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Clinical Case Seminar CCS5 (1-5)

Atypical onset of prolactinoma in an adolescent girl

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Abstract

Prolactin is one of the main pituitary hormones secreted from the pituitary gland and plays an important role in reproductive functions. Hyperprolactinemia (HPRL), with a prevalence of 0.4% to 5%, is considered a frequent endocrinopathy, although rare in childhood. HPRL can be related to pathological conditions, such as tumors (adenoma) or systemic diseases. With respect to prolactinomas, clinical signs manifest with mass compression of the optic chiasm and/or anterior pituitary gland and PRL hypersecretion. Here we report a case of a15-year old girl who came to our observation due to severe episodes of headache(every 3 days) during the last year, accompanied by two incidents of amaurosis (lasting 5-10 minutes, with spontaneous resolution) and also lately spontaneous galactorrhoea (for 1 month). Brain MRI identified a "pituitary microadenoma (6 mm), with minimal blood component in context and sinking the floor of the *sella turcica*". The patient underwent neurosurgical evaluation, which excluded pituitary apoplexy. She started medical treatment with cabergoline (0.25 mg twice a week), with progressive resolution of symptoms and normalization of prolactin levels. Although prolactinoma is a rare condition in pediatric patients, it must be considered as a possible diagnosis in presence of galactorrhoea and headache, even without irregularities of the menstrual cycle.

Key-Words: prolactinoma, galactorrhoea, pituitary apoplexy, cabergoline.

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Introduction

Prolactin (PRL) is one of the main pituitary hormones secreted from the pituitary gland and plays an important role in reproductive functions. Hyperprolactinemia (HPRL), with a prevalence of 0,4% to 5%, is considered a frequent endocrinopathy, although rare in childhood (1-2).

A number of physiological states including pregnancy, breast-feeding, stress, exercise and sleep can cause prolactin elevation, but the most frequent cause of non-tumoral HPRL is medications, with neuroleptics/antipsycotic agents being the most common, followed by antidepressant, opiates, cocaine, gastrointestinal medications (metoclopramide, domperidone and ranitidine) and antihypertensives (verapamil, methyldopa) (3,4). Moreover, renal insufficiency may lead to HPRL caused by decreased dopaminergic tonus due to uremia and diminished prolactin excretion (3).

Primary hypothyroidism may also lead to moderate HPRL due to the stimulating effect of Thyrotropin-stimulating hormone (TSH) on lactotrophic cells (3,4).

However, HPRL can be related to hypothalamic disease (such as craniopharyngiomas), by inhibiting dopamine secretion, and pituitary disease, where prolactinoma represents one of the most frequent forms of pituitary adenoma (3)

With respect to prolactinomas, clinical signs manifest with mass compression of the optic chiasm and anterior pituitary gland or PRL hypersecretion. As reported in current literature, headache is the most common complaint followed by vision impairment in cases where the tumor is enlarged (3).

In childhood and adolescence, menstruation disorders and galactorrhea are the most common signs in girls, while delayed puberty is usually observed in boys (3).

In cases where PRL concentration is extremely high (>100 ng/ml; normal range 5-20) and/or associated with clinical symptoms, a single measurement could be sufficient to diagnose HPRL (5).

Moreover, it is important to consider that for an adequate PRL measurement, the blood sample should be drawn after a 30-min rest in the supine position, without stress, after a night's fasting or at least 1 hour after eating. Where there is doubt, two or three blood samples should be drawn at 15-20 min intervals after the application of an intravenous catheter (3).

When secondary causes of HPRL have been excluded, imaging studies such as CT (Computed Tomography) and/or MRI (Magnetic Resonance Imaging) should be performed.

However, enlargement of pituitary gland does not always suggest an adenoma, but it may be due to lactotroph hyperplasia during physiological conditions (puberty, lactation, pregnancy).

While for asymptomatic HPRL female patients (due to idiopathic HPRL or pituitary microadenomas) monitoring without any pharmacological treatment can be sufficient, symptomatic patients should receive medical treatment.The gold standard medical primary therapy is with dopamine agonists (DA) (Cabergoline, Bromocriptine) (6).

Surgery with a transsphenoidal approach, followed by low-dose of DA agonist, is offered to children who do not respond to sole medical treatment or in cases of pituitary macro adenoma with crucialvisual preservation. Unfortunately, sucho perative intervations are associated with higher risk of morbidity due to iatrogenic hypopituitarism (3).

Case Report

A 15-year old girl came to our observation due to severe headache occuring every 3 days over the last year with resolution after Ketoprofen administration. During the last year two episodes of amaurosis (lasting respectively 10 and 5 minutes) with spontaneous resolution were observed. Moreover, for about a month referred spontaneous galactorrhoea.

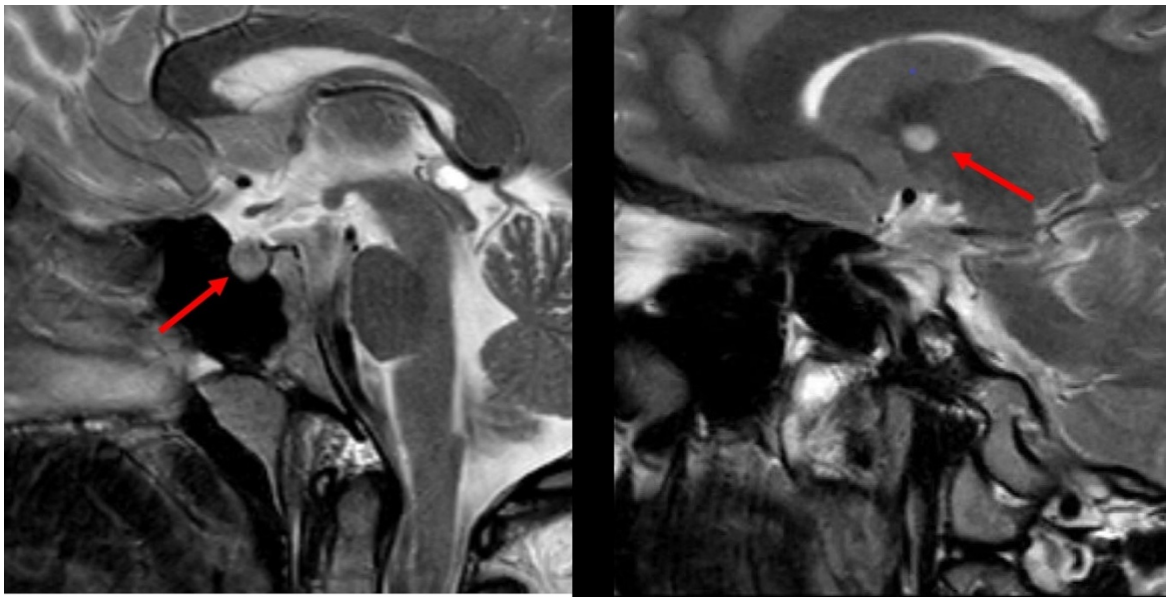
She had a three-year gynecological life with regular menstrual periods. Based on the anamnesis, there was no evidence of chronic assumption of drugs with possible hyperprolactinaemic action.

Table 1 Results of PRL serum levels in our patient

Time of blood sampling	Prolactin (µUI/ml)
0’	2124.00
30’	2055.00
60’	1943.00
Normal range	[N.V. 102.0-496.0]

At physical examination, we discovered the presence of milky secretion following the squeezing of both nipples. Seriated PRL samples showed persistently high values (Table 1). The possibility of a genetic component of prolactinoma has not been investigated, because the parents did not give informed consent. Mammary ultrasound showed “enhanced fibroglandular component and slight bilateral ductal ectasia, more evident in the left side. Axillary lymph nodes with general features of reactivity” and negative mammary secretion swab. Brain MRI identified a “pituitary microadenoma (6mm), with minimal blood component in context and sinking the floor of the *sella turcica*. As casual finding, in left nucleo-capsular region a circumscribed roundish lesion (6 mm), hyperintense in long TR scans, compatible with hamartoma”*(Figure 1).* The patient underwent neurosurgical evaluation, which excluded the pituitary apoplexy. She started medical treatment with cabergoline 0.25 mg twice a week, with progressive resolution of symptoms and normalization of prolactin levels. A successive neuroradiological evaluation showed a regression of the size of the microadenoma. Now, she is still in therapy with cabergoline.

Figure 1. On the left: pituitary microadenoma. On the right: left nucleo-capsular lesion, probable hamartoma.



Discussion

Although pituitary adenoma is a rare condition in pediatric patients, it must be considered as a possible diagnosis in presence of galactorrhoea and headache, even without irregularities of the menstrual cycle. In the presence of this main symptom, the diagnostic procedure should be started

immediately. Other symptoms, not pathognomonic, but typical in cases with midline lesions are headache and vision impairment. In these patients it is necessary to proceed with neuro-radiological examination to confirm the diagnosis of prolactinoma.

Given the young age of the girl, we could have also considered investigating a genetic component responsible for tumor development. In fact, genes known to be involved in pituitary tumorogenesis include aryl hydrocarbon receptor interacting protein (AIP) and multiple endocrine neoplasia type 1 (MEN1) mutations, which are usually associated with various subtypes of pituitary adenoma (7). Unfortunately, we had no immediate possibility of executing a genetic investigation, because the parent did not give the permission.

Otherwise, a condition that should be excluded in thesec cases is the pituitary tumour apoplexy, a rare endocrine emergency resulting from ischaemia and necrosis of a pituitary tumour, requiring life saving rapid replacement with hydrocortisone (8). Sudden onset of headache, nausea, vomiting, deterioration of visual eld and acuity and even blindness, diplopia, ophthalmoplegia, and altered mental status are the most common presentations of pituitary apoplexy (9).

Apoplexy may occur spontaneously or as a result of numerous predisposing factors, but for the majority of patients it does not have any specific cause. Infarction of pituitary adenomas is the product of an imbalance between their high rate of demand for nutrients and their inherently limited blood supply that makes them vulnerable to infarction. Administration of DAs is one of the known risk factors for pituitary apoplexy because it promotes tumor regression due to lactotroph cell size reduction and degenerative and necrotic changes in tumor cells (9).

In our patient, the presence of amauroris in absence of other clinical signs of emergency and a neuro-chirurgical consultation allowed us to exclude the presence of this condition. In addition, there was no evidence of involvement of antero-pituitary functionality.

Usually, follow-up includes periodic PRL evaluation and MRI control. Discontinuation of DA therapy is indicated after at least 2 years of treatment, normalization of PRL levels, and no more MRI image of pituitary adenoma (7).

Due to the rarity of the pathology in pediatric age and peculiarity of the case, we consider its description in the literature useful for its didactic value.

Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant.

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