Prolactinoma in Children and Adolescents

H.L. Fideleff H.R. Boquete M.G. Suárez M. Azaretsky

Endocrinology Unit, Department of Medicine, Hospital T. Alvarez, Buenos Aires, Argentina

Key Words

Peripubertal prolactinomas • Pediatric hyperprolactinemia • Dopamine agonists • Hyperprolactinemia • Asymptomatic hyperprolactinemia

Abstract

The evolution of prolactinomas in children and adolescents continues to be controversial. Girls have more prevalence of microprolactinomas and their signs and symptoms are related to hyperprolactinemia and the resulting hypogonadotropic hypogonadism. In males, the greater incidence of macroadenomas results in the presence of neuro-ophthalmologic signs. The larger prevalence of macroadenomas in males is consistent with findings in adults and would not be related to a later diagnosis. In patients with asymptomatic hyperprolactinemia, the presence of altered proportions of PRL isoforms should be evaluated. The diagnosis of prolactinoma requires both radiographic evidence of pituitary adenoma and laboratory analysis documenting the presence of sustained hyperprolactinemia. Because of their effectiveness and tolerance, dopaminergic agonists are the initial therapy of choice in pediatric age patients. Finally, molecular biology and genetic studies have brought new insights into the pathogenesis, clinical behavior and different therapeutic responses.

Copyright © 2009 S. Karger AG, Basel

Introduction

Prolactinomas are the most common hormone-secreting pituitary tumors, with an estimated prevalence in the adult population of 100 per million [1]. These tumors have been reported in patients from 2 to 80 years [2], occurring most frequently in women from the second to the fifth decades of life. Even if prolactinomas are rare in children and adolescents, they represent 50% of all pituitary adenomas, which accounts for 2% of all intracranial tumors [3, 4]. In children and adolescents, symptoms usually include functional alterations resulting from elevated prolactin (PRL) (delayed puberty in both sexes, and amenorrhea and galactorrhea in girls) and/or tumor mass effects (headaches, visual field defects, neurological disorders, among others) [2]. The implications of oligo-symptomatic or asymptomatic hyperprolactinemia raise many doubts. The few data currently available on the concentrations of the various isoforms in normal children and adolescents in different physiological and pathological situations (e.g. prolactinomas) add more doubts on the roles of these isoforms. The advances in the knowledge of tumor pathogenesis, the contributions of molecular biology and a long-term follow-up of patients have led to new approaches in the clinical and therapeutic management.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com© 2009 S. Karger AG, Basel
0301-0163/09/0724-0197\$26.00/0Accessible online at:
www.karger.com/hreH.L. Fideleff, MD, PhD
Endocrinology Unit, Department of Medicine, Hospital T. Alvarez
Aranguren 2701 (C1406FWY) Buenos Aires (Argentina)
Tel. +54 11 4611 6666, ext. 2933, Fax +54 11 4612 6563
E-Mail hugofideleff@arnet.com.ar

Fig. 1. Regulatory pathways of prolactin (PRL) secretion. TRH = Thyrotropin-releasing hormone, VIP = vaso-active intestinal peptide, PACAP = pituitary adenylate cyclase-activating polypeptide, ANP = atrial natriuretic peptide, DA = dopamine.

Regulation of Prolactin Secretion

Regulation of PRL secretion in physiological conditions is a complex mechanism involving many neurotransmitters, neurohormones, neuropeptides, various metabolic substances and different systemic hormonal signals. Stress and suckling, as well as estrogen levels, are the most important physiological stimuli of PRL secretion. Agents such as estrogens, 5-OH-tryptamine, nor-adrenaline, opioids and galanine stimulate PRL secretion through a decreased activity of the pituitary tuberoinfundibular dopaminergic system. Conversely, other neurotransmitters tend to reduce PRL secretion through an increase in tuberoinfundibular dopaminergic activity. The different regulatory pathways are depicted in figure 1.

Pathogenesis

In recent years, many papers have been published which have clarified some aspects of the pathogenesis of pituitary adenomas. The pituitary tumor-transforming gene (PTTG) was isolated from rat pituitary tumor cells in 1997 and identified as a pituitary-derived transforming gene [5]. PTTG has been shown to be tumorigenic in vivo, through regulation of the basic fibroblast growth factor (BFGF) secretion and inhibition of chromatid separation [5–7]. BFGF modulates angiogenesis and tumor formation and progression in many tissues including the pituitary gland. Overexpression of PTTG has been shown in all hormone-secreting adenomas including prolactinomas [8]. Estrogens promote tumorigenesis in the pituitary gland by PTTG induction, which results in an increase of BFGF and of vascular endothelial growth factor

Table 1. Prolactinomas: markers of aggressiveness

Marker of aggressiveness	Clinical expression
Ki-67MIB-1 LI (proliferation)	Resistance to DA No relation with tumor size Possible association with malignant progression Highly correlation with invasiveness
PCNA (proliferation)	Associated with tumor recurrence
Cyclin D1 (cell cyclin)	Associated with tumor aggression
Cyclin E (cell cyclin)	Elevated in macroprolactinomas
PNCAM (cell-to-cell adhesion)	Associated with invasive prolactinomas and metastasis in rats but not in humans
E-cadherin/catenin/p120 complex (cell-to-cell adhesion)	Decreased in invasive prolactinomas

LI = Labeling index; DA = dopamine agonist; PCNA = proliferating cell nuclear antigen; PNCAM = polysialylated neural cell adhesion molecule.

Table 2. Prolactinomas: genetic alterations in invasiveness

Genetic alteration	Biological expression
Retinoblastoma (RB) (11q13): deletion (LOH)	Transition to an invasive state
hst (11q13): estrogen-induced overexpression	Induction of FGF-4 Increase of growth, proliferation and angiogenesis
PTTG (5q33): estrogen-induced overexpression	Increase of bFGF expression, VEGF expression, angiogenesis and tumor progression.
Edpm5: variability between ran strains	Change in angiogenic switch, alterations in tumor angiogenesis upon estrogen stimulation

LOH = Loss of heterozygosity; bFGF = basic fibroblast growth factor; VEGF = vascular endothelial growth factor; PTTG = pituitary tumor-transforming gene.

(VEGF) production. These findings suggest the importance of estrogens in the formation and progression of pituitary adenomas via a paracrine mechanism involving angiogenesis [9].

Different growth factors are expressed in the pituitary gland and released in the extracellular fluid. In addition to the previously mentioned VEGF, the fibroblast growth factor (FGF) is also involved in angiogenesis. Another factor related to the behavior of prolactinomas is the epidermal growth factor (EGF), which is expressed under normal conditions in pituitary cells and its binding sites are located mainly in lactotrophs and somatotrophs. It

should be noted that the EGF-binding sites are present in 76.5% of prolactinomas [10].

Additionally, the role of the high mobility group A 2 (HMGA2) gene in the genesis of pituitary adenomas in humans has been recently demonstrated [11]. The HMGA2 proteins are low-molecular-weight nuclear factors that interact with the minor groove of many AT-rich promoters and enhancers [12]. It has been recognized that HMGA2 is substantially expressed in tumor cells from human prolactinomas [11]. Interestingly, microarray analyses identified 726 unique genes that were statistically significantly different between prolactinomas and

Fig. 2. **a** MRI: microadenoma 8 mm (arrow) in a 14-year-old female. **b** MRI: macroadenoma in a 15-year-old male (pretreatment). **c** MRI: empty sella post-treatment in the same patient.

normal glands, whereas proteomic analysis identified 4 differently upregulated and 19 downregulated proteins [13]. All these molecular alterations and different genetic mutations have contributed to the understanding of the genesis of prolactinomas, to the variable clinical behavior (more or less aggressiveness) and to the different therapeutic responses (dopamine-sensitive, dopamine-resistant) (tables 1, 2).

Clinical Features

The clinical manifestations of prolactinoma vary mainly according to gender, age of onset, tumor size and PRL levels. Girls have a higher prevalence of microprolactinomas, therefore their signs and symptoms are more related to hormonal alterations (fig. 2a). Hyperprolactinemia is a cause of hypogonadotrophic hypogonadism, which leads to delayed puberty, primary and secondary amenorrhea, gynecomastia and/or galactorrhea. Clinical manifestations in males include delayed puberty, gynecomastia and galactorrhea, but we have observed a more frequent occurrence of neuro-ophthalmologic signs (visual disturbance, headaches, etc.) given the higher incidence of macroadenomas [14] (fig. 2b, c). The higher prevalence of macroadenomas in males coincides with findings in adults, where this has been partially attributed to delayed referral and/or onset of symptoms as compared to females. The same assumption could be made for pediatric age. However, our experience does not support this hypothesis, since the time elapsing between the onset of symptoms and diagnosis was similar in both

genders (mean for females: 2.4 years; mean for males: 2.6 years) [14]. Consequently, the most plausible explanation would be a difference in tumoral biology between the two genders, as it has been assumed in adults. This seems to be counterintuitive concerning the estrogen-PTTG pathway, since men have lower estrogen levels than women. However, this discrepancy may be explained by the observation that, although men have lower estrogen levels, their tumors express more estrogen receptors than those in women [15]. On the other hand, the enzyme aromatase is present in human pituitary supporting the possible local conversion of testosterone to estrogen. This could be one possible paracrine factor in the development and aggressiveness of prolactinomas [16]. Paradoxically, Burdman et al. [17] have recently shown that the most aggressive tumors were those negative for estrogen receptors within prolactinomas. In certain tumors, the regulatory mechanisms might not be operating properly and estrogen receptors might not be necessary for the regulation of PRL levels, and therefore absent. With these considerations in mind, the absence of estrogen receptors in prolactinomas should be a sign of anaplasia and a more aggressive behavior. Unlike other hypothalamic-pituitary organic processes, prolactinomas are not usually associated with short stature in pediatric patients [18]. In our experience, only 3 patients presented short stature and growth velocity arrest, which confirms that this is not a frequent reason for referral in young patients with prolactinomas [14].

Galactorrhea is not a constant sign in pediatric patients, as it has been reported in 30–50% of girls [14, 18]. This contrasts with the prevalence of galactorrhea in

adult females, which accounts for up to 80% [2]. In males, the percentage of gynecomastia is close to 50% and this condition is frequently associated with galactorrhea (50–75% depending on the authors) [14, 18] (fig. 3). Nevertheless, pubertal gynecomastia is a common finding in normal adolescents (up to 60%), therefore, in pubertal males with prolactinoma and gynecomastia it is difficult to confirm that this condition is due to hyperprolactinemia. There are isolate reports of prepubertal boys with gynecomastia in whom it is reasonable to establish a relationship with elevated PRL [18].

Elevated PRL causes alterations of the gonadotropic axis, inhibiting pulsatile Gn-RH secretion. There have been reports of a direct inhibitory effect on the testicular and ovarian function. In addition, a LH inhibition due to an increased opioid tone observed in hyperprolactinemia, has also been implicated as a cause of amenorrhea in hyperprolactinemic patients [19]. Such alterations appear in adolescent females as delayed puberty (48% in our experience), primary amenorrhea (14–41%), secondary amenorrhea (29–45%) and oligomenorrhea (up to 29%) [14, 18]. In males, in our experience, in addition to the neuro-ophthalmologic disorders we have found delayed puberty in 27% [14]. To date, and to our knowledge, few data are available on the impact of hyperprolactinemia on bone metabolism in children and adolescents [20]. In adult patients, discussions are ongoing on the possibility of a direct effect or an effect mediated via hypoestrogenism [21, 22]. Colao et al. [23] found significantly lower values of bone mineral density in adolescent patients with hyperprolactinemia than in their sex- and age-matched controls and also lower bone mineral density values corrected for age in the adolescent patients with hyperprolactinemia than in the young adult patients.

Headache is the most common neuro-ophthalmologic symptom (64–77% of males, and 17–30% of females), but it is not consistently related to tumor size or to PRL levels [24]. Visual field defects are present depending on tumoral size. In our experience, this alteration has been observed in 7% of females and 64% of males, due to the predominance of macroprolactinomas in the latter group [14]; likewise, Colao et al. [18] reported visual field defects in 2/17 females and 5/9 males. In some cases, the severity of visual disturbance may be such that may lead to blindness [25], exophthalmia [26] and, rarely, it may be associated with an endocranial hypertension syndrome [14].

These symptoms are clearly associated with aggressive tumors. It should be noted that the mechanisms of aggressive biological behavior of some prolactinomas have not yet been fully defined. The specific markers of ag-

Fig. 3. Gynecomastia in a 15-year-old male with a microprolactinoma.

gressiveness of prolactinomas reported include proliferation factors, proteins related to the cellular cycle, adhesion molecules, extracellular matrix components, local growth factors and tumoral angiogenesis, apart from some specific genetic disorders [9].

Diagnosis

The diagnosis of prolactinoma requires both radiographic evidence of pituitary adenoma and laboratory analysis documenting the presence of sustained hyperprolactinemia, after other potential causes of secondary elevation of PRL have been ruled out. Given the increase in PRL during normal puberty, adequate gender- and age-specific reference values are required. Because of the pulsatile secretion of PRL and as it is a stress hormone, at least 2 elevated PRL values are needed, which should have been obtained on different days. According to the International Consensus of the Pituitary Society, 2–3 samples separated by 15–20 min should be obtained to avoid the effect of pulsatile secretion [2]. In our experience, samples obtained on different days with a previous 20-min rest would be adequate to confirm hyperprolactinemia.

Baseline PRL measurement itself has a high diagnostic value. In the cases of prolactinomas, PRL concentration is generally related to tumor size. However, moderately increased levels of PRL do not rule out the presence of a tumor. In addition, slightly increased values, a normal MRI and no clinical symptoms, suggest the possible presence of PRL isoforms with minor or no biologic activity.

Asymptomatic hyperprolactinemia has also been reported in pediatric patients [27, 28] due to abnormal elevation of PRL isoforms. Additionally, the presence of glycosylated PRL and macromolecular forms in healthy children and adolescents of both genders should not be considered pathological, as we have confirmed [unpubl. data]. Even if Sephadex G100 column chromatography is the gold standard for the characterization of PRL macromolecules (Big Big-PRL and Big-PRL), this is a laborious and expensive method. For this reason, for Big Big-PRL measurement, simpler methods have been developed (precipitation with PAS, PEG, etc.) [29, 30].

Prior to the introduction of modern imaging methods (CT and MRI), dynamic tests for PRL secretion were developed to distinguish prolactinomas from other causes of hyperprolactinemia. Sulpiride, nomifensine, metoclopramide, TRH and domperidone have been used among others [31]. All these tests are non-specific and blunted PRL responses occur in patients with prolactinomas, hypothalamic tumors and non-tumoral hyperprolactinemia. Additionally some patients with prolactinomas have normal PRL responses to these dynamic tests. For these reasons, it has been stated that the provocative tests are not useful in the differential diagnosis of hyperprolactinemia. They are expensive, time-consuming and do not add more information than available from measurement of basal PRL [32].

Hyperprolactinemia in children and adolescents in the presence of a pituitary adenoma detected by MRI or CT is consistent with the diagnosis of prolactinoma; however, it should be noted that any pituitary mass compressing the stalk may cause elevation of PRL. Furthermore, approximately 10% of the general population may have asymptomatic pituitary microadenomas (incidentalomas) [2]. Therefore, the presence of an image of these characteristics in a patient with moderate hyperprolactinemia would not confirm the diagnosis of prolactinoma. Undoubtedly, the diagnosis of PRL-secreting adenoma should be confirmed by histopathology but, as these tumors are rarely treated with surgery, such confirmation is generally based on the response to drug therapy. Thus, normalization of serum PRL levels associated with considerable tumor size shrinkage (50–75%) or complete remission would confirm the diagnosis. It is important to remember the enlarged pituitary that is sometimes observed, especially in normal females, during puberty. In these cases, the superior margin of the pituitary gland takes the form of a tent. However, normally, there is no elevation of PRL levels and therefore this should not lead to an erroneous diagnosis of prolactinoma.

In patients with macroprolactinoma, an assessment of the visual field should also be performed, because of the possibility of an involvement of the via optica [2]. According to the suggestions of the Pituitary Society [2], this test would not be required for microadenomas.

Therapeutic Approaches

Dopaminergic agonists are the initial therapy of choice in children, adolescents, as well as in adults, because of their effectiveness and tolerance [33].

The goals of therapy are to ensure a normal pubertal development, to restore and/or maintain an adequate gonadal function, to shrink the pituitary tumor mass as well as to achieve an adequate peak bone mass and ensure future fertility.

Bromocriptine, cabergoline, pergolide and quinagolide exert their action by binding to D2 dopamine receptor, a G-protein-coupled receptor, expressed in the pituitary lactotrophs, leading to an inhibition of the PRL synthesis and secretion. The interaction with the D2 receptor reduces adenylate cyclase activity and the signaling pathways downstream of this enzyme. Stimulation of these receptors also inhibits inositol phosphate production and phospholipase C activity. The final consequence of the inhibition of these signaling cascades appears to be the repression of the PRL gene transcription. Furthermore, bromocriptine inhibits the pituitary lactotroph mitosis and growth. This effect, coupled with an induction of perivascular fibrosis and cell necrosis, results in tumor shrinkage [34].

Even if the effects of the dopaminergic agonists are similar to each other, each agonist has its own specific features. Data published on children and adolescents are still limited.

Bromocriptine. Generally, as in adults, the therapeutic doses of bromocriptine are in the range of 2.5–15 mg/day, with a standard dose between 5 and 7.5 mg/day in split doses. Adverse effects can be reduced by initiating therapy at a single dose of 1.25 mg/day and using an incremental dosage schedule. The evaluation of several series of children and adolescents with prolactinomas treated with bromocriptine as primary drug therapy shows that the mean effectiveness reported in the normalization of PRL serum levels or in the restoration of gonadal function in this population is slightly lower than that observed in adults (67.7%) [34].

Cabergoline. Unlike other dopaminergic agonists, cabergoline has a long half-life, being administered once or

Table 3. Pharmacological therapeutic options

Drug	Dose range	Main adverse effects
Bromocriptine	2.5–15 mg/day	Gastrointestinal: nausea and vomiting. Abdominal pain
Cabergoline	0.5–3.5 mg/week	Cardiovascular: orthostatic hypotension. Cardiac valves alterations (pergolide and cabergoline: long-term and high-dose treatments)
Quinagolide	0.03–0.5 mg/day	Neurological: headache. Drowsiness, dizziness or vertigo. Fatigue or weakness
Pergolide	50–250 µg/day	Psychiatric: exacerbation of psychoses. Mood alterations

twice weekly. The long action of cabergoline is due to its low clearance and slow elimination from the pituitary tissue, to its high affinity binding for D2 dopaminergic receptors and an extensive enterohepatic recycling. In children and adolescents, cabergoline has been used at variable doses (0.5–3.5 mg/week). In our series of 40 peripubertal children with prolactinomas followed up for 2–20 years, cabergoline was used as initial therapy in 7 patients. PRL returned to normal in 6 patients, while moderate hyperprolactinemia persisted in 1 patient. In all cases, either significant tumor shrinkage or complete remission was achieved [14]. Other authors have reported similar experiences as regards the efficacy of cabergoline in the treatment of prolactinomas [18].

Quinagolide. This is a non-ergot dopaminergic agonist, 35 times more potent than bromocriptine and the effective dose ranges from 0.03 to 0.5 mg/day administered orally. In pediatric patients, data are limited. In a series published some years ago, quinagolide (0.075–0.6 mg/day) was administered to 15 bromocriptine-resistant children with prolactinomas. Normalization of PRL levels and tumor shrinkage were achieved in 5 of them; it is likely that the other 10 patients might have been partially resistant to the drug [18].

Pergolide. Pergolide mesylate is a semisynthetic ergot alkaloid derivative, which is 10–100 times more potent than bromocriptine (standard dose: 50–250 µg/day). The tolerability and effectiveness of pergolide are similar to those of bromocriptine, however the data on the effectiveness of pergolide in children and adolescents are limited [34].

In prolactinomas, limiting factors of dopaminergic agonists include, in addition to drug intolerance, the development of resistance because of the intrinsic nature of the tumor, which depends on the density of dopaminergic receptors and its binding agonist affinity. In these pa-

tients, an alternative agonist should be indicated before concluding that the drug therapy is ineffective [2, 35].

As regards the adverse effects of dopaminergic agonists, even if their incidence has not been systematically investigated in the pediatric population, events similar to those observed in adults have been reported. Reported events are mainly gastrointestinal, cardiovascular and neurological. The most common gastrointestinal effects are nausea and vomiting, which are usually transient, although in 3–5% of patients their severity has led to discontinuation of therapy [34]. Orthostatic hypotension occurs in approximately 5% of patients at the initiation of therapy. Exacerbation of preexisting psychosis has been also associated with the use of dopaminergic agonists [36, 37]. A recent report of cardiac valve regurgitation in patients with Parkinson's disease treated with pergolide and cabergoline has raised new concerns about long-term safety of dopamine agonists [38]. Aortic valve calcification and mild tricuspid regurgitation have also been reported in long-term treatment of prolactinomas [39, 40] (table 3).

In hyperprolactinemia due to hypothalamic-pituitary tumors, surgery is an option for extreme cases, depending on the type of tumor and the clinical conditions. In macroprolactinomas, surgery should be reserved for cases in which drug therapy has failed or for neurosurgical emergencies. When surgery is performed, the transsphenoidal approach represents the standard of care, except in little children in whom the sphenoid sinus is not pneumatized [14].

External radiotherapy is rarely used to treat prolactinomas. It is indicated only after failed surgery and/or drug therapy [2]. In our experience, radiotherapy has not been required to treat children and adolescents.

Conclusions

The new concepts gained and a better understanding of the physiology and pathophysiology of hyperprolactinemic conditions have changed the diagnostic and therapeutic options. Diagnosis and follow-up of prolactinomas in pediatric and adolescent age show some gender-

dependent differences in their clinical presentations. These differences cannot be accounted for only in terms of the time of evolution, and suggest a greater aggressiveness in males. In the majority of patients, drug therapy can control the disease effectively, restore PRL levels to normal and achieve gonadotropic axis restoration.

References

- 1 Colao A, Lombardi G: Growth hormone and prolactin excess. *Lancet* 1998;352:1455–1461.
- 2 Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Bronstein MD, Brue T, Capabianca P, Colao A, Fahlbusch R, Fideleff H, Hadani M, Kelly P, Kleinberg D, Laws E, Marek J, Scanlon M, Sobrinho LG, Wass JA, Giustina A: Guidelines of the pituitary of the pituitary society for the diagnosis and management of prolactinomas. *Clin Endocrinol* 2006;65:265–273.
- 3 De Menis E, Visentin A, Billeci D, Tramontin P, Agostini S, Marton E, Conte N: Pituitary adenomas in childhood and adolescence. Clinical analysis of 10 cases. *J Endocrinol Invest* 2001;24:92–97.
- 4 Partington MD, Davis DH, Laws ER Jr, Scheifhauer BW: Pituitary adenomas in childhood and adolescents. Results of transphenoidal surgery. *J Neurosurg* 1994;80:209–216.
- 5 Zhang X, Horwitz GA, Prezant TR, Valentín A, Nakashima M, Bronstein MD, Melmed S: Structure, expression, and function of human pituitary tumor-transforming gene. *Mol Endocrinol* 1999;13:156–166.
- 6 Zou H, McGarry TJ, Bernal T, Kirschner MW: Identification of a vertebrate sister-chromatid separation inhibitor involved in transformation and tumorigenesis. *Science* 1999;285:418–422.
- 7 Heancy AP, Horwitz GA, Wang Z, Singson R, Melmed S: Early involvement of estrogen-induced pituitary tumor-transforming gene and fibroblast growth factor expression in prolactinoma pathogenesis. *Nat Med* 1999;5:1317–1321.
- 8 Zhang X, Horwith GA, Heaney AP, Nakashima M, Prezant TR, Bronstein MD, Melmed S: Pituitary tumor-transforming gene expression in pituitary adenomas. *J Clin Endocrinol Metab* 1999;84:761–767.
- 9 Gürlek A, Karavitaki N, Ansorge O, Wass JA: What are the markers of aggressiveness in prolactinomas? Changes in cell biology, extracellular matrix components, angiogenesis and genetics. *Eur J Endocrinol* 2007;156:143–153.
- 10 Jaffrain-Rea ML, Petrangeli E, Lubrano C, Minniti G, Di Stefano D, Sciarra F, Frati L, Tamburrano G, Cantore G, Gulino AI: Epidermal growth factor binding sites in human pituitary macroadenomas. *J Endocrinol* 1998;7:45–50.
- 11 Fedele M, Pierantoni GM, Visone R, Fusco A: Critical role of the HMGA2 gene in pituitary adenomas. *Cell Cycle* 2006;5:2045–2048.
- 12 Jacks T, Fazeli A, Schmitt EM, Bronson RT, Goodell MA, Winberg RA: Effects of an RB mutation in the mouse. *Nature* 1992;359:295–300.
- 13 Evans CO, Moreno CS, Zhan X, McCabe MT, Vertino PM, Desiderio DM, Oyesiku NM: Molecular pathogenesis of human prolactinomas identified by gene expression profiling, RT-qPCR, and proteomic analyses. *Pituitary* 2008;11:231–245.
- 14 Fideleff HL, Boquete HR, Sequera A, Suárez M, Sobrado P, Giaccio A: Peripubertal prolactinomas: clinical presentation and long-term outcome with different therapeutic approaches. *J Pediatr Endocrinol Metab* 2000;13:261–267.
- 15 Stefaneanu L, Kovacs K, Horvath E, Lloyd RV, Buchfelder M, Fahlbusch R, Smyth H: In situ hybridization study of estrogen receptor messenger ribonucleic acid in human adenohypophysial cells and pituitary adenomas. *J Clin Endocrinol Metab* 1994;78:83–88.
- 16 Kadioglu P, Oral G, Sayitoglu M, Erensoy N, Senel B, Gazioglu N, Sav A, Cetin G, Ozbek U: Aromatase cytochrome P450 enzyme expression in human pituitary. *Pituitary* 2008;11:29–35.
- 17 Burdman JA, Pauni M, Heredia Sereno GM, Bordón AE: Estrogen receptors in human pituitary tumors. *Horm Metab Res* 2008;40:524–527.
- 18 Colao A, Loche S, Cappa M, Di Sarno A, Landi ML, Sarnacchiaro F, Faccioli G, Lombardi G: Prolactinomas in children and adolescents. Clinical presentation and long-term follow-up. *J Clin Endocrinol Metab* 1998;83:2777–2780.
- 19 Melmed S, Kleinberg DL: Anterior pituitary; in Larsen PR, Kronenberg HM, Melmed S, Polonsky KS (eds): *Williams Textbook of Endocrinology*. Philadelphia, Saunders, 2002, p 177.
- 20 Galli-Tsinopoulou A, Nousia-Arvanitakis S, Mitsiakos G, Karamouzis M, Dimitriadis A: Osteopenia in children and adolescents with hyperprolactinemia. *J Pediatr Endocrinol Metab* 2000;13:439–441.
- 21 Naliato ECO, Farias MLF, Violante AHD: Prolactinomas e densidade mineral óssea em homens. *Arq Bras Endocrinol Metab* 2005;49:183–195.
- 22 Bussade I, Naliato ECO, Mendonça LMC, Violante AHD, Farias MLF: Redução da densidade mineral óssea em mulheres na menacme com prolactinoma. *Arq Bras Endocrinol Metab* 2007;51:1522–1527.
- 23 Colao A, Di Somma C, Loche S, Di Sarno A, Klain M, Pivonello R, Pietrosante M, Salvatore M, Lombardi G: Prolactinomas in adolescents: persistent bone loss after two years of prolactin normalization. *Clin Endocrinol* 2000;52:319–327.
- 24 Kane LA, Leinung MC, Scheithauer BW, Bergstrahl EJ, Laws ER Jr, Groover RV, Kovacs K, Horvath E, Zimmerman D: Pituitary adenomas in childhood and adolescence. *J Clin Endocrinol Metab* 1994;79:1135–1140.
- 25 Semple P, Fieggen G, Parkes J, Levitt N: Giant prolactinomas in adolescence: an uncommon cause of blindness. *Childs Nerv Syst* 2007;23:213–217.
- 26 Krassas GE, Pontikides N, Kaltsas T: Giant prolactinoma presented as unilateral exophthalmos in a prepubertal boy: response to cabergoline. *Horm Res* 1999;52:45–48.
- 27 Fabre-Brue C, Roth E, Simonin G, Palix C, Martin PM, Brue T: Macroprolactinemia: a cause of hyperprolactinemia in childhood. *J Pediatr Endocrinol Metab* 1997;10:411–417.
- 28 Fideleff HL, Ruibal G, Boquete H, Pujol A, Sequera A, Sobrado P: Macroprolactinemia in childhood and adolescence: a cause of asymptomatic hyperprolactinemia. *Horm Res* 2000;53:16–19.
- 29 Sapin R, Kertesz G: Macroprolactin detection by precipitation with protein A-Sepharose: a rapid screening method compared with polyethylene glycol precipitation. *Clin Chem* 2003;49:502–505.
- 30 Smith TP, Kavanagh L, Healy ML, McKenna J: Technology insight: measuring prolactin in clinical sample. *Nat Clin Pract Endocrinol Metab* 2007;3:279–289.

- 31 Fideleff HL, Azaretzky M, Boquete HR, Pujol AB, Honfi M, Suárez MG, Fideleff G, Giaccio AV: Tumoral versus non-tumoral hyperprolactinemia in children and adolescents: possible usefulness of the domperidone test *J Pediatr Endocrinol Metab* 2003; 16:163–167.
- 32 Chahal J, Schlechte J: Hyperprolactinemia. *Pituitary* 2008;11:141–146.
- 33 Gillam MP, Molitch ME, Lombardi G, Colao A: Advances in the treatment of prolactinomas. *Endocr Rev* 2006;27:485–534.
- 34 Gillam MP, Fideleff H, Boquete HR, Molitch ME: Prolactin excess: treatment and toxicity. *Pediatr Endocrinol Rev* 2004;2:108–114.
- 35 Colao A, Lombardi G, Annunziato L: Cabergoline. *Expert Opin Pharmacother* 2000;1: 555–574.
- 36 Turner TH, Cookson JC, Wass JA, Drury PL, Price PA, Besser GM: Psychotic reactions during treatment of pituitary tumours with dopamine agonists. *Br Med J* 1984;289:1101–1103.
- 37 Le Feuvre CM, Isaacs AJ, Frank OS: Bromocriptine-induced psychosis in acromegaly. *Br Med J* 1982;285:1315.
- 38 Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G: Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med* 2007;356:39–46.
- 39 Kars M, Delgado V, Holman ER, Feelders RA, Smit JW, Romijn JA, Bax JJ, Pereira AM: Aortic valve calcification and mild tricuspid regurgitation but no clinical heart disease after 8 years of dopamine agonist therapy for prolactinoma. *J Clin Endocrinol Metab* 2008;93:3348–3356.
- 40 Colao A, Galderisi M, Di Sarno A, Pardo M, Gaccione M, D'Andrea M, Guerra E, Pivonello R, Lerro G, Lombardi G: Increased prevalence of tricuspid regurgitation in patients with prolactinomas chronically treated with cabergoline. *J Clin Endocrinol Metab* 2008;93:3777–3784.