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Recurrent Vaginal Bleeding in A Prepubertal Girl.

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Summary:

We present the case of an 8-year-old girl, without signs of pubertal development, who has presented vaginal bleeding on two occasions in the last month. This reason for consultation, which is infrequent and causes concern both in the family and in the girl, should always be studied when it occurs outside the neonatal period. Its management and coordination must be carried out by the primary pediatrician, since in most cases it will require complementary examinations and consultations with other medical specialists.

This work has a double objective; first of all, to describe the differential diagnoses to be taken into account in these cases, and second, to develop the diagnosis that is reached in our patient, which is part of the so-called variants of normal pubertal development.

Key Words: prepubertal vaginal bleeding; early menarche; benign vaginal bleeding; precocious puberty

Introduction

Vaginal bleeding in a prepubertal age is an infrequent reason for consultation that generates great concern in parents and should be carefully evaluated by the pediatrician, since its etiology encompasses a wide range of entities.

The management of these girls must be carried out and coordinated by their family pediatrician, since it usually requires specific complementary examinations and, possibly, the request for evaluation by other medical specialists.

The objective of this work is to carry out a review of the multiple causes that must be considered when faced with a girl with SVEPP, whether isolated or recurrent, and to describe the diagnosis of the girl that motivates this report.

Clinical case

8-year-old girl with bleeding in her underwear detected by parents, twice in the last month, separated by a period of 3 weeks. On the first occasion, the bleeding was single, minimal, self-limited, and asymptomatic. The second bleeding occurred in the morning when getting out of bed, with similar characteristics to the previous one, which led to a consultation with the family pediatrician.

Background: is the first daughter of a healthy couple, the result of a first controlled pregnancy without anomalies. Birth at term and with adequate weight, without a history of relevant pathologies, with growth and development according to their age and sex and correct immunizations according to the vaccination schedule. They receive a varied diet, deny a history of trauma and of ingestion or application of medications or products that may contain estrogens, and their hygiene habits are adequate. No previous hematological disorders were reported in the family or in the patient.

First assessment: On physical examination the patient is afebrile, lucid, reactive, normotensive and normo-colored. There are no hemorrhagic lesions, café-au-lait spots on the skin, or signs consistent with pubertal development. Palpation of the neck does not reveal a goiter, and the abdominal region is soft, painless, and without visceromegaly. In the exploration of the genital region no lesions were observed,

introitus with normal characteristics and an intact hymen, without the presence of discharge or foul-smelling discharge. The anal region does not show alterations and there is not pruritus. Their weight-bearing development is at the 50th percentile for height and 75th for weight, remaining constant in the last 3 years, that is, without observing an increase in growth speed. The initial complementary examinations consisted of a blood test without anemia, platelet deficiency or coagulation alterations, negative urine sediment and anteroposterior radiograph of the left hand-wrist compatible with a bone age of seven and a half years, based on the reference atlas. by Greulich & Pyle. After these first results within the normal range, it was decided to hospitalize to complete studies and assess possible recurrence of bleeding.

Hospitalization: the girl keeps a good general status and without new bleeding episodes. During her stay, she was evaluated by gynecology, describing a genital examination without alterations or internal traumatic injury. The pelvic region is explored by ultrasound, reporting ovaries and uterus of sizes concordant to their age (uterine longitudinal diameter: 37 mm., body/neck uterine ratio <1; ovarian volume: 0.7 cc). No cysts were seen in the ovaries or adnexal masses, or foreign objects on clinical examination. Vaginal culture was negative.Likewise, it was controlled by endocrinology, expanding the blood tests initially requested, with results within normal limits (Table 1).

Determination	*Outcome*
TSH	3.86 mU / ml (0,5 to 4.28 mU / mL)
Free T4	0.9 ng / dl (0.65 to 1.06 ng / dl)
Baseline FSH	2.05 U / L (tanner I girls: 0.05-2.41 U / L)
Baseline LH	0.09 U / L (tanner I girls: 0.01-0.21 U / L)
Basal 17 b estradiol	<10 pg / ml (tanner I girls: 5-10 pg / ml)

Table 1: Blood tests

Evolution and diagnosis: With a clinical history without relevant data, a physical examination according to age and normal complementary studies, the diagnosis of isolated premature menarche (IPM) was made, being indicated periodic follow-up by family pediatrician.

Discussion

Vaginal bleeding in a prepubertal (VBPP) age outside the neonatal period is a sign that should be studied [1]. Given the diversity of possible diagnoses, starting point for the management of these girls is a detailed medical history and a careful physical examination. These basic tools can provide us signs or indicative symptoms of a certain etiology or guidelines to continue with the rational study by another medical specialist and or complementary exams.

In the differential diagnosis of these patients, we must include:

- Trauma

Trauma to the genitourinary region is one of the most frequently reported diagnoses as a cause of VBPP, being the vast majority accidental [1.2]. In them, the clinical observation coincides with the story of the minor or the family, usually the girls are injured while playing or they slip and straddle an object or surface such as the horizontal bar of the bicycle or the edge of the bathtub. Lesions by this mechanism rarely produce deep lacerations and generally spares the hymen and vagina [2].

On the other hand, there is the trauma caused by sexual abuse, which must always be considered. In this case, the family report does not usually coincide with the type of injuries, these are usually extensive and / or deep, frequently affecting the hymen region [2,3,4]. This possibility should also be considered with recurrent episodes of vulvovaginitis or suspicious microbiology of sexually transmitted disease (*Chlamydia trachomatis, Neisseria gonorrhea, Trichomona vaginalis, and herpes viruses*).

- Vulvovaginitis.

Vulvovaginitis is, along with trauma, the most common cause associated with VBPP [1.2]. The term vulvovaginitis is associated with inflammation of the external female genital tract, resulting in erythema, itching, dysuria, vaginal bleeding, or discharge. anatomical characteristics and habits may predispose to the development of this entity [5]. The possibility of pinworm disease should always be considered in the presence of persistent itching, especially if it is predominantly nocturnal; in this case, both the copro-parasitological test and the Graham test will be of diagnostic utility.

- Foreign Objects

It is a cause to be considered mainly in girls who have recently started their toilet in the bathroom independently or in those whose hygiene habits are not correct, since the most frequently reported object is toilet paper [2]. In addition to toilet paper, multiple elements have been described in the literature, such as hair clips, toy pieces or bottle caps [1.2]. A percentage of these girls will present bleeding as the only symptom, while in other cases it may be associated with abdominal pain or foul discharge. It is important to highlight that in patients without a certain diagnosis the symptoms may persist for months and even years. Ultrasound of the pelvic region can help in cases where the physical examination does not offer positive results and the anamnesis or symptoms guide us to this etiology.

- Urethral prolapse

Urethral prolapse in girls is an uncommon cause of VBPP, but it should be considered among the probable etiologies. It occurs more frequently in prepubertal women of black ethnicity and manifests with usually painless bleeding although occasionally it may be accompanied by dysuria [6].

Diagnosis is made by inspection by observing a red or purple circular mass between both labia majora surrounding the urinary meatus [3]. Urological evaluation should be performed.

- Tumors

Among the benign tumors, vaginal polyps, introital warts, hemangiomas, Müllerian papilloma, and rhabdomyosarcoma are described [5]. The rhabdomyosarcoma is the most common soft tissue sarcoma of childhood and its variant, botryoid sarcoma mainly involves the genitourinary region [1.5]. Typically affects preschool-age girls, with a peak incidence around the age of 3

[1.2]. It is a tumor whose growth usually begins in the anterior wall of the vagina, near the cervix, presenting with an intra-labial mass with a characteristic “bunch of grapes” morphology.

- Lichen sclerosus.

It is a chronic mucocutaneous disorder that involves the labia minora, perineal and anal areas. Upon inspection, in initial stages, erythematous papules are observed that subsequently give way to atrophic and hypopigmented plaques, with the pattern in the shape of an "eight" that encompasses the vulvar and anal regions characteristic of this condition [5]. The symptoms are varied, prevailing vulvar itching, dysuria, and constipation. The characteristics of the vulvovaginal epithelium of the prepubertal girl, thin and with poor protection, can lead to bleeding generated by scratching that causes itching in this condition [1].

- Precocious Puberty

Precocious puberty (PP) in girls is defined as the appearance of secondary sexual characteristics, thelarche, 2.5 standard deviations before the reference age, specifically for the Caucasian population in developed countries before the age of 8 in girls [9]. Physio pathologically, PP is classified into two groups:

-*Peripheral Precocious Puberty (PPP).* The production of sex steroids is autonomous and is not accompanied by activation of the hypothalamic-pituitary-gonadal axis. Typically, girls with peripheral precocious puberty have elevated baseline estradiol levels and very low or undetectable pituitary gonadotropins.

A girl with VBPP associated with café-au-lait spots should arouse the suspicion of McCune-Albright syndrome. This is a multisystemic entity, due to somatic mutations of the GNAS gene, and is clinically defined by the triad: polyostotic fibrous dysplasia, café au lait macules on the skin, and autonomic endocrine hyperfunction [7]. Although café au lait spots are usually present in the neonatal period, it will be the symptoms of endocrine alterations or bone dysplasia that will alert of this disease.

The exposure to exogenous estrogens or possible use of contraceptives it can be an exogenous cause of PPP and VBPP. The anamnesis should include the investigation of the possible ingestion of medications that contain estrogens, or a history of application of topical estrogens [1.5]. The latter case should be considered mainly in girls who have received topical estrogen treatment for the fusion of the labia minora. In these patients, both the duration of the prolonged treatment and the excess amount of cream applied can be the origin of vaginal bleeding

Estrogen-secreting ovarian or adrenal tumors are examples of endogenous causes of PPP and VBPP. In these cases, the bleeding vaginal tends to be recurrent and irregular. Pelvic ultrasound and magnetic resonance imaging are complementary examination for its diagnosis.

-*Central Precocious Puberty (CPP).* It is due to the premature onset of the pulsatile activity of gonadotropin-releasing hypothalamic hormone (GnRH), being in most cases of idiopathic cause. The GnRH stimulates the production of hormones at the pituitary level follicle stimulating (FSH) and luteinizing (LH). LH acts on the ovaries in the synthesis of estrogens, while FSH promotes the development of oocytes [8]. Likewise, there is an increase in the levels of growth hormone and insulin-like growth factor-I that condition an increase in growth speed and bone maturation in synergy with estrogen synthesis. For this reason, in a girl with VBPP, it should be valued if she presents early pubertal signs (Tanner stages), growth rate, bone age, characteristics of internal genitalia, and levels of FSH, LH and estradiol.

If the anamnesis, physical examination, or initial complementary studies indicate a probable CPP, the study and follow-up of the patient will be coordinated with the specialist in pediatric endocrinology. It should be borne in mind that although exceptional, vaginal bleeding can be the first manifestation of CPP.

- Primary hypothyroidism (Van Wyk-Grumbach Syndrome).

Undiagnosed or under-treated hypothyroid girls may have breast development, and / or vaginal bleeding, along with a marked alteration in their growth rate [5.8]. The disorder is attributed to the fact that severe primary hypothyroidism can lead to vaginal bleeding due to activation of the gonadal pituitary axis with increased gonadotropin secretion; this represents an exceptional cause.

- Munchausen syndrome

This entity is not described in the literature as part of the differential diagnoses in a girl with VBPP, but we believe it is very important to think about it, since vaginal bleeding fulfills a distinctive characteristic of this syndrome: caregivers often describe undetectable signs and symptoms to the physician at the time the patient is evaluated. Therefore, this diagnostic possibility must be considered so as not to expose patients to unnecessary tests.

Isolated premature menarche (IPM)

It is an entity rare, self-limited, and benign, that occurs in girls 1 to 9 years of age, in whom vaginal bleeding is observed that may be single or recurrent, in the absence of other precocious pubertal signs [8,9,10]. The IPM together with the isolated premature thelarche and precocious pubarche, are part of the so-called variants of the normality of pubertal development [9]. Both, the etiology, and pathophysiology, are still uncertain. Although various hypotheses have been proposed that try to explain them as endometrial hypersensitivity to circulating estrogens, recurrent functioning ovarian cysts, or transient activation of the hypothalamic-pituitary-ovarian axis with excessive production of FSH [5,9,10].

This is a diagnosis of exclusion and is guided in the beginning by the history and physical examination. Vaginal bleeding is usually the first and only episode in most cases. Although cases with 2 or more episodes, or small recurrent bleeding for more than 1 year of evolution, were reported [9.10]. The average age of presentation is 7 years, with a range between one year and 9 years of age [9.10].

Within the family background of these girls, there is no history of precocious puberty and the mother's age at menarche was normal [10]. On physical examination, these girls are in Stage I of the Tanner Sexual Maturity Index. The evaluation of the genitalia is advisable to take place within the context of the general physical examination and with the presence of a parent[1.] Before the physical examination it is important to generate trust and empathy in both the patients and their parents. The classic gynecological position

and that of "frog legs" in the smallest are preferable to the genupectoral, because in general girls prefer to watch what one is doing. In this position, both the labia majora are grasped with the index and thumb fingers of each hand and a slight traction is exerted on these to be able to visualize the introitus, hymen, and urethra [1.5].

As complementary studies, it will be requested analytics that include blood clotting and platelets, basal estradiol, basal LH, basal FSH, Thyrotropin (TSH) Thyroxine (T4) Free, pelvic and adrenal ultrasound and left-hand radiography to assess bone age. The use of ultrasound is aimed at excluding both the presence of pathologies and foreign objects not identified in the physical examination. In cases of IPM, ovaries with prepubertal characteristics and a uterus without adnexal masses are observed, although the presence of ovarian microcysts with a diameter less than 9 mm is not uncommon, being a finding that is considered normal [9.10]. The need to perform an LHRH test will be assessed individually, mainly in cases in which an increase in growth rate, advance of bone age or presence of early thelarche is observed, to rule out a typical or atypical central precocious puberty.

Once the diagnosis is made, it is important to inform and reassure to the parents and the patient about the mildness of the condition and the lack of need for treatment. While the natural evolution is to self-limitation, without affecting later pubertal development, fertility or final height [8,9,10] it is periodic monitoring of these girls is essential to rule out progression to PP [9]. Table 2 summarizes the key points of this entity.

-The IPM is a benign and self-limited entity in time. -The diagnosis is of exclusion of other causes of vaginal bleeding. -Its distinctive characteristics: Tanner stage I sexual development index, without acceleration of growth rate or bone age. -Complementary studies: ✓ Coagulation and platelet study. ✓ Basal estradiol, FSH, LH, TSH and FT4. ✓ Left hand-wrist X-ray for bone age. ✓ Pelvic and adrenal ultrasound. -The evolution does not affect pubertal development, fertility, or final height. -Does not require treatment. -Regular surveillance by your family pediatrician to rule out progression to precocious puberty.

Table 2: Key points of Isolated premature menarche.

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