (70%). The median total duration of treatment was >10 years (124.5 months) and the median cumulative cabergoline dose was 277.8 mg at last follow up. None of the patients developed significative changes in valvular status [68]. Based on the results of Colao *et al* and Kars *et al*, particular attention was paid to the tricuspid valve. It is important to note that mild tricuspid regurgitation on echocardiography can be found in up to 70% of the general population. Only four patients in our patient series had grade 2 tricuspid regurgitation at baseline, versus five patients at last follow up. According to these prospective data, the use of cabergoline is generally considered safe in the endocrine setting at the prescribed dose range. To date, only three cases of confirmed cabergoline associated valvular disease have been reported. The most recent case concerned a 52-year-

old woman with a 25-year history of treatment for a macro-prolactinoma. The cumulative dose was much higher than described in prospective studies (4192 mg). The patient developed severe aortic regurgitation [69].

Another safety issue related to dopamine agonist use in the treatment of hyperprolactinemia is that of pathological impulse control disorder [70, 71]. Like with the cardiac valvular issues described above, this problem was initially characterized in patients treated with dopamine agonists for Parkinson's disease and movement disorders at much higher doses than are used in hyperprolactinemia/prolactinoma treatment. Impulse control disorders seen with dopamine agonists include pathological gambling, compulsive shopping, hypersexuality, binge-eating, or the repetitive performance of purposeless mechanical activities (known as "punding") [72]. The etiology of this complex disorder is thought to be related to a hyperdopaminergic state in specific regions of the brain [73]. In Parkinson's disease patients these impulse control disorders occur in >13% of patients [74]. As reviewed recently by Norohna and colleagues, in endocrine practice dopamine agonist-induced impulse control disorder appears to be seen less frequently than in Parkinson's disease, but proper epidemiological data are clearly lacking [70]. Despite its rarity, when it does occur the severity of the symptoms can have devastating economic or social consequences for patients and their families, depending on the behavioral manifestation of the disorder. Discontinuation of the dopamine agonist is generally associated with a very rapid disappearance of the unwanted compulsions. Increased awareness of the potential for impulse control disorder is necessary among endocrinologists and during interactions with patients in the clinic the opportunity should be taken to discuss this rare but important side effect of an otherwise well tolerated therapy.

Conclusions

Hyperprolactinemia due to prolactinoma is a frequent problem in endocrine practice. Epidemiological studies have confirmed the higher prevalence of pituitary adenoma than previously thought, with prolactinomas representing the majority of cases. Epidemiological studies have also highlighted interesting differences between sexes and across age groups, raising the question of the influence of sex hormones in the pathogenesis of prolactinomas. Although treatment with dopamine agonists is usually effective and safe, evaluation of resistant cases has identified some important radiological and epidemiological factors that contribute to poor responses, such as, cavernous sinus invasion, male sex and genetic features. Dopamine agonists are generally well tolerated at the dose ranges used in endocrine practice but clinicians and patients should be aware of rare potential risks such as impulse control disorders and possibly cardiac valvular disease.

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