Pubertal arrest secondary to untreated giant prolactinoma
Detención puberal secundario a prolactinoma gigante no tratado

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ABSTRACT
The most common pituitary tumors are prolactinomas which are rarely found in children and adolescents. Similarly, hyperprolactinemia is a rare endocrinopathy in childhood. The hypersecretion and production of prolactin as well as the compression produced by prolactinoma compromises the functioning of the hypothalamic-pituitary-ovarian axis, probably due to impaired gonadotropin pulsatility, together with the presence of adrenal and thyroid insufficiency. This functional syndrome may cause delayed puberty, primary or secondary amenorrhea, galactorrhea, and pubertal arrest. The onset of telarche and puberty is age appropriate, but arrest of pubertal development before menarche is a rare disorder known as pubertal arrest. Dopaminergic agonists are the first choice of treatment. A case of pubertal arrest secondary to untreated giant prolactinoma is presented.

Key words: Puberty arrest, Prolactinoma, Hyperprolactinemia

INTRODUCTION
Pituitary microadenomas are more common than macroadenomas and more frequent in women. Prolactinomas are the most common pituitary tumors and account for approximately 40% of all pituitary adenomas(1). The resulting hyperprolactinemia can cause primary amenorrhea, pubertal arrest and delayed puberty in adolescents(2). Pubertal arrest secondary to hyperprolactinemia is a rare condition characterized by the onset of telarche and puberty at appropriate ages, but with absence of menarche. Treatment with dopaminergic agonists should be initiated regardless of the size of the adenoma(3). A case of pubertal arrest secondary to untreated giant prolactinoma is presented.

CASE REPORT
A 20-year-old female patient presented with headaches, amenorrhea and visual disturbances of 3 years of evolution. The patient had been diagnosed with prolactinoma 5 years before, being treated with cabergoline and levothyroxine for 14 months, discontinuing the treatment due to economic problems. She referred pubarche at 12 years old and telarche at 13 years old. She denied a history of hot flashes, hirsutism, virilization and galactorrhea. Her birth weight was 4,500 grams and height was 52
centimeters. The paternal and maternal heights recorded were 184 centimeters and 169 centimeters, respectively. Both parents were healthy and denied family history of endocrine disorders.

On physical examination, the patient was in good general condition with a weight of 60 kilograms and height of 165 centimeters (body mass index 22.1 kg/m²). The breasts and axillary-pubic hair corresponded to stages 3 and 4 of the Tanner scale, respectively. The external genitalia showed normal development on visualization, but pelvic examination revealed a slightly atrophic vagina and small uterus. She had no galactorrhea, hot flashes, virilization or hirsutism. Visual defects and diplopia were detected on visual field examination.

Pelvic ultrasound showed a hypoplastic uterus with a length of 43 millimeters and right and left ovarian volumes of 3.0 and 3.5 mL, respectively. Magnetic resonance imaging revealed the presence of a pituitary tumor measuring 40 x 32 x 27 millimeters in diameter filling the suprasellar cistern with compression of the optic chiasm (Figure 1). Laboratory alterations were compatible with persistent panhypopituitarism (Table 1). The karyotype was 46.XX. Skull radiography was normal. In view of the findings, the possibility of pubertal arrest secondary to untreated prolactinoma with suppression of the hypothalamic-pituitary axis was considered.

The patient restarted treatment with carbegoline, hydrocortisone and levothyroxine, hoping to trigger ovulation and menstruation. The hormonal profile at 6 months showed normalization of prolactin and thyroid hormone concentrations (Table 1). However, serum estrogen concentrations remained slightly below normal values, despite normal serum concentrations of progesterone, follicle-stimulating hormone and luteinizing hormone. The prolactinoma decreased in size to 14 x 12 x 10 millimeters with disappearance of the visual alterations. However, after 13 months of treatment, amenorrhea persisted. The patient continues to be followed up and treated on an outpatient basis.

Figure 1. Magnetic resonance images. The arrow points to the pituitary tumor mass of 40 x 32 x 47 mm with compression of the optic chiasm and suprasellar extension.
**DISCUSSION**

Prolactinomas are the most frequent pituitary adenomas. On the other hand, hyperprolactinemia produces less than 1% of cases of primary amenorrhea\(^\text{!!}\). Although they are more common in females, they are rare in puberty and can manifest as pubertal arrest. In such cases, although patients attain telarche, adrenarche and pubertal growth, prolactinoma results in arrest of pubertal development just prior to menarche\(^\text{5}\). Hyperprolactinemia inhibits the functioning of the hypothalamic-pituitary-ovarian axis, probably due to altered gonadotropin pulsatility, together with the presence of adrenal and thyroid insufficiency.

Giant prolactinomas may induce primary hypothyroidism because enlargement of the pituitary causes thyrotrophic hyperplasia and predisposes to the development of thyrostimulating hormone-secreting pituitary adenomas\(^\text{6}\). It may also be secondary to increased hypothalamic release of thyrotropin-releasing hormone or disruption of hypothalamic dopamine as a result of pituitary expansion\(^\text{7}\).

Serum prolactin concentrations increase slightly at the time of puberty in normal girls. However, the mechanism by which excessive prolactin concentrations in adolescence result in delayed menarche is unknown. One hypothesis suggests that elevated concentrations could interfere directly or through modification of neurotransmitter turnover with hypothalamic release of gonadotropin-releasing hormone or desensitize pituitary gonadotropin cells, leading to decreased gonadotropin secretion, interfering with ovarian steroid production\(^\text{8}\).

The symptoms produced by giant prolactinomas can vary depending on the age and sex of the patient. While it can cause hypogonadism, loss of libido and infertility, it can also induce, on rare occasions, delayed or arrested puberty and short stature in girls and adolescents\(^\text{2}\). The main cause of pubertal arrest is hypogonadism related to inhibition of gonadotropin-releasing hormone due to hyperprolactinemia. However, it can also be secondary to tumor compression, as somatotroph and gonadotroph cells are more susceptible to damage secondary to compression than to tumour compression\(^\text{9}\).

Galactorrhea is the most important manifestation for the suspicion of hyperprolactinemia and is present in 84% of patients with giant prolactinomas. Patients with primary amenorrhea associated with hyperprolactinemia without galactorrhea may be considered more common than previously thought\(^\text{8}\). Hypoplasia of the internal reproductive organs is a recognized consequence of pubertal arrest. This condition associated with hyperprolactinemia is more common at younger ages\(^\text{5,10}\). The uterus increases between 30 and 60 millimeters in size during puberty in response to estrogens. The ovaries also increase in size due to the effect of gonadotropins. Untreated hyperprolactinemia alters estrogen concentrations and inhibits ovarian and uterine growth. On the other hand, the uterus is more sensitive to the effects of estrogens compared to the breast and other peripheral tissues\(^\text{10}\). Hypogonadotropic hypogonadism at critical stages of puberty, together with low thyroid and growth hormone concentrations, may contribute to these alterations.

The optimal treatment of pubertal arrest due to prolactinomas or hyperprolactinemia is difficult to establish, due to the few cases described. These patients should be treated as early as possible due to their severe clinical consequences\(^\text{8}\). The treatment of girls and adolescents with primary amenorrhea should be the same as that of adult women with secondary amenorrhea due

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Pre-treatment values</th>
<th>Post-treatment values</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin, ng/mL</td>
<td>196</td>
<td>23</td>
<td>12 - 20.0</td>
</tr>
<tr>
<td>Follicle-stimulating hormone, IU/L</td>
<td>15.1</td>
<td>10.7</td>
<td>3 - 22</td>
</tr>
<tr>
<td>Luteinizing hormone, IU/L</td>
<td>5.0</td>
<td>5.6</td>
<td>3 - 10</td>
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<tr>
<td>Thyrostimulating hormone, mIU/mL</td>
<td>1.0</td>
<td>21</td>
<td>0.4 - 6.0</td>
</tr>
<tr>
<td>Free T4, ng/mL</td>
<td>0.6</td>
<td>1.8</td>
<td>0.8 - 2.2</td>
</tr>
<tr>
<td>Estrogen, pg/mL</td>
<td>20.6</td>
<td>23.0</td>
<td>25 - 400</td>
</tr>
<tr>
<td>Progesterone, pg/mL</td>
<td>2.9</td>
<td>3.5</td>
<td>2 - 25</td>
</tr>
<tr>
<td>Cortisol 8 am, picog/dL</td>
<td>5.2</td>
<td>11.0</td>
<td>6 - 18</td>
</tr>
</tbody>
</table>

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**Table 1. Hormonal values before and after treatment.**
to hyperprolactinemia. Dopaminergic agonists (bromocriptine and cabergoline) normalize serum prolactin concentrations with great efficacy and safety, with few adverse reactions in adolescent girls[1,11].

Several studies have shown that dopaminergic agonists are also effective and safe in patients with prolactinomas. In cases of giant pituitary tumors, higher than conventional doses may be necessary to obtain biochemical and clinical responses[12]. In cases of giant prolactinomas, the dose should be gradually increased until the effective dose is reached. The goal is to minimize the side effects of high dose treatment, such as tumor herniation with compression of the optic chiasm and pituitary apoplexy[13].

There are reports of resolution of pubertal arrest with growth of the reproductive organs at early ages following treatment with dopaminergic agonists[5,10]. In cases where amenorrhea persists despite normalization of hormone concentrations, treatment with gonadotropin-releasing hormone analogues and/or estrogens may be useful. However, because of the unclear relationship between estrogens and the development of pituitary adenomas, oral contraceptives should probably not be administered to induce menstrual cycles or as contraceptives in this group of patients[8].

In those cases with prolactinomas resistant to dopaminergic agonists, surgical debulking of these tumors may be chosen to prevent pituitary apoplexy or to ensure rapid optic decompression and improve vision[14]. However, surgical resection is difficult in cases of giant tumors due to the suprasellar, parasellar and infrasellar extension of the tumor and biochemical cure is rare, even if tumor resection is complete. Many patients require pharmacological treatment after surgery[15]. In addition, the possibility of developing panhypopituitarism should be considered.

In conclusion, pubertal arrest caused by prolactinomas is a rare disorder characterized by the absence of menarche after telarche and puberty. Giant prolactinomas are rare tumors seen in adolescents that can induce pubertal arrest through tumor expansion and effects of hyperprolactinemia by inhibiting gonadotropin-releasing hormone activity. First line treatment is with dopaminergic agonists.

References


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