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LETTER TO EDITOR

Meningiomas after cyproterone acetate exposure: Case reports in twin sisters☆

Abbreviation

MRI magnetic resonance imaging

TRAF7 TNF receptor-associated factor 7

Introduction

Meningioma is the most common intracranial tumor mainly occurring in women and developed from meningeal arachnoid cells [1]. Presence of hormonal receptors on meningioma is well established with a predominance of progesterone receptors [2]. Genetic alterations were also reported in patients with meningioma [3—5]. Recently, cyproterone acetate, a synthetic progestogen with anti-androgenic properties (indicated in France for major hirsutism in women) was associated with a dose and time-dependent risk of meningioma [6]. Since 2018, in France, a systematic brain magnetic resonance imaging (MRI) in exposed patients is recommended by the French health authorities [7]. However, the role of genetic factors in the occurrence of meningioma after cyproterone acetate exposure remained discussed.

We reported 2 cases of meningiomas in 35 years old homozygous twin sisters exposed to cyproterone acetate, levonorgestrel and ethinylestradiol.

Case report 1

Three frontal meningiomas were diagnosed in an asymptomatic woman. The patient was exposed to cyproterone acetate for hirsutism (50 mg/day) and to estroprogestative contraception containing levonorgestrel and ethinylestradiol (respectively 50 μg/30 μg during 6 days; 75 μg/40 μg during 5 days and 125 μg/30 μg during 10 days). Hirsutism was stable since teenage years without notion of high severity hirsutism and decreased slightly with cyproterone acetate. Cyproterone acetate was taken for 8 years and stopped 6 months before meningioma diagnosis and estroprogestative contraception was taken for 7 years and stopped the day of brain MRI. Imaging results showed a 35 mm width right frontal meningioma and two left frontal meningiomas (unspecified sizes). A control MRI, performed 6 months later, showed a decrease in the right frontal meningioma width (new width: 31 mm) and stability of the two others. There was no significant worsening of hirsutism during meningioma follow-up. Causality between meningiomas and drugs containing sexual hormones was evaluated ''plausible'' (I2) for cyproterone acetate exposure and ''possible'' (I1) for levonorgestrel/ethinylestradiol exposure according to the French pharmacovigilance method [8].

Case report 2

A frontal meningioma was diagnosed in the homozygous twin sister also asymptomatic. She was exposed to cyproterone acetate for hirsutism (50 mg/day) and estroprogestative contraception containing levonorgestrel and ethinylestradiol (respectively 50 μg/30 μg during 6 days; 75 μg/40 μg during 5 days and 125 μg/30 μg during 10 days). Hirsutism was stable since teenage years without notion of high severity hirsutism and decreased slightly with cyproterone acetate. Cyproterone acetate and estroprogestative contraception were taken for 9 years and respectively stopped one year and two years before the meningioma diagnosis. The patient was also exposed to estradiol (2 mg/day) for one year (stopped 5 months before meningioma diagnosis) and to levothyroxine (100 μg/day) for 11 years (uninterrupted). A systematic brain MRI found a right frontal 15 mm width meningioma. A control MRI performed 6 months later showed a significant decrease in the meningioma width (new width: 9.5 mm). There was no significant worsening of hirsutism during meningioma follow-up. Causality between meningiomas and drugs containing sexual hormones was evaluated ''plausible'' (I2) for cyproterone acetate exposure and ''possible'' (I1) for levonorgestrel/ethinylestradiol and estradiol exposure according to the French pharmacovigilance method [8].

Discussion

Meningiomas in homozygous twins are rare. As far as we know, these reports are the first ones published in twins after a long duration of cyproterone acetate exposure. These two case reports support the hypothesis of genetic susceptibilities in meningioma occurrence after exposure to cyproterone acetate. The pathophysiological mechanism of meningioma development after cyproterone acetate is generally explained through the presence of hormonal receptors on meningiomas and more frequently progesterone ones [9]. The long-term exposure to 50 mg/day of cyproterone acetate and the decrease in meningioma width after stop-

☆ These observations are registered in the French pharmacovigilance database under the reference TO20190673 and TO20190674 (18 April 2019).

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ping this drug strengthen its causality. Levonorgestrel and ethinylestradiol were also suspected even if the low dose of exposure suggested a lesser involvement in the meningioma development. The decrease in meningioma sizes in both twins after discontinuing hormonal drugs strengthens the causal relationship between these drugs and the adverse drug reaction. As ever reported above, genetic alterations were also described in meningiomas [3—5]. The main ones were NF2 gene aberrations on chromosome 22 (3,4) but others were identified such as mutations in TNF receptor-associated factor 7 (TRAF7) gene coding for the pro-apoptotic E3 ubiquitin ligase [5]. A statistically significant relationship between up or down-regulation of some gene expression and the presence of progesterone receptor was found in Claus' study [3], mainly genes located on the long arm of chromosome 22 but also on chromosome 2,3 and 4. Another study [9] found a significantly lower frequency of NF2 mutations and a significantly higher frequency of TRAF7 mutations in progestin-associated meningiomas compared to control meningiomas (not driven by progestin). Genomic alterations in the Phosphatidylinositol 3-kinase (PI3K) pathways were also found to be associated with progestin-responsive meningiomas [9,10]. Millis et al. [10] showed overexpression of progesterone receptors in 33% of solid tumor cases with PI3K pathway mutation against only 13% in solid tumor cases without PI3K pathway mutations. Due to the size and location of meningiomas in the two sisters here, no surgical treatment was required and no genetic analyses could be performed. However, the simultaneous occurrence of meningiomas after similar exposure to cyproterone acetate (dose and duration exposure) in these two homozygous twin sisters suggests that a common genetic mutation could influence the occurrence of this adverse drug reaction. In clinical practice, the discovery of a meningioma should systematically lead to search exposure to cyproterone acetate or any other direct or indirect modulator of progesterone receptor.

Disclosure of interest

The authors declare that they have no competing interest.

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