Case Report

Can Hormonal Contraceptive Therapy be a useful treatment in Fibromyalgia? A Case Report

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Abstract

Fibromyalgia (FM) is a common cause of central chronic widespread musculoskeletal pain, often accompanied by fatigue, cognitive disturbance, psychiatric symptoms, and multiple somatic symptoms. Its pathogenesis is still unknown and the treatment unsatisfactory. We reported a case of a young adult female affected by deep endometriosis, who developed FM symptoms soon after the interruption of the continuous contraceptive treatment and that recovered after that contraceptive treatment was restarted. To date, a relation between FM and female hormonal cycle has been demonstrated by few studies and evidences are inconclusive. This case report highlights the need of further investigation into the pathogenetic pathway of FM and the possible role of contraceptive treatment in improving patients' quality of life.

Keywords: Fibromyalgia; Contraceptive; HPA-axis; Cellular distress; Chronic pain; Hormonal imbalance; Endometriosis

Abbreviations: FM- Fibromyalgia; HPA- Hypothalamus-pituitary-adrenal; OC-Oral contraceptive

1. Introduction

Fibromyalgia (FM) is a common and still little understood syndrome characterized by a constellation of symptoms: centralized musculoskeletal pain amplification, fatigue, cognitive disturbance, psychiatric symptoms, and multiple somatic symptoms [1,2]. Since FM was recognized in 1981, its pathophysiology has been mysterious, both its diagnosis and propositions for therapy challenging [3], while a specific biomarker or a correlated genetic pattern have yet to be found. Despite its classification undergoing important changes over time [3-5], there still exists a strong disagreement between the definition criteria and the clinicians opinion [6], that today remains the diagnostic gold standard [7]. A genetic predisposition is responsible for about the half of the risk of developing FM, while environmental stimuli are responsible for the other half. In general, patients may recall a history of repeated physical [8] and/or psychological trauma (such as war [9] or car accidents [10]), a history of certain types of infections (eg. MERS, SARS-CoV, SARS-CoV-2 [11], Epstein-Barr virus, Lyme disease, Q fever, viral hepatitis, coxsackie B [12], parvovirus) [13] and a history of certain pharmacological treatment (eg. chemotherapy) [14]. Intriguingly, the common trait of the above mentioned processes is the blast of a sudden and unexpected overloads of cellular distress, that can prompt to a dysfunction of hypothalamus-pituitary-adrenal (HPA) axis [15] and vagal neurological signaling. It is been highlighted as 35-40% of survivors of traumatic brain injury developed some degree of hypopituitarism over years [10] and that TNF and IL-1 can stimulate pituitary cells to release hormonal precursors through the activation

of their genetic expression [16,17]. FM presents a prevalence of 4-6% [18], it can develop at any age, with a constant prevalence for men and a peak between 55-64 years old in women [19], and with a female: male ratio of 2:1. This gender gap highlights the fundamental role of sex hormones in the disease. While testosterone is protective in FM, the roles of female sex hormones are controversial and a sharp decrease in their blood level seems to worsen or even trigger the disease. Accordingly, in female gender the incidence of FM increases after menopause and symptoms show a worsening during the premenstrual phase and in the post-partum [20]. In this frame, evidences of the effect of hormone replacement therapy on FM clinical course are still lacking, contradictory and derived by anecdotal or retrospective studies. A Chinese epidemiological study comparing 38243 subjects with dysmenorrhea with 38243 subjects without dysmenorrhea showed, as expected, that the prevalence of FM was significantly higher in the population with dysmenorrhea than others. Interestingly, within this group, the prevalence of FM was significantly lower in subjects taking contraceptive therapy [21]. On the contrary, a small study carried out on healthy young women showed that, assuming contraceptive treatment eliminates the cyclic hormonal fluctuation of the induced pain, without reducing the number of tender points or the entity of the perceived pain overall [22-29]. We reported a case of a 31 years old female affected by deep endometriosis, which developed FM symptoms soon after the interruption of the continuous hormonal contraceptive treatment and that recovered after the HC treatment was restarted. Moreover, further hypotheses on the role of female sexual hormones in FM will be postulated.

2. Index Case Presentation

A 31-year old female was diagnosed in 2016 with deep endometriosis, during a routine trans-vaginal examination, showing a small typical right ovary endometrioma. She had noticed the emergence of a moderately painful menstrual cycle during the previous few months, that ameliorated with nonsteroidal anti-inflammatory drugs (NSAID). At the time, she was of a healthy status and practiced sport at a competitive level. She recalled a history of celiac disease, treated with a gluten free diet, and Hashimoto thyroiditis, with a preserved glandular function. She was a victim of a life-threatening traffic accident with post-traumatic stress disorder in 2006 that was later addressed and resolved. Approximately two months after the deep endometriosis diagnosis, she started to observe continuous pelvic pain, for which daily oral treatment with dienogest was prescribed. Unfortunately, after a while she experienced mood deflection and nervousness, so subsequently had her therapy switched to a cyclic oral contraceptive (OC) pills with ethinyl estradiol/dienogest, which ended mood alterations, but prompted persistent painful spotting [30-35]. Finally, the therapy was switched to a continuous hormonal treatment with ethonogestrel/ethinilestradiol by way of an endo-vaginal ring, without the bleeding break, that was then sufficiently tolerate by the patient. Indeed, the patient complained of experiencing excessive energy and persistent stress. Despite such side effects, she continued to follow the hormonal therapy, achieving pain control and clinical stabilization of the endometriosis. In 2018 the patient decided, on her own initiative, to withdrawal the treatment. A few hours after the endo-vaginal ring suspension, she acutely developed diarrhea, generalized arthromyealgis and fatigue. Inflammatory bowel diseases were excluded by means of negativity of the fecal calprotectin and autoimmunity routine screening and

thyroid function showed normal results. A clinical suspect of FM was therefore executed. Soon after, in agreement with her gynecologist, the hormonal ring treatment with ethonogestrel/ethinilestradiol was started again, with the immediate resolution of the above-mentioned symptoms. In 2019, in consideration of her desire to procreate, hormonal therapy was withdrawn a second time. The patient experienced a terrible flaring up of FM with a relatively painless menstrual bleeding however. She met the American College of Rheumatology (revised-2016) FM case definition criteria [36-40], with a Widespread Pain Index (WPI) score of 18/19 and a Symptom Severity Scale (SSS) score 8/12. Psychotherapy with both a psychological and somatic approach was carried out. An anti-inflammatory diet (gluten, lactose and processed sugar free) was also followed, yoga and meditation were implemented and 20 acupuncture sessions were performed. Her clinical condition slowly and progressively improved over 12 months, enabling the patient to remain hormonal therapy free, albeit not entirely reaching the previous healthy state. She complained of mild leg stiffness during the evening, sporadic fatigue, poor resistance to effort and several episodes of mental fog. At this moment the WPI score was 7/19 and the SSS score 5/12. The patient did not get pregnant and was a hired for a high-level job. In consideration of her pervious healthy state, she independently decided to start a mild progesterone supplementation with endo-vaginal natural progesterone 200 mg at 8:00 in the morning, together with endo-vaginal natural progesterone 100 mg at 20:00 in the evening, to further improve her mild FM symptoms and allow her to cope better with her daily activities. She benefitted from this therapy and has been without symptoms and menstrual bleeding for 4 months (WPI score 0/19; SSS score 1/12).

3. Discussion

As far as we know, this is the first case report that shows a clear link between FM symptoms and contraceptive therapy. Interestingly, two possible interpretation can be assumed: 1) due to the high prevalence of inflammatory comorbidities and even autoimmune diseases in women with endometriosis, the FM was masked by use of contraceptive therapy [23]; 2) the patients developed FM as a collateral effect of the continuous contraceptive therapy, to which she has never completely adapted, and that may have caused epigenetic changes in cells function [41]. The key role of hormones in determining the incidence and severity of FM, is becoming increasingly clear. Nevertheless, evidences derived by clinical studies are poor and pathogenetic mechanism still ambiguous. It is known that the prevalence of FM is higher in female than male gender after puberty, while, in pediatric ages it is of a similar level in both sexes [23]. As a result, it is reasonable to consider a protective role of testosterone in the development of the disease. Accordingly, a pilot study conducted over 12 subjects affected by FM, which investigated the therapeutic action of transdermal testosterone gel, showed a significant reduction of the pain and fatigue symptoms, proportionally to the increase of the serum testosterone concentration serum [24]. Curiously, while FM is more prevalent in women, its' incidence increases after the menopause and the childbirth, when the sexual hormones abruptly declines. This suggests an ambivalent role of female sexual hormones in the syndrome, that may act in pleiotropic ways and the possible protective role of a slightly fluctuating hormonal concentration. Additionally, we have to keep in mind that hormonal sensitivity, which depends on genetics and epigenetics factors, that determines the entity of receptor response to stimuli, is fundamental in understanding the individual hormonal function [24,25]. Sexual hormones can deeply interact with pain modulation mechanism on multiple levels, involving peripheral and central nociceptive cells, microglia and opioid systems. A small study conducted over 8 women with FM, showed a significant and inverse relationship between pain severity and progesterone as well as testosterone, with a statistically significant 25.6% of pain reduction rate between the lowest and the highest progesterone blood level. Moreover, cortisol seems to interacted with progesterone to influence pain perception, in reducing it when progesterone concentration is average, and slightly increasing it when blood progesterone is high or low26. Supporting this evidence, Maximo et al. observed that healthy users of hormonal therapy with etonogestrel and levonogestrel in vaginal ring and a subcutaneous progesterone implant or intra uterine device (IUD) showed a significantly higher pain thresholds than did nonusers of hormonal contraceptives or different contraceptives users altogether. Interestingly, etonogestrel and levonogestrel showed, among progestins, the greatest agonist effects on androgen receptors [27]. Moreover, the depot formulation guarantees a more stable drug bioavailability then the oral formulation [28]. All the above evidence supported the central role of progesterone as an anti-inflammatory, neuroprotective, and analgesic agent [28]. Conversely, however, the role of estradiol and its metabolites in pain modulation is contradictory and unresolved, because of its double action as a pronociceptive and an antinociceptive agent [29]. Moreover, estradiol also acts indirectly as modulator of pain and mood, by influencing the function of the serotonin reuptake transporter (SERT), depending on the time of the exposure to the ligand [30]. Interestingly, in ovariectomized rats muscular, nociception increased, and the exogenous supplementation of estradiol causes an antiallodynic effects

only belatedly after the administration, suggesting an epigenetic mechanism [31]. Finally, no conclusive evidences have been found with regards to the painkiller effect of estradiol in FM [26]. We can therefore summarize that endometriosis and FM have a common matrix: a neuroendocrine disequilibrium thus contributing to the progression of both the diseases. In fact, neurogenic mechanisms are described in endometriotic lesions and they affect the peripheral and central nervous system of these patients, increasing pain sensitivity and stress reactivity [23]. In that context, testosterone and progesterone supplementation could ameliorate FM symptoms, not only due to their anti-inflammatory and painkiller functions, but also due to their modulatory activity on stress response. Interestingly, both progesterone and testosterone are steroids hormones involved in stress response, like cortisol. Progesterone is directly synthetized by the adrenal gland in response to a stressor, equally in female and male gender [32] and is a precursor in cortisol biosynthesis. This may mean that, when women have lower levels of circulating progesterone, less cortisol may be synthesized and vice versa. When HPA axis is chronically dysfunctional, precursors to sex hormones are being used in priority to produce cortisol and other necessary stress hormones in the adrenal gland. Additionally, progesterone competitively binds to corticosteroid binding globulin, potentially resulting in higher levels of bioavailable cortisol [33]. Remarkably, hypocortisolaemia was associated to depression in patients affected by chronic fatigue syndrome (CFS) [34]. Ycaza Herrera et al. proved that physical stress increased progesterone and cortisol. Moreover they found that baseline progesterone and cortisol levels were positively correlated as well as the magnitude of progesterone and cortisol rises after stress induction [35]. Notably, it has been demonstrated that gender, menstrual

cycle and contraceptive use largely influence the HPA responsiveness to psychosocial stress in healthy subjects. Nevertheless, data about the impact of contraceptive therapy on stress response are lacking and contradictory. Kirshbaum et al. found that OC users presented a significant lower salivary-free cortisol after stress induction, without a reduction in ACTH and cortisol secretion with respect to non-contraceptive users and men, and explain the phenomenon with the enhancing effect of ethinyl-estradiol on the cortisol binding globulin (CBG) synthesis [36]. On the contrary, Fujimoto et al. suggested that long term use of combination OC results in increased adrenal responsiveness to ACTH mediated by an estrogens-facilitating effect in increasing in the sensitivity of the gland [36]. Notably, in the case of our patient, as drug therapy for FM, she has never taken anything outside of hormonal therapy and has maintained a good quality of life both during the year of combined estrogen-progestin treatment and during the months of progestin solo supplementation. Finally, we also want to mention the possibility that FM itself, in this sporadic case, was triggered by the use of continuous hormone therapy, to which the patient has never been able to fully adapt. Interestingly, has been demonstrated that therapy with high doses of progestins (e.g. megestrol acetate [37] and medroxyprogesterone acetate [38] can affect the HPA axis leading to inhibition of ACTH release, resulting in adrenal insufficiency. Such hormones may also exert a weak glucocorticoidlike activity, resulting in clinical manifestations of Cushing syndrome and diabetes [42]. Finally, Veldman et al. described a case of chronic fatigue syndrome in a patient with dysmenorrhea membranacea, a disease associated with high levels of progesterone that was triggered by contraceptive hormone therapy and also resolved soon after the hormone was interrupted [39].

4. Conclusions

We are convinced that the optimal FM treatment has to be patient-centered, multidisciplinary and integrated. In this context, our clinical case opens an important reflection on the potential therapeutic role of hormonal therapy in FM. More in general, we believe that progestogen, at least those with androgenic activity, can be involved in the optimization of the treatment of chronic pain conditions such as FM, both for its anti-inflammatory, pain-relieving function and for its capability to regulate the cortisol answer to stressors. To test this hypothesis, randomized clinical trial, possibly differentiating the hormone therapies (e.g. testosterone gel, dehydroepiandrosterone, combined estrogen-progestin and progestins alone) are needed. In addition, further studies on the interactions between progesterone and cortisol in stress response, both for healthy people and patients affected by FM are required.

Disclosure and conflict of interests

None of the authors have any disclosures to make with no conflict of interest

Ethical approval

The patient described in the case report gave their written consent to use her data. Written informed consent to publish this information was obtained from study participant. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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