Novel Insights from Clinical Practice

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Beneficial Effects of High Doses of Cabergoline in the Treatment of Giant Prolactinoma Resistant to Dopamine Agonists: A Case Report with a 21-Year Follow-Up

Lucas Faria de Castro[a] Maria de Fátima Magalhães Gonzaga[b] Luciana Ansaneli Naves[b] José Luiz Mendonça[c] Benicio Oton de Lima[d] Luiz Augusto Casulari [b]

[a]Medical Clinic Service, Brasília University Hospital, Brasília, Brazil; [b]Endocrinology Service, Brasília University Hospital, Brasília, Brazil; [c]Clinic of Radiology, Brasília, Brazil; [d]Neurosurgery Service, Base Hospital, Federal District, Brasília, Brazil

Established Facts

- Prolactinomas are more common in adults and are associated with hypogonadotropic hypogonadism.
- They are rarely resistant to treatment with dopamine agonists.

Novel Insights

- Prolactinomas may occur in children younger than 10 years old.
- Gonadal function may be preserved despite high prolactin levels.
- The use of cabergoline for several years can lead to a cystic degeneration of the tumor resistant to dopamine agonists, but it cannot be ruled out that this outcome may represent the natural development of the tumor.

Keywords
Prolactinoma · Childhood · Dopamine agonists · Resistance · Treatment

Abstract
Introduction: Prolactinomas are pituitary tumors with a very low prevalence in childhood and adolescence compared to adulthood. This condition is preferentially treated with dopamine agonists. Resistance to these drugs is rare. ***Case Report:*** We describe the case of a boy diagnosed with macroadenoma at the age of 9 and followed up for 21 years. He did not fully respond to treatment with dopamine agonists. His initial prolactin level was 2,400 ng/mL (in males, normal values are <16.0 ng/mL) and never normalized. At the last assessment, his prolactin level was 21.5 ng/mL, recorded after 21 years of treatment with the dopamine agonist cabergoline at a dose as high as 4.5 mg per week. Although the prolactin level remained elevated throughout the follow-up period, the patient never presented a low testosterone level and had normal pubertal development. An MRI of the sella turcica showed that the tumor became progressively cystic

E-Mail karger@karger.com
www.karger.com/hrp

Lucas Faria de Castro
SQNW 310, Bloco A, 514, Setor Noroeste Brasília – DF
Brasília, DF 70687-215 (Brazil)
E-Mail unb.lucas@gmail.com

and disappeared, but a normal pituitary gland was observed. The pituitary gland retained its normal functions despite a partially empty sella. ***Discussion:*** Long-term treatment with high doses of cabergoline may cause cystic degeneration of a prolactinoma considered to be resistant to this treatment, but we cannot rule out the possibility that this outcome represents the natural development of the tumor.

Introduction

Prolactinomas are benign neoplasms originating in prolactin-secreting pituitary cells. Their etiopathogenesis is still unclear but may be related to changes of hypothalamic origin or to monoclonal mutations of the lactotroph [1, 2]. In women, prolactinomas can cause menstrual changes and galactorrhea, whereas in men the main complaint is loss of libido [3].

In a study on the prevalence of pituitary tumors in Liège, Belgium, researchers reported that prolactinomas accounted for 66% of all pituitary tumors; the remaining 34% comprising nonsecretory tumors (14.7%), somatotropinomas (13.2%), and Cushing's disease (5.2%) [4]. Although pituitary adenomas have a much lower occurrence in childhood and adolescence compared to adult life [5], prolactinomas make up approximately 50–70% of the diagnosed pituitary adenomas in individuals younger than 20 years [6–10]. In this age group and in adulthood, these tumors are more common in girls than in boys. At young ages, macroprolactinomas are more prevalent than in adulthood, when microprolactinomas are more frequent [11].

Both young and adult patients are generally responsive to dopamine agonists (DAs), which makes these drugs the first treatment option for prolactinomas [11]. A few studies have evaluated the long-term efficacy of DAs in children and adolescents with prolactinomas [6, 12–14]. In addition, resistance to treatment with DAs, either bromocriptine or cabergoline, is uncommon in these age groups [15, 16].

We report the case of a male patient, diagnosed with a prolactinoma at age 9, who was resistant to treatment with bromocriptine and cabergoline. He was followed up from diagnosis until completion of the last assessment, after 21 years of treatment, when the patient was 30 years old. Clinical evaluation, pituitary function, prolactin levels, and tumor mass behavior in response to treatment with dopamine receptor agonists are discussed below.

Case Report

At presentation, our patient was a 9-year-old male with a history of continuous tension headache for 2 months, with visual loss that was initially bitemporal and evolved to binasal hemianopsia, and short stature. His family history included a 4th-degree cousin who had a pituitary tumor. An MRI showed a tumor mass in the region of the sella turcica, with compression of the optic chiasm and invasion of the cavernous sinus (Fig. 1a). A transcranial biopsy of the lesion was performed, and histochemical analysis showed the presence of a pituitary tumor.

The prolactin levels before and after treatment with bromocriptine are shown in Figure 2. The initial prolactin level was 2,400 ng/mL (normal values in males are <16.0 ng/mL). Treatment with bromocriptine, increasing the dose from 5.0 to 12.5 mg per day, resulted in a decrease in his prolactin level (493 ng/mL), but this value did not return to normal after 34 months of treatment.

The patient was then considered resistant to bromocriptine, and the medication was switched to cabergoline at 1.0 mg per week. Figure 3 shows the effect of cabergoline treatment on the prolactin values. The prolactin level also failed to normalize with this treatment, even when cabergoline was administered at 4.5 mg per week. After 21 years of treatment with DAs, the patient's prolactin level was 21.5 ng/dL. During this time, the patient did not have any complications related to the high doses of DAs, and cardiac valve disturbance was excluded due to 2 normal echocardiographic studies. The first cardiac evaluation was done after 5 years of DA use, and the last after 21 years of follow-up.

At 14 years of age, the height of the patient was 1.52 m, he weighed 48 kg, and was in Tanner's stage III of puberty. At age 15, his height was 1.54 m, showing that height and growth velocity remained low for his age. His IGF-1 level was 170 ng/mL (standard deviation score [SDS] between –1 and 0 to age), which was low for his age. Also, the assessment of growth hormone (GH) secretion with the insulin-induced hypoglycemia test (or insulin tolerance test, ITT) and the clonidine stimulus did not unequivocally show deficient GH secretion [17]. The levels of plasma GH in ng/mL after insulin and clonidine stimulus were <0.05 and 0.05 (basal); 0.05 and 0.05 (after 30 min); 2.3 and 5 (after 60 min); 5.1 and 7 (after 90 min), and 3.3 measured only to insulin stimuli (after 120 min), respectively.

Based on the clinical evaluation of the patient, GH replacement therapy was started with a subcutaneous administration of the hormone at a dose of 5.0 IU per day. When the patient was 16 years old and still receiving GH treatment, his IGF-1 level was 600 ng/mL (SDS +2), which was normal for his age. He reached a final height of 1.64 m. At the last assessment, when the patient was 28 years old, his IGF-1 level was 255.6 ng/mL (SDS +1), a result considered normal for the patient's age group.

The patient developed secondary sexual characteristics without hormonal intervention. At that time, his follicle-stimulating hormone (FSH) level was 2.3 mIU/mL, the luteinizing hormone (LH) level was 2.1 mIU/mL, his testosterone level was 470 ng/dL, the thyroid-stimulating hormone level was 1.6 mIU/mL, his thyroxine level was 1.3 ng/dL, and the cortisol level was 11.3 μg/dL.

An assessment of the testicular function showed that the patient's testosterone levels ranged from 241 to 670 ng/dL, his FSH levels ranged from 1.84 to 3.78 mIU/mL, and his LH levels ranged from 1.2 to 3.49 mIU/mL. The evaluation of the thyroid function was always unremarkable, with thyroid-stimulating hormone lev-

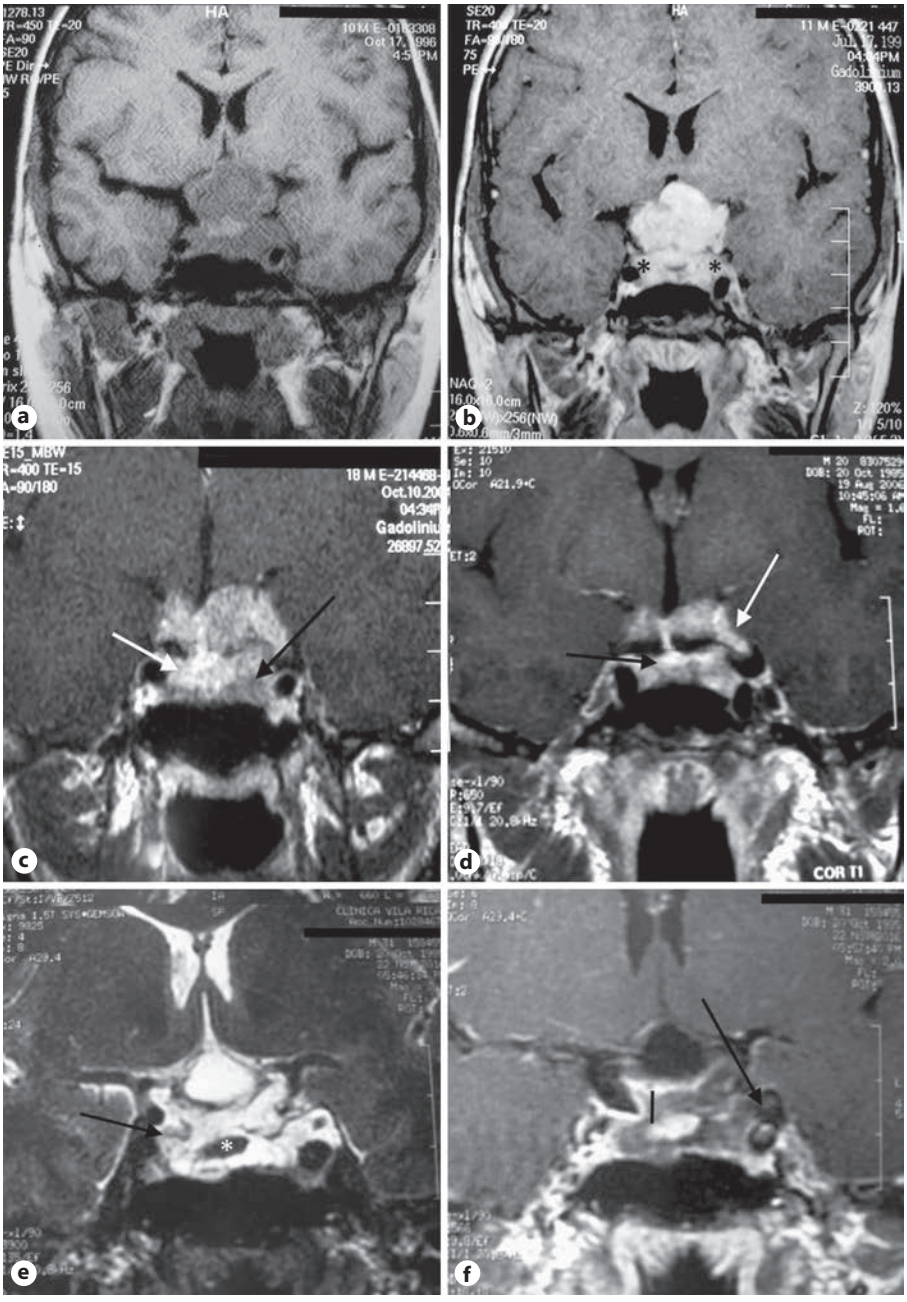

Fig. 1. Magnetic resonance image of the sella turcica before treatment (**a**) and at different time points during the treatment with dopaminergic agonists (**b–f**). **b** Image in T1, with no contrast, showing the pituitary adenoma with bilateral invasion of the cavernous sinuses (*) after 9 months of bromocriptine use. **c** Image taken after 41 months of agonist use (34 months of bromocriptine and 7 months of cabergoline) in T1, showing normal pituitary tissue (white arrow) wrapped by diffuse cystic areas (black arrow). **d** Image taken after 10 years and 3 months of dopaminergic agonist use, showing tumor reduction, but with compression and deviation of the chiasm (white arrow) and deviation of the pituitary stem to the right (black arrow). **e** Contrast image after 14 years of dopaminergic agonist use, showing the increase of the cystic area around the pituitary gland (black arrow); the normal pituitary parenchyma is indicated with the white asterisk. **f** Image obtained after 21 years of dopaminergic agonist use in T2, showing an increase in the suprasellar cistern (black line) and tumor decrease, but with persisting left carotid invasion (black arrow).

els ranging from 1.1 to 3.1 mIU/mL, and free thyroxine levels ranging from 0.9 to 1.3 ng/dL. The assessment of the adrenal function was also considered to be normal, with cortisol levels ranging from 9.7 to 20.9 μg/dL and ACTH levels ranging from 25 to 55 pg/mL. During the ITT, we observed a cortisol concentration of 30 μg/dL. All of these values are within the normal range for age.

When the patient was 28 years old, we performed a genetic evaluation but observed that there were no mutations in the AIP and MEN1 genes. At age 31, the patient was evaluated for the existence of large NEM-1 deletions, but the results were also negative.

At the last clinical evaluation (21 years after the clinical diagnosis), the patient underwent an MRI evaluation (Fig. 1). This image showed a cystic degeneration of the tumor and a partially empty sella, but a normal pituitary gland was observed. Furthermore, normal pituitary function was found. In terms of metabolic assessments, the levels of calcium, phosphorus, parathyroid hormone, total and fraction cholesterol, triglycerides, glycemia, insulin, urea, creatinine and uric acid, as well as liver and renal functions, were all considered unremarkable.

The evolution of the different MRI over time of the sella turcica is given in Figure 1. The patient was evaluated preoperatively

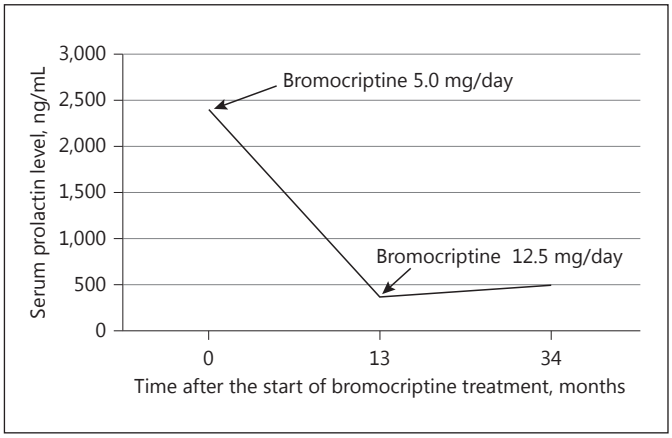

Fig. 2. Variation in serum prolactin levels during the 34 months of bromocriptine treatment. Our patient's prolactin level decreased after 13 months of treatment but remained elevated despite a higher dose (12.5 mg daily).

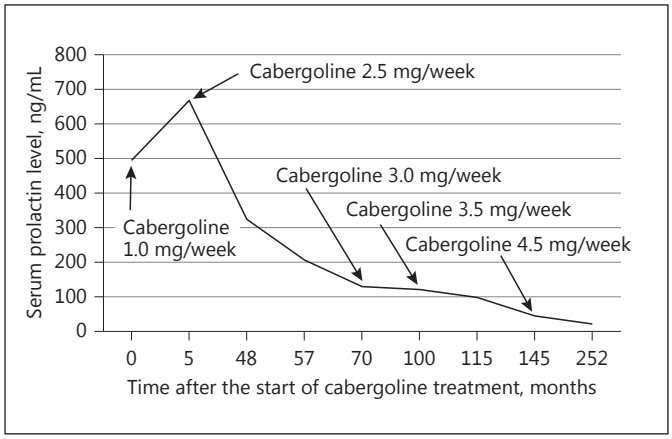

Fig. 3. Variation in serum prolactin levels during the 145 months of cabergoline treatment. Our patient's prolactin level decreased only after 48 months of cabergoline treatment (2.5 mg weekly) but remained elevated. At 252 months (or after 21 years of treatment), even with a cabergoline dose of 4.5 mg weekly, his prolactin levels had not normalized (21.5 ng/mL).

(Fig. 1a), at 9 months of bromocriptine treatment (Fig. 1b), at 41 months of DA treatment, with the last 7 months on cabergoline (Fig. 1c), at 124 months of DA treatment, with the last 90 months on cabergoline (Fig. 1d), at 167 months of DA treatment, with the last 133 months on cabergoline (Fig. 1e), and at 252 months of cabergoline use (Fig. 1f).

The study was approved by the Ethics Committee of the Verhum Clinic, Brasília, DF, Brazil. The patient signed the informed consent form.

Discussion

We present a rare case of a prepubertal, 10-year-old, male patient with macroprolactinoma which was considered resistant to the DAs bromocriptine and cabergoline. The child was followed up for 21 years.

A diagnosis of prolactinoma in an individual under 20 years is very rare [8, 11–14]. The patient described here was 9 years old when the diagnosis of prolactinoma was made. This tumor is very uncommon in children younger than 10 years of age. For example, in a study conducted at 3 French tertiary reference centers over a period of 30 years, only 77 patients younger than 20 years were diagnosed with prolactinomas, and only 2 of these cases reported were in patients younger than 10 years (the patients were 4.5 and 10 years old) [11]. Other studies on prolactinomas in children report the same low frequency: one 10-year-old patient in 41 children [8], one 7.4-year-old patient among 21 observed cases [13], and one 7-year-old patient among 26 diagnosed cases [12].

Male gender is another uncommon characteristic compared to the described cases. In all reports of patients older than 20 years, prolactinoma was more frequent in women [8, 11–14, 18–20]. In the study by Steele et al. [8], for example, of the 29 prolactinoma patients reported, only 1 was a male patient. Saranac et al. [21], however, reported that 5 out of the 11 patients in their study were male.

At the initial presentation, our patient's the main complaint was his short stature. However, he also reported a history of continuous tension headache for about 2 months, in addition to visual loss, which was initially bitemporal and later evolved into binasal loss. The onset of symptoms may occur precociously between 8 and 16 years of age in women; however, the age at diagnosis is usually higher, when patients are between 15 and 19 years old. In males, symptoms can occur between 8 and 17 years of age; however, the diagnosis is usually made when patients are between 13.8 and 19 years old [14]. Also, tension headache symptoms and visual impairment are more frequent in men than in women, which may reflect the higher frequency of macroadenoma in men [11–14]. In girls, symptoms are more related to excessive prolactin, such as menstrual changes and galactorrhea [11, 14, 18, 19]. Galactorrhea and gynecomastia have also been described in men [12, 21] and in obese patients in a small

sample [21], but these conditions were not observed in the patient described here.

Our patient suffered from a pituitary macroadenoma with invasion of the cavernous sinus on both sides and compression of the optic chiasm (Fig. 1). Some studies reported that macroadenomas occur more frequently in males [11, 12, 14, 22], and other studies reported no microadenomas in male patients [19, 20]. The most plausible explanation for this difference between genders is a variance in tumor biology, also observed in adults, which may involve estrogenic differences [22, 23].

Prolactinomas should preferentially be treated with DAs [24]. In older case studies, bromocriptine was the most commonly used drug [14, 18], and quinagolide was used in cases of resistance to bromocriptine [12]. Studies with long-term follow-up showed that treatment with bromocriptine [12, 18] or cabergoline [12, 20] preserved the reproductive ability in men and women [18] and prevented complications during pregnancies [12, 18, 20].

Another peculiar characteristic of our case was the resistance to both bromocriptine and cabergoline, as most prolactinoma patients in childhood and adolescence [13, 14, 18, 20] and adulthood [2, 24] respond to treatment with these DAs. Resistance to bromocriptine is defined as the absence of normalization in prolactin levels when patients are treated with the maximum tolerable dose or with 15 mg daily [25, 26]. On the other hand, resistance to cabergoline is defined as the lack of normalization in prolactin levels and no decrease in tumor mass by at least 50% at a dose of 2.0 mg per week [23, 26–28]. Our patient met these criteria for both agonists.

The recommended treatment for patients resistant to bromocriptine is to switch to cabergoline [26], as was done in our patient. However, our patient did not respond to treatment with cabergoline either (Fig. 2, 3). Cases of pituitary adenomas resistant to DAs in young patients are associated with age, a higher concentration of prolactin, and tumor size [11], and all of these conditions were present in our patient.

Treatment of macroprolactinomas with cabergoline has been shown to lead to a decrease in tumor size by more than 80% in most patients (61%) within 6 months to 2 years [29] after starting the treatment. Other authors have also shown this effect in patients younger than 20 years [11–14, 20, 21]. However, despite the use of bromocriptine for 34 months and cabergoline for 252 months at high doses (4.5 mg per week), the tumor in our patient did not disappear, but rather it became cystic. In an analysis of prolactinoma cases resistant to cabergoline, we noticed that the tumor disappeared in only 19% of the cases: 35.7% of which were microadenomas and 15.1% were macroadenomas, with residual adenoma in 53.3% among the macroadenomas and 26.7% among the microadenomas [23]. It has been suggested that a decreased tumor size in response to bromocriptine treatment could be due to the direct action of this molecule on the tumor. However, it may be that a decrease or cystic degeneration of the adenoma is its natural development [30]. Bromocriptine has a decreasing effect on prolactinomas by exerting an inhibitory action on mitosis and tumor cell growth, and by inducing perivascular fibrosis and cellular necrosis [22]. This could explain the cystic degeneration observed in our patient's tumor. The prolactinoma of our patient may be considered to be partially resistant to DAs because cystic degeneration of the tumor occurred and our patient's prolactin level dropped to 22.5 ng/mL. In addition, the tumor did not grow during treatment as may happen in cases of complete resistance to agonists [23, 26]. This last fact enabled us to treat our patient with clinical measurement only, without considering surgical options which are reserved for tumors that continue to grow [23, 26]. Interestingly, our patient had an affected 4th-degree cousin whose tumor was resistant to bromocriptine and cabergoline.

In another study, a macroprolactinoma resistant to cabergoline was described in an 11-year-old boy who had multiple endocrine neoplasia type 1 (MEN1) [31]. Mutations in the AIP or MEN1 genes have been found in 14% of all patients younger than 20 years with macroprolactinoma. A mutation in MEN1, but not in AIP, has been associated with resistance to cabergoline [11]. In our patient, we found no mutation in these genes.

At presentation, our patient was below the 3rd percentile for height for his gender and age. During the first year of treatment, his growth rate remained low, and he was diagnosed as having GH deficiency. He then started GH replacement therapy, which was maintained until the age of 16 years. Growth deficiency has been reported in another study [11] in 24% of all patients with similar characteristics to those of our patient, in 4 patients in a group of 11 children [21], and in only 1 individual among a sample of 26 adolescents [12]; however, other authors found no growth deficiency in a study with 39 children [20].

Stimulatory tests for the evaluation of GH secretion did not show unequivocal hormone deficiency responses: ITT had a maximum GH peak of 5.1 ng/mL and of 7.0 ng/mL after clonidine. Both occurred within 90 min of the start of the tests, which has been described as the best time to evaluate the response to clonidine [32]. According to a study review by Araújo et al. [17], GH stimulation tests

are subject to criticism for several reasons. These tests are not physiological, abnormal responses to the stimuli are arbitrary (they can be <10, 7, 5, or 3 ng/mL), healthy children may have inadequate responses, there is assay variability for GH levels, and there is a weak correlation between test responses and growth. For example, children treated for acute lymphoblastic leukemia with chemotherapy and radiotherapy of the central nervous system may develop GH deficiency [33, 34]. The predictive value for height <10th percentile was 33% for ITT and 28% for clonidine, when considering a GH peak of <5 ng/mL. When this peak was 7.0 ng/mL, the positive predictive value for ITT was 83% and 50% for clonidine. Thus, in patients treated for acute lymphoblastic leukemia, the value of these tests for the diagnosis of GH deficiency was not good, especially compared to clonidine [33].

Based on this, we considered that our patient had a short stature and a delayed growth rate, and hormone replacement therapy was started. The patient only showed a partial response, as he did not reach his expected height. This may have been due to a delay in GH replacement therapy (started at 14 years) and due to the facts that he had no sex hormone deficiency and that his bone maturation was not delayed.

Our patient's IGF-1 level at the age of 28 years was normal. It is known that some patients who have GH deficiency and received treatment present normal values when submitted to new stimulation tests [35]. In addition, the fact that the patient had a large tumor could have compromised his GH secretion level. Thus, after the tumor had partly decreased, GH secretion may have improved. This has been described in other prolactinoma cases in childhood [18]. However, some patients have been reported to have become GH deficient in adulthood despite DA treatment [12].

Another interesting fact is that our patient never presented altered testosterone, FSH, and LH secretion levels, even when prolactin reached high levels. This was surprising because hyperprolactinemia blocks the secretion of FSH and LH by exerting an inhibitory action on the hypothalamic gonadotropin-releasing hormone, which decreases the production of kisspeptin by the arcuate and paraventricular nuclei of the hypothalamus [for reviews, see 22, 36]. Therefore, a delay in the onset of puberty is a very frequent manifestation in both males and females [11, 14, 18, 21] but is not always present [12, 20]. When treated with bromocriptine [11, 14, 18] and cabergoline [11, 12, 14], most patients have a normal puberty. However, the patient described here had a puberty and normal testicular development until the last evaluation at age 30 years despite his hyperprolactinemia (22.5 ng/mL). Our patient's tests for macroprolactin were always negative, and no other form of prolactin was evaluated. It is possible that high prolactin levels may explain the lack of signs and symptoms in patients with hyperprolactinemia [37]. We have no other explanation for this situation, and, to the best of our knowledge, no such case has been described to date.

Other alternatives for the treatment of tumors resistant to DAs include transsphenoidal surgery which, in a few cases, improved the response to these molecules [23]. Radiotherapy has been shown to control prolactin levels in a few patients, including some with DA suspension [38], but this has not been observed by others [23].

Our patient was initially submitted for transcranial surgery because the diagnosis of prolactinoma had not been considered, probably due to the fact that pituitary adenomas are a rare pathology in childhood. It is, therefore, recommended that patients with a mass in the sellar, parasellar, or suprasellar region that invades adjacent structures undergo hormonal evaluation for the identification of secretory pituitary adenomas. In our case, the procedure was indicated due to the presenting symptoms associated with tumor invasion and also due to biopsies of the lesion. The tumor was carefully resected near the eye, and the material was sent to be histopathologically analyzed.

Surgery as primary treatment has most frequently been reported in older studies [14], taking into account the compressive symptoms. However, the results were not good: of 9 patients undergoing surgery, only 1 presented restored gonadotrophic function [14]. In another study, surgery for microadenomas was associated with a cure rate of 70%, but 25% of the patients experienced recurrence. The same study reported a cure rate of 33% for macroadenomas and a long-term recurrence rate of 33% [19]. Another study reported poor surgical outcome and a recurrence rate of 67% in children with prolactinoma [39]. Surgery may also require complementation with cabergoline treatment or radiotherapy [13, 40]. However, an important observation was that patients that underwent surgery for the partial removal of the tumor had an improved response to DAs [23]. Promising surgical outcomes have also been described [41].

In summary, during 21 years of follow-up, the prolactin levels in our patient never normalized. We registered a level of 22.5 ng/mL at the last evaluation, at a time when the patient was treated with 4.5 mg cabergoline per week. However, our patient never developed hypogonadotropic hypogonadism, as is frequently the case in hyperprolac-

tinemia patients. His initial GH deficiency regressed, as shown by the normalization of the IGF-1 levels. The tumor has become predominantly cystic, which may reflect the long-term action of DA therapy despite the resistance of the tumor. However, we cannot rule out that this outcome may reflect the natural history of the tumor, as suggested by other authors [30].

We conclude that the medical treatment of prolactinomas resistant to DAs may have good long-term results without the need for surgery or radiotherapy, which may potentially lead to significant morbidity in patients with pituitary macroadenomas.

Disclosure Statement

All authors declare that they do not have any conflicts of interest.

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