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Clinical manifestations, evaluation and management of hyperprolactinemia in adolescent and young girls: a brief review

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Summary. Hyperprolactinemia (HPrl) is considered as a rare endocrinopathy in childhood. In children and adolescent girls, there are three major categories of HPrl causes; physiological, pathological and iatrogenic. Through hypogonadotropic hypogonadism, prolactin hypersecretion and production leads to the typical functional syndrome which is observed in female children and adolescents; delayed puberty, primary or secondary amenorrhea and/or galactorrhea. Regarding prolactinomas, clinical signs manifest with mass compression of the optic chiasm and anterior pituitary gland or prolactin hypersecretion. Targeted identification of HPrl is of significant importance for proper management and follow-up. The aim of this review is to focus on the evaluation of HPrl in adolescent and young girls. In addition, we aimed to summarize the current knowledge regarding the proper management of such cases. (www.actabiomedica.it)

Key words: hyperprolactinemia; adolescent girls; visual field defects; dopamine agonists

Introduction

Hyperprolactinemia (HPrl) with a prevalence of 0.4% to 5% is considered a frequent endocrinopathy, although rare in childhood. Prolactin is one of the major pituitary hormones that is secreted from the pituitary gland and plays an important role in reproductive functions. The normal serum prolactin concentration level in female children and adolescents is between 5 and 20 ng/ml (1, 2).

Prolactin is produced from the lactotropic cells of the anterior pituitary lobe in response to a singular and unique tonic inhibitory (dopamine) signal that is prevalent on the stimulatory TRH (thyrotropin-releasing hormone) hormonal signals (3).

The elevated prolactin levels in interruption of peduncle or in obstruction of portal venous system is due to loss of inhibitory action of dopamine.

Several agents such as stress, suckling, estrogens, TRH, vasoactive intestinal polypeptide (VIP) and oxytocin, among others, act as stimulants of prolactin release directly to anterior lobe or by reducing the inhibitory action of dopamine (3, 4).

The primary activity of prolactin is its lactotrophic effect on the epithelium of the mammary gland as well as regulating gonadal function by inhibiting GnRH excretion and secretion of Follicle stimulation hormone (FSH) and Luteinizing hormone(LH) (5, 6). Interestingly, prolactin also demonstrates regulatory effects in the immune system, lactation, adipose tissue and insulin secretion (7-9).

The clinical manifestations of HPrl are various but usually specific and easy to recognize only in adolescence, while in childhood onset symptomatology is neurologic with headache and visual deficit. Once the presence of prolactin hypersecretion is identified,

further evaluation to establish the underlying cause is necessary in order to preserve and restore normal growth potential early in childhood (1, 2). In general, there are three major categories of HPrl causes in childhood: physiological, pathological and iatrogenic.

The aim of this review is to focus on the evaluation of HPrl in adolescent and young girls. In addition, we aimed to summarize the current knowledge regarding the proper management of such cases.

Etiology and risk factors

There are several different conditions that are linked to prolactin over production and secretion.

Natural causes include the circadian rhythm, where an acrophase shift is observed during morning hours (2.00 am to 5.00 am). Prolactin concentration elevates in several conditions such as during Rapid eye movement (REM) sleep, physical activity, high-protein diet, hypoglycaemia, stress (before and during venipuncture procedure) and pregnancy. Pathological conditions of HPrl can be divided into three groups; tumors, systemic diseases and miscellaneous (1, 2).

Although rare, pediatric prolactinoma represents one of the most frequent forms of pituitary adenoma (10). Pituitary adenomas in children and adolescents are benign disorders with an estimated incidence of 0.1/1,000,000 (11). These tumors may be hormone-secreting (e.g. prolactinoma) or non-hormone-secreting (e.g.incidentalomas) (12).

Pediatric prolactinoma predominantly is detected in early puberty. The exact etiology remains enigmatic although in most of the cases they are sporadic forms. Girls are affected more frequently with microadenomas (<10 mm in diameter) where prolactinomas tend to be smaller and less aggressive compared with boys.

Clinical symptoms, prolactin hypersecretion and typical brain magnetic resonance imaging (MRI) findings confirm the diagnosis. Pediatric prolactinoma may also coexist with hormonal deficiencies in thyroid stimulating hormone (TSH) and growth hormone (GH) which is more common in macroadenomas (10-40 mm) (13).

Notably, incidentalomas are asymptomatic pituitary lesions that are more prominent in children than prolactinomas and they should also be taken into consideration (14).

Other lesions, like congenital colloid cyst, may also cause HPrl due to obstruction of portal venous system termed as "pseudoprolactinomas" (5). Systemic diseases include a variety of conditions causing HPrl. Chronic renal failure can cause HPrl due to reduction of prolactin clearance. Polycystic ovarian syndrome (PCOS) induces HPrl as a result of stress, obesity and hypoglycaemia (6). Additionally, endocrine disorders like Cushing's disease and Addison's disease may also result in increased lactotropin secretion (10). Recently, Sharma LK et al. (15) detected in a cohort study that HPrl accompanies a third of children with subclinical hypothyroidism and >50% of children with overt hypothyroidism.

Miscellaneous conditions include genetic syndromes such as multiple endocrine neoplasia type 1 (MEN 1) and McCune-Albright syndrome (MAS), inflammatory diseases (lymphocytic hypophysitis, meningitis), injury of pituitary infundibulum and seizures (epilepsy, febrile seizures) (3, 6, 10).

Iatrogenic HPrl may be induced due to various medications such as dopaminergic receptor antagonists (e.g. metoclopramide), estrogens, antidepressants (e.g. tricyclic agents), antihypertensive drugs (e.g. verapamil), opiates, antipsychotics (e.g. risperidone, haloperidol), oral contraceptives, antiepileptics and gonadotropin-releasing hormone (GnRH) agonists (triptorelin) (10).

From all of these risk factors mentioned above, pharmacological treatments (antiepileptics, antipsychotics) and pituitary adenomas are considered to be the most frequent HPrl causes in childhood and adolescence (2, 16).

Clinical manifestations and complications

The clinical manifestations of prolactinoma vary mainly according to gender, age of onset, tumor size and PRL levels (4).

Regarding prolactinomas, clinical signs manifest with mass compression of the optic chiasm and anterior pituitary gland or prolactin hypersecretion. According to the literature, headache is the commonest com-

plaint followed by vision impairment in cases where the tumor is enlarged, although it remains unknown if hormonal hypersecretion represents the primary cause of the headache.

Interestingly, Thomas Breil et al. (12) in a retrospective study confirmed 3 macroadenomas (>1 cm) reached to the suprasellar area accompanied by hemianopia, optic atrophy and anterior pituitary hormone imbalances.

According to current knowledge, pituitary adenomas may lead to unilateral or bilateral visual symptoms when their sizes go beyond 1cm in diameter. In the early stages, diplopia or visual field defects are mostly observed. Bitemporal hemianopsia and superior temporal visual field impairment are detected in the majority of children. Rarely, sudden visual loss, papilledema and complete opthalmoplegia are diagnosed (17).

Surgery is required if visual disturbance is detected at the time of diagnosis of pediatric prolactinoma, in order to decompress the optic chiasm and further to preserve the visual function (12).

Elevated PRL causes alterations of the gonadotropic axis, inhibiting pulsatile Gn-RH secretion. Such alterations appear in adolescent females as delayed puberty (48%), primary amenorrhea (14-41%), secondary amenorrhea (29-45%) and oligomenorrhea (up to 29%) (4, 18).

In the past, Dong-Yun Lee et al. (19) retrospectively studied 1704 young women with menstruation related problems. They observed that secondary amenorrhea and abnormal uterine bleeding are mainly due to idiopathic causes of HPrl other than prolactinomas or medications.

In PCOS hyperinsulinaemia causes hyperandrogenaemia by inhibiting androgen catabolism. Subsequently, aromatase conversion of androgens leads to estrogen hyperproduction which stimulates prolactin secretion either directly in lactotropic cells or by inhibiting dopamine tone (6). Primary hypothyroidism in children stimulates TRH release, which shows an endogenous trophic effect in lactotropic cells leading to elevated prolactin levels in blood.

Overt hypothyroidism in adolescent and young girls has been associated with pituitary hyperplasia, enlargement and rarely with various pituitary hormonal imbalances (20-22).

Medications and other conditions cause HPrl by reducing dopaminergic inhibition signals or by lack of prolactin clearance (23).

Complications related to chronic untreated HPrl are apparent in female adults and mainly include three groups; functional (menstrual issues, ovulatory abnormalities, infertility), skeletal (stature defects, osteoporosis, osteopenia, osteomalacia) and psychometric irregularities (24, 25).

Colao et al. (26) described an impaired bone health with decreased bone mineral density in relation to sex and age in adolescent patients with hyperprolactinemia.

Diagnosis and screening

Clinical diagnosis and assessment of HPrl in adolescence is determined by the symptoms of the functional syndrome (primary or secondary amenorrhea, galactorrhea) and the presence of any pre-existing medical condition that could lead to HPrl.

It is widely accepted that HPrl in the absence of clinical symptoms is not diagnostic (27). An adequate physical examination (including gynecological examination) should be conducted, in order to assess patient's mammary glands (galactorrhea), skin (acne, hair growth indicative for PCOS) and any clinical sign which could be linked to a certain medical disorder (10).

For the diagnosis of HPrl, blood sample through venipuncture should be obtained without excessive venipuncture stress, in the morning hours (2 hours post-awakening) in order to avoid any false positive HPrl due to circadian acrophase shift (10).

Screening through evaluation of prolactin levels is suggested in children and adolescent girls with short stature and/or obesity because they are in a higher risk (28).

Due to the pulsatile secretion of prolactin, a single measurement of prolactin concentration > 20 ng/ml is not reliable for the diagnosis of HPrl in childhood (27).At least two abnormal prolactin values in samples obtained on different days with a pre-test 20-min free interval are suggested to confirm HPrl.

In cases where prolactin concentration is extremely high (>100 ng/ml) and or associated with clinical symptoms, a single measurement is adequate (27).

As far as the prolactinoma is concerned, prolactin levels >100 ng/ml demonstrates a high predictive and diagnostic value (29). A prolactin level higher than 500 ng/ml is diagnostic for macroprolactinoma.

In adolescent girls with prolactinoma, serum prolactin levels are 10 times greater in macroadenoma compared to microadenoma.

Moderate elevation of prolactin cannot exclude the possibility of tumorous etiology other than various organic or functional causes, and may be due to prolactinoma (1st measurement), incidentaloma or other masses that can compress the pituitary stalk (6). Particularly, it should also be noted that prolactin level <200 ng/ml with compatible history of medication indicates drug-induced (iatrogenic) HPrl (30).

In the presence of HPrl, several systemic conditions should be excluded.

Detection of renal failure by measuring blood urea nitrogen and creatinine levels is mandatory for all cases. Moreover, evaluation of thyroid function tests is recommended in all children and adolescents with HPrl, with a TSH ≥4.00 mIU/L having high sensitivity and specificity in identifying HPrl related to hypothyroidism (15). Furthermore, exclusion of PCOS and a pregnancy is essential for the adolescent girls (6).

During diagnosis of HPrl there are two major pitfalls that should be taken into consideration; the presence of macroprolactinemia, and the "hook effect".

Prolactin circulates in three distinct molecular isoforms; monomeric 23 kDa (biological active), dimeric 50 kDa, and macroprolactin 150 kDa (biological inactive) (3).

The current knowledge have indicated that macroprolactinaemia accounts for up to 26% of biochemical HPrl and, thus it is important to exclude macroprolactinaemia in young patients with HPrl, which is described as the formation of aggregates of monomeric prolactin and IgG with size of 150-170 kDa (6). As far as the macroprolactin molecule is concerned, it does not bypass the endothelial barrier, thus resulting in poor bioactivity and false positive increased levels of prolactin (6).

Macroprolactinemia represents a frequent benign cause of misdiagnosis and mismanagement in children and adolescents with HPrl, due to the high rate of analytical errors during biochemical analysis, resulting in false-high/low levels of serum prolactin, especially in asymptomatic patients (12).

The recommended laboratory method used in prolactin interpretation for macroprolactinemia screening is polyethylene glycol precipitation (PEG) , which provides a better estimation of monomeric bioactive form of prolactin since there is a possible form of a combined HPrl (monomeric + macro) (31-33).

In a young asymptomatic girl, with slightly elevated prolactin and negative MRI findings, prolactin isoforms should be suspected (4). "Hook effect" occurs when artificially low concentrations of prolactin detected by immune radiometric assay (IRMA) test, coincide with a macroprolactinoma. Large amount of serum prolactin saturates the antibodies used in IRMA test, resulting in this artifact, thus falsely suggesting the presence of a non-secreting macroadenoma (34). This phenomenon creates the need for multi-evaluation of prolactin levels with clinical symptoms and MRI before making a definite diagnosis (12).

In the previous decades, dynamic tests for prolactin secretion (metoclopramide, TRH) had been used to facilitate the differential diagnosis of prolactinomas since prolactin response in TRH stimulation is distinctively blunted in prolactinoma cases (35). However these tests demonstrate low specificity.

In a large retrospective study Famini P et al. observed 47 % of patients suffering from hyperprolactinemia or hypogonadism with a normal pituitary gland on MRI. Parallel, MRI detected prolactinoma in 40% and incidentaloma in 37 % of cases. Thus, when secondary causes of HPrl have been excluded, imaging studies such as computed tomography (CT) and/or MRI should be performed (36). However, enlargement of pituitary gland does not always suggest an adenoma, but it may be due to physiological conditions (puberty, lactation, pregnancy) as a result of lactotroph hyperplasia (37).

In cases of severe or persisting HPrl of any degree in addition to circadian rhythm disturbances, with a concurrent detection of a pituitary mass in MRI or CT scan, prolactinoma should be suspected (27). Definite diagnosis of prolactinoma can be made rarely through biopsy and preferably through adequate size reduction of tumor or total remission after proper medical management of HPrl (4). However, well noted, neuro-

ophthalmologic findings still maintains its importance in diagnosis and management of such conditions (17).

Other investigations include detection of pituitary auto-antibodies for lymphocytic hypophysitis (38), and determination of MEN 1 mutation gene (in prolactinomas) and/or chromogranin A for investigation of possible genetic diseases associated with HPrl (39-43).

Therapeutic approach

The main targets of management are the resolution of HPrl symptoms, the normalization of pubertal development, the sufficient restoration of gonadal function, the shrinkage of the pituitary tumor, maintenance of bone mass and the preservation of future fertility (4).

Symptomatic HPrl is indicative for medical treatment, whereas asymptomatic girls, due to idiopathic HPrl or pituitary adenomas (incidentalomas, microprolactinomas) should be monitored without initial treatment.

In children with hypothyroidism, pituitary function is often restored after proper thyroid hormone replacement therapy. Adequate medical therapy of PCOS returns prolactin levels to normal range in these patients (6).

Rarely, kidney transplantation is curative in cases of renal failure (44).

As far as drug-induced HPrl is concerned, withdrawal of the responsible medication is necessary, since elevation of prolactin is a dose-dependent phenomenon (45, 46).

Careful estimation of risk-benefit profile of the incriminated drug is essential especially in children and adolescents receiving antipsychotic therapy, where a withdrawal might result in exacerbation of psychotic symptoms. Thus additional medical treatment for the alleviation of HPrl should also be considered (28).

The gold standard primary therapy in accordance with formal guidelines, are dopamine agonists (DA) due to their efficacy in regularizing prolactin levels in any case with HPrl (including micro- and macroadenomas) (47-51). These include semisynthetic ergot alkaloid derivatives, mainly bromocriptine or cabergoline, and hardly pergolide or quinagolide (12).

Through the tuberoinfundibular pathway, they directly act via a strong stimulation of postsynaptic G-protein-coupled D2 dopamine receptors and/or partial stimulation of D1 dopamine receptors. The restriction of the signaling cascades of adenylatecyclase, phospholipase C and inositol phosphate results in repression of prolactin by inhibiting the transcription of prolactin gene in lactotropic cells (4, 28).

As in adults, bromocriptine is administered in children and adolescents in the dose range of 2.5-15 mg/day, standardized with split doses of 5 and 7.5 mg/day, twice a day (4). In addition to the aforementioned mechanism of action, bromocriptine prevents mitosis and growth of lactotropic cells, initiates cell death and promotes perivascular fibrosis, thus resulting in reduction of tumor mass (52).

Saranac L et al. (3) observed that bromocriptine treatment in 11 young individuals (including 6 female patients) with HPrl, either due to microprolactinoma or fuctional HPrl, achieved full restoration of gonadal function, normalization of prolactin levels and reduction in tumor mass within half year of therapy in all cases.

However, several case studies of children and adolescents with prolactinoma indicate that the mean efficacy of bromocriptine in normalizing prolactin levels and restoring gonadal function is lower than that reported in adult studies (52).

Well of note, it was previously observed that bromocriptine monotherapy in children with prolactinoma and short stature due to GH deficiency is able to improve growth and GH secretion without additional GH therapy (53). Furthermore, combined therapy with bromocriptine and GH replacement was efficient in children with macroprolactinoma and coexisting GH deficiency (49).

Although great in tolerance and efficacy, bromocriptine is well-known for its various adverse effects such as nausea, vomiting, orthostatic hypotension and mood disturbances, which represent the primary reasons for treatment discontinuity (54). Initially, a single dose of 1.25 mg/day and wise titration is beneficial in order to reduce such symptoms (4).

Parallel, cabergoline should be offered in children and adolescents with an initial dosage of 0.25-0.5 mg once weekly and gradually increase by 0.5 mg every 4

weeks, in order to reach a medium dose ranging from 0.5 mg up to 3.5 mg twice and once weekly respectively, preferably administered in the night for more tolerant results (55). A monthly re evaluation of prolactin levels is necessary for the adjustment of ideal carbegoline dose (12). The advantage of the low frequency of administration of cabergoline unlike other DAs is due to its long half-life, owing to its low pituitary clearance, prolonged enterohepatic cycling, and strong binding with D2 dopamine receptors (4, 18).

Apart from that, cabergoline has been reported by numerous studies to demonstrate a better efficacy and tolerance contrary to bromocriptine (56,57). A recent retrospective study by Breil et al. (12) reported that cabergoline therapy in children and adolescents with prolactinomas demonstrated a great efficacy and tolerance in normalizing prolactin levels, reducing symptoms and diminishing tumor size. It was also observed that microprolactinomas required lower dosage of cabergoline than macroprolactinomas.

Similar results have been reported by previous authors regarding carbegoline therapy in pediatric patients with prolactinomas (4, 18), where adequate restoration of growth in cases of concurrent prolactinomas and GH deficiency was achieved through monotherapy with cabergoline (12, 58).

Concerning the use of quinagolide and pergolide in children and adolescents with HPrl the available information is limited (52). Adverse effects of DAs can be divided into four main groups; gastrointestinal, cardiovascular, neurological, and psychiatric.

Gastrointestinal effects include nausea, vomiting, and abdominal pain and they are often responsible for treatment discontinuity in 3-5% of cases. Cardiovascular effects include orthostatic hypotension basically at the initial stage of therapy. Other rare effects are mild tricuspid regurgitation and aortic valve calcification, which have been reported in high-dose and long-term therapy in prolactinoma cases. Neurological effects include fatigue, drowsiness, headache, dizziness, and vertigo. Deterioration of psychotic episodes and mood alternations represent the prominent psychiatric effects (4).

Regarding treatment of prolactinomas in the pediatric population, dopamine agonists seem to be safe and effective in the reduction of the tumor size and normalization of the circulating prolactin. Surgery is offered in children who do not respond to medical treatment or in cases where visual preservation is crucial, because operative innervations are associated with a higher risk of morbidity due to iatrogenic hypopituitarism.

Transsphenoidal approach is the gold standard surgical method in pediatric patients, apart from children < 10 years old where sphenoid sinus is still hypoplastic. However, surgery is not fully curative and an additional post-operative maintenance with a low-dose of DA agonist is essential in all pediatric patients with macroprolactinomas (28). Rarely, radiation is suggested in malignant prolactinomas (12).

Moreover, all children presenting with pituitary apoplexy should be closed monitored and treated with corticosteroids. In cases where sudden loss of vision is confirmed, urgent craniotomy and decompression of the optic nerve and chiasm is performed (3).

In general, follow-up includes prolactin measurements and MRI control. Prolactin serum levels should be estimated every 2-4 weeks initially, and every 6-12 months after normalization. MRI scan is suggested after 1 year of therapy in microadenomas and after 3-4 months in macroadenomas in addition to proper visual field evaluation in the latter situation. According to current formal guidelines, discontinuation of DA therapy is indicated after ≥2 years of treatment, normal prolactin levels, and no MRI image of pituitary adenoma (14). A recurrence rate up to 64% has been observed within first year of DA treatment withdrawal (59-61). In cases of drug intolerance or resistance with a persistent HPrl and no tumor suppression, clinicians should shift to another medical agent (51, 62).

Conclusion

Targeted identification of HPrl is of significant importance for proper management and follow-up. Although the level of prolactin provides major clues in making a decision, the clinicians should take into consideration the pitfalls that incorrectly mask a physiologic state such as macroprolactinemia or the "hook effect."

Further studies should be conducted considering the efficacy, tolerance, dosage and follow-up of medi-

cal treatment especially with DAs in children and adolescents, in order to establish specific guidelines.-

Future issues

Although there is a broad literature regarding HPrl, there are no large epidemiologic studies on hyperprolactinemia among children and adolescent girls. The available publication is limited about the clinical manifestations, efficacy of medical therapy, and long-term outcome.

The newly advanced field of genetic medicine will have a major impact in studying prolactin receptor gene alterations in different anatomical brain areas and their relations with stress and aging (3). Moreover, a better understanding of several molecular and genetic variations will help unraveling the pathogenesis of prolactinomas, thus aiding the development of a causal management (12). The role of various isoforms of prolactin in children and adolescents is yet to be investigated, as well as the impact of asymptomatic HPrl (4).

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