CEOG Clinical and Experimental Obstetrics & Gynecology

Recurrent multiple endometrial polyposis in patient treated by antipsychotic drugs

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Summary

Irregular uterine bleeding and profuse menstrual bleeding often occur in patients treated by antipsychotics, antiepileptics, and some antihypertensive drugs. Such bleedings represent an important problem in clinical practice, especially when related to antipsychotic treatment. Nonetheless, this problem has not been often analyzed in references. This paper describes a recurrent multiple endometrial polyposis accompanied by profuse menstrual bleeding in a patient undergoing a multi-year treatment of bipolar affective disorder by antipsychotics and discusses the possibilities of prevention of irregular and profuse menstrual bleeding in patients that must use antipsychotic therapy in order to treat a psychiatric illness.

Key words: Abnormal uterine bleeding; Endometrial polyps; Antipsychotics.

Introduction

Bleeding disorders are some of the most frequent gynecological problems. There are many causes of bleeding disorders. The most frequent causes are hormonal disturbances, which account for up to 90% of cases, followed by organic changes in the uterus such as myomas, adenomyosis uteri, or endometrial polyps, in up to 70% of causes [1]. Irregular and profuse menstrual bleedings in patients treated by antipsychotics, antiepileptics, and some antihypertension represent a separate issue because irregular bleedings occur as side effects of application of these drugs. According to reference data, some antihypertensive drugs, such as, for example, angiotensin-converting-enzyme (ACE) inhibitors and angiotensin receptor blockers could promote the onset of endometrial polyps in hypertensive women and cause irregular and/or profuse uterine bleeding as a side effect of drug application [2]. Concerning antipsychotics, basic antipsychotic effect of neuroleptics is related to blocking of dopamine receptors, thus causing the side effects of these drugs to be related to blocking of dopamine receptors in different parts of the central nervous system as well. Following this mechanism, neuroleptics acting upon D2 receptors, cause undesired endocrine effects such as hyperprolactinemia and galactorrhea which are caused by their action in the tuberoinfudibular region. Hyperprolactinemia is an unwanted adverse effect present in several typical and atypical antipsychotics [3, 4]. Increased serum prolactin levels result in decreased kisspeptin expression in Kiss1 neurons in both the hypothalamic arcuate and anteroventral periventricular nuclei, mediated by prolactin receptors expressed on both populations of Kiss1 neurons. Suppression of kisspeptin, in turn, reduces gonadotropin-releasing hormone (GnRH) release and results in loss of the ovulatory GnRH surge [5]. This leads to reduced pituitary gonadotropin (luteininzing hormone, LH and follicle stimulating hormone, FSH) secretion and loss of adequate ovarian stimulation, which results in hormonal changes causing prolonged estrogen stimulation during the entire menstrual cycle. Prolonged estrogen stimulation leads to changes in receptor concentration on endometrial cells, as well as changes in cell proliferation marker concentrations and apoptosis (Ki 67 and Bcl-2) in cells [6]. Concentration of estrogen receptor on endometrial cells increases while cell apoptosis marker concentration Bcl-2 declines. This opens up the possibility for development of organic lesions in the endometrium such as endometrial polyps and endometrial hyperplasia resulting in irregular uterine bleedings.

Case Report

This paper describes a case of recurrent multiple endometrial polyposis in premenopausal patient treated against bipolar affective disorder by antipsychotics. Endometrial polyposis always developed after an episode of exacerbation of bipolar affective disorder which was treated by high doses of neuroleptics.

Patient`s gynecological history showed that the patient was 12 years of age when she got her first period. Menstruations were regular, characterized by 28-day cycles, normal considering quantity and intensity of bleeding, and lasting around four days, until her twenties when treatment of bipolar affective disorder started. Several months after the introduction of neuroleptics in therapy, patient started to complain about more profuse menstrual bleedings. That is when the first complete gynecological examination was performed including colposcopy with cervical cytology and transvaginal ultrasonographic exam. Gynecological findings were normal. Nevertheless, gynecological discomforts patient com-

Revised manuscript accepted for publication March 19, 2014

plained about continued. Menstrual cycles became more and more profuse, especially during the first two days, additionally disturbing her mental state. Therapy by linestrenol five mg tablets twice a day during the second half of the cycle was suggested. Patient accepted this therapy and took linestrenol (together with previously prescribed antipsychotics) for two or three years. Her menstrual cycles were still profuse, especially during the first two days, but pain intensity reduced. Although it was suggested to the patient to report for a gynecological exam after the third linestrenol cycle, patient failed to do so. After some three to four years, a progression of affective bipolar disorder occurred, causing patient to be hospitalized and treated by high doses of neuroleptics. Even though patient reacted well to prescribed therapy, after discharge from psychiatric institution, profuse prolonged bleeding started, lasting around ten days, forcing the patient to come in for a gynecological exam. After a conservative treatment during which bleeding was stopped by medications, contrast sonohysterography was indicated, showing endometrial polyposis inside the uterine cavity. Patient refused the recommended hysteroscopy, instead of which explorative curettage monitored by ultrasonography was accepted by the patient and performed. During the course of the intervention, more than 30 small endometrial polyps, averaging one cm in size, were evacuated from the uterine cavity. Histopathological examination showed that these were endometrial polyps without signs of cellular atypia. A thin endometrium was verified by the ultrasonographic exam performed after the intervention. Over the next three years, the patient did not show up for gynecological exams. No discomforts were present and menstrual cycles were regular. After this period, an exacerbation episode of the underlying psychiatric disease occurred, followed by an increase in the dose of neuroleptics after which illness again came to a remission phase. Then the patient reported again for a gynecological exam because of the same discomforts – prolonged and painful menstrual bleeding. Due to the fact that patient came in for a gynecological exam on the third day of the menstrual cycle while profuse bleeding was still present, a transvaginal ultrasonographic examination was performed and endometrial polyposis was visualized in the uterine cavity; polyps were made clearly visible by the presence of blood in the uterine cavity. Explorative curettage monitored by ultrasonography was performed again. In the curettage material, obtained from the cavity, a large number of small endometrial polyps (over 20) was found and subjected to histopathological analysis. Histopathological diagnosis once again confirmed the case of endometrial polyps without cellular atypia. Ultrasonographic exam performed after explorative curettage once again verified a normal, thin endometrium. Significance of regular six-month gynecological checkups was explained to the patient so she began to report regularly for gynecological control exams. No discomforts were present and transvaginal ultrasonographic exams confirmed normal gynecological ultrasonographic findings. Finally, after another exacerbation episode of the psychosis, about four to five years after the last explorative curettage, patient showed up with the same gynecological discomforts – profuse, painful, and prolonged menstrual bleeding, calling for the third explorative curettage monitored by ultrasound, once again yielding more than 30 endometrial polyps subsequently verified histopathologically too. Patient age after the third explorative curettage was 41, patient gave no births and had no miscarriages, and was of normal osteomuscular constitution and normal nutritional status.

Given that the patient was monitored gynecologically before the increase in the dose of neuroleptics, that it was confirmed that her cycles were mostly anovulatory, that the hormonal status verified a mild hyperprolactinemia during the entire course of the menstrual cycle and that the gynecological discomforts, accompanied by ultrasonographic image of nonhomogeneous thickened endometrium with subendometrial vascularization consistant with endometrial polyposis, appeared after the increase of the dose of neuroleptics over a four to six month period, the question arose whether neuroleptics do influence the occurrence of endometrial polyps.

Discussion

Psychotropic medications, particulary select antipsychotics, are a common cause of drug – induced hyperprolactinemia [7]. Numerous studies discuss the consequences of psychotropic-induced hyperprolactinemia, but data on endometrial polyposis in patients subjected to antipsychotic treatment, such as the case of recurrent multiple endometrial polyposis described in this paper, is very scarce [7-9]. According to data from references, the most frequent undesired effects caused by hyperprolactinemia in premenopausal patients using antipsychotic therapy are menstrual irregularities, galactorrhea, and infertility.

Monitoring of the clinical symptomatology of menstrual irregularities in patients on antipsychotic therapy is important, not only for the prevention of profuse uterine bleeding, but for prevention of organic lesions in the endometrium such as, for example, endometrial polyps. Reference data clearly show the efficiency of progestagen therapy such as, for example, levonorgestrel intrauterine system or oral progestagen therapy in patients who suffered from endometrial polyposis [10].

Some authors believe that baseline prolactin level should be determined at the beginning of the antipsychotic therapy and that serum prolactin levels should be tested every three months. Furthermore, each patient should be subjected to a thorough gynecological examination at the beginning of administration of antipsychotic therapy. In cases of anovulatory cycles, that are a common finding, hormonal therapy should be introduced in order to prevent profuse, prolonged, and irregular uterine bleeding, as well as to prevent the occurrence of organic lesions in the endometrium such as, for example, above described endometrial polyps i.e. multiple endometrial polyposis.

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