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Menstrual Migraine and Treatment Options: Review Hormonal Therapy in the Prevention of Menstrual Migraine

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Abstract

Hormonal migraine is defined as the unilateral severe headaches that occur in reproductive aged women usually 7 days premenstrual to 3 days after onset of menses. This Short Commentary focuses on the fact that neurologists, major editors and pharmacists ignore and discount the facts that hormones, not pharmaceutical medications, define the cause, the biomarkers and treatment of this disease.

The problems for most internists treating migraine and headaches are four-fold: they are unfamiliar with the hormonal parameters that influence migraine in both men and women, uncomfortable in prescribing male and female hormones having insignificant training in medical school, the products have been generic for more than 50 years so pharmaceutical representatives do not educate physicians in alternatives to expensive and less effective abortive medications for headaches, and only a rare physicians perform Occipital Nerve Blocks (ONB) to eliminate Tension-Type Headaches (TTH). Should any breakthrough bleeding occur, the physician treating the woman with migraine headache will need to consult with a gynecologist? The following medication protocols are readily available to prevent hormonal migraine by preventing the fluctuation in hormones at menstruation: women's migraine can be prevented.

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Introduction

The recent review article in JAMA and Headache ignored 40 years of clinical research that identified menstrual migraine as caused by hormonal fluctuation and that the hormonal prevention therapies described herein have proven more effective than all the abortive therapies [1,2]. The neurologist, internists and family practitioner physicians shun preventative hormonal therapy because of their unfamiliarity for what to tell their patients about hormonal therapies, risks and minor complications such as menstrual spotting.

Even the republication of a smaller subset of my original work [3] with leuprolide acetate in migraine by Murray and Muse [4] with the supported by Tap-Abbott pharmaceuticals was not included in the 'unbiased' review article puts objectivity, physiology and intent to suppress information at the forefront of my objections to standard medical therapy [1-2].

Migraine headaches are a gender specific disease

Women of reproductive age have six times more migraine then men and 80 percent occur in proximity to their menstrual period. The migraine frequency and severity may worsen with estradiol containing oral contraception, and hormones prescribe at menopause; migraines often improve in later pregnancy and off hormone therapy as in the menopause. The hormonal origins of migraine were delineated by neurologist Somerville [5] in 1972 when he observed that the drop in estradiol, not progesterone, at menstruation triggered the migraine in this population of women sufferers. Lichten et al. [6] confirmed that the estradiol threshold was 50 pg/ml. Although Somerville [7] attempted prophylactic program with implanted estradiol pellets failed due to poor pellet design, prevention of hormonal/menstrual migraine does occur in two-thirds of this population by keeping the estradiol level above the threshold (Greenblatt's [8], Magos et al. [9], Lichten's [10] with long-acting estradiol pellets). Dennerstein et al. [11] reported success with the estradiol patch. Lichten et al. [12] use of daily oral danazol was equally successful by maintaining the serum estradiol level below the threshold. By preventing the fluctuation in estradiol the estrogen receptors in the carotid notch remain stabilized; only under fluctuating estrogen conditions do these hormonally driven

Table 1: Laboratory Tests during Medication Therapies.

Date	CBC	Metabolic	TSH	Estradiol	Testosterone	SHBG	F.A.I.
07-06-10	Wbc 9.4	Mag 4.9	1.8		40	118	1.11%
Danozol	CRP 0.1						
10-06-10							
Mixed Androgen Injections							
12/28/2015			9.7	FSH <4.4	<1	42	n/a
				E2= 18			
7/13/2016	Hgb14.2		0.2	8.3	134	32	13.80%
				E2 = 33			
09/06/1017	CRP <0.1		1.3	FSH=8.3	51	50	3.36%

Note: treatment kept the estradiol serum level below 33 pg/ml and the Free Androgen Index 4-12 times the baseline measurement on danazol.

vascular migraines occur.

Case Presentation

EW is a 36-year old woman who started having her menses at age 14. Her adolescent years were marred by both severe menstrual pain and migraine occurring in close proximity to the onset of her menses. With oral contraception making her symptoms worse; she underwent laparoscopy at age 21 that showed endometriosis. Treatment with danazol 200 mg three times and then twice daily due to side effects failed to relieve her menstrual pain. She conceived and bore twins in late 2007 and another baby by caesarian section in 2009. Both the menstrual pain and migraines recurred with such severity that she was scheduled for hysterectomy and bilateral oophorectomy by her gynecologist. She then started in 2010 weekly injections of nandrolone and stanozolol weekly injections (Mixed Androgen Therapy (MAT) based on the previous published use of this protocol in a case of severe endometriosis [13]. This woman's endometriosis pain, menses, migraines, and premenstrual syndrome disappeared as her poor libido and muscle tone improved. She has remained on the Mixed Androgen Therapy (MAT) successfully now for 8 years without any complaint.

Medication protocol

The mixed androgen therapy consists of 20 mg of nandrolone and 10 mg of stanozolol given as a single weekly intramuscular injection. Stanozolol is chemically related to danazol [14] and will lower estradiol levels dependent on dosage of the pharmaceutical agent. Standard stanozolol dosage is 6 mg per day giving comparable biochemical effects of 600 mg of danazolol. The dose utilized is one-quarter the FDA approved dose given weekly. Nandrolone is the FDA approved first derivative of testosterone. Standard intramuscular dosage in the literature ranges to 100 mg per week for women. Nandrolone cannot be aromatized to estradiol nor reduce by 5-a reductase to Dihydrotestosterone (DHT). Therefore, without *in vivo* estradiol production, the estradiol serum level has remained below 15 pg/ml. Androgen prevents both the menopausal flashes and vaginal atrophy. Reduction in naturally produced DHT reduces hirsutism, acne, facial hair and increases muscle development and libido. Spironolactone 100 mg daily is prescribed as a protective agent against hirsutism development.

Results

Her laboratory tests appear in Table 1. The increase in the FAI from ineffective danazol therapy to effective Mixed Androgen Therapy (MAT) with stanozolol and nandrolone was 1.11% to 13.6% or 13-fold. The higher FAI put the patient into remission both for migraine and endometriosis. She remains migraine and endometriosis pain and symptom free now 8 years after starting the Mixed Androgen Therapy (MAT).

Discussion

The previous understanding of the physiology of both endometriosis and menstrual migraine are now focused on prevention. Prevention of migraine occurs by preventing the fluctuating estradiol levels and the estradiol threshold being as of key importance. Similarly, prevention of endometriosis pain depends on lowering the estradiol threshold low enough to prevent growth of the endometrial implants. Dickey et al. [15] documented that the most severe pain with endometriosis responded to higher doses of danazol that lowered the serum estradiol levels in a dose-dependent manner. Estradiol levels, per se, have been related directly to the pain that occurs with endometriosis. However, until the case report at the American college of obstetricians and gynecologists meeting in April 2014 [13], few realized that there was a more complicated physiology ongoing. Lichten [13] presented that the mixed androgen therapy of nandrolone and stanozolol would successfully relieve pain in the most severe case of endometriosis after failures of all standard therapies of danazol, leuprolide medical therapy and then hysterectomy with oophorectomy. In this case report here in with endometriosis and migraine, the use of the same protocol with nandrolone and stanozolol brought relief to both. The Mixed Androgen Therapy (MAT) not only lowered the serum estradiol levels below measureable levels and reduced the bio available free estradiol to treat endometriosis concurrent with present thinking, but it primarily raised the Free Androgen Index (FAI) multiple fold higher than danazol. In doing so, these medications improved the healing anabolic effects of nandrolone and suppressed by 80 percent the sex-hormone-binding globulin that is the denominator of the Free Estradiol and the Free Testosterone indices. The key is that the mixed androgen therapy addresses not only *in vivo* estradiol and testosterone levels but by lowers SHBG, this therapy blocks the entry of xenoestrogens through the androgen receptor. Observed, thereafter, there is improved recovery and potential long-term remissions as the xenoestrogens are not able to enter the cell and populate the nuclear estrogen receptors.

Lichten explains that there are two forms of estrogens: *in vivo* (bio-available) estradiol and estrone and in vitro (environmental/xenoestrogen) derivatives from bisphenol-A, dioxin, persistent organochlorine pesticides (DDT), jet fuel, flame retardants, manmade hormones, and other manmade chemicals working in

association to potentiate each other. Both natural estrogens and xenoestrogens induce an increase in the Sex Hormone Binding Globulin (SHBG) from the liver. As SHBG binds 98 percent of anabolic hormones (testosterone, nandrolone, DHT), "SHBG is an oestrogen amplifier" [16]. Laboratory testing cannot measure serum levels of xenoestrogens.

Burke and Anderson [16] in 1972 defined the Free Androgen Index (FAI) as the ratio of total testosterone divided by SHBG. Higher levels of FAI force estradiol levels to be minimized. Therefore, the addition of nandrolone to raise the TT and lower levels of SHBG optimize the anabolic potential and minimize the estradiol effects, no matter what is observed in the laboratory testing. Similarly, he defined the free estradiol index as the ratio of total testosterone divided by sex-hormone binding globulin.

While danazol is able to lower estradiol less than 25 pg/ml and raises the FAI by 2 to 3 fold, the mixed androgen therapy lowers estradiol level below 15 pg/ml and raises the FAI by 4 to 40-fold. The mixed androgen therapy suppresses the Hypothalamic-Pituitary Axis (HPA) minimizing the hot flush, flashes, and menopausal symptomatology often experienced with danazol and leuprolide acetate.

Biomarker

Lichten et al. [6] in 1996 recorded observations that menstrual migraine is an epigenetic disease due to the genetic disposition for migraine and 20 the epic-(add on) fluctuation in estradiol at menstruation. The serum estradiol threshold level for migraine and/or endometriosis could be considered a biomarker as the carotid notch that become unstable when the serum estradiol falls below approximately 50 pg/ml.

Instead of relying on estradiol levels alone, the use of the Free Androgen Index (FAI) relies on the anti-estrogen therapy of nandrolone and stanozolol which preferentially improve upon the results observed with danazol. Because bio-available estradiol, Free Estradiol Index (FEI) is secondary to changes in both sex-hormone-binding globulin and total testosterone the use of the single measurement of bio available testosterone, The Free Androgen Index (FAI) incorporates all the biomarkers into just one.

Conclusion

The term migraines, especially as it applies to women of reproductive years, are predominant observation close to menstruation and are designates as a hormonal event. Biochemically researchers have confirmed that for migraineurs, both characteristics of the drop in estradiol levels occurs and in genetic predetermined individuals must occur. In the 20 years since publication of the migraine prevention article by Lichten et al. [12] with danazol, the increased failure of danazol therapy may be due to the increased accumulation of xenoestrogens in the environment. As these xenoestrogens may be as potent as estradiol in their affinity for the androgen and estrogen receptors, an improved therapy to lower estrogen levels is seen here with use of a combination of nandrolone and stanozolol weekly self-intramuscular injections. Evaluation and treatment is best accomplished by using the Free Androgen Index (FAI) as the biomarker that increases with the Mixed Androgen Therapy (MAT) more so than danazol. MAT may prove to be more effective in therapy for hormonal migraine, endometriosis and the s women experience around menstruation.

For women with severe headaches, after collecting the hormonal history (association with menstrual cycle, oral contraception, absence with pregnancy), the good doctor now will use the positive response to Occipital Nerve Blocks (ONB) to reduce the tension-type headaches; avoiding scattergun prescriptions, C-T scans and chiropractic manipulations. With tension type headaches being managed, hormonal suppression medications delineated above is started on the third day of the menstrual cycle. Typically with the weekly mixed androgen injections, the premenstrual migraine disappears along with the menses.

Physicians who treat migraines and headaches must recognize that migraine is a gender specific medicinal disease; observing the incidence of migraine during reproductive years favors women 6:1. Clearly, the cause is hormonal and effective preventive treatment is the result of both lowering estradiol and establishing a stable hormonal milieu. The reality is that the internists, family practitioners and neurologists avoid hormonal therapy because of a lack of knowledge and fear of dealing with gynecologic issues. Hopefully the availability of the mixed androgen therapy that will prevent almost 100% of breakthrough bleeding side-effects will encourage the physician treating migraine and headaches to seek out the cause, the biomarker and treat with MAT hormonal therapy. Treating the preventable cause is always superior to chasing the symptoms.

Prevention Treatment: Stabilizing Estradiol Levels above the Threshold

Based on these observations, various researchers have tried to stabilize estradiol levels above or below the observed 50 pg/ml threshold to prevent fluctuation and migraine. In summary, five physician researchers from neurology, psychiatry and three gynecologists have proven so.

1. Somerville [7]: estradiol implantation of pellets. Due to poor dissolution rates, failed.

2. Greenblatt [8]: Greenblatt used estradiol pellets compressed at 50,000 psi since 1950; the greater pressure and a superior matrix maintained the 25 mg pellet integrity for 6 to 8 weeks. Available from compounding pharmacies, Greenbelt's reported showed long term effective migraine prevention for up to 20 years with 25 mg to 75 mg per implantation. Magos et al. [9] in England and Lichten's [10] in the United States confirmed Greenblatt's findings with the higher PSI pellets. The addition of 25 of testosterone may be advantageous for numerous reasons including libido, mental focus, endurance and its antidepressant effects.

3. Dennerstein [11] observed that the estradiol serum level could be maintained with the estradiol topical patch. Dosage can range from one or two 0.1 mg% patch once to twice per week. Higher estradiol levels may precipitate menstrual bleeding. As higher doses of estradiol may induce menstruation cycling, daily progesterone 100 mg at bedtime has been implored. Should the patient undergo major gynecologic surgery, post-operatively, she may resume the hormone patches or implanted pellets to maintain estradiol stability [11].

4. The short action of estradiol tablets (hours) and the wide variations of estradiol intramuscular injections do not work well for prevention of menstrual migraine. However, estradiol tablets placed sublingually may abort a woman's hormonal migraine allowing time to institute an aforementioned medical stabilizing regimen. Steven Silverberg, president of the American Headache Society has

commented that 'hormonal therapy' can safely be instituted 'after the menses has occurred.

Treatment: Stabilizing Estradiol Levels below the Threshold

1. Lichten's [12] in 1991 established in his study of resistant hormonal migraine sufferers that danazol 200 mg taken twice daily for 25 of 28 days per month dramatically suppressed these taciturn migraines in 67 of 81 sufferers in at 12-months. Some of these women had had migraines for more than 10 years and became to the most part, migraine free on danazol. The author explains that danazol as an anabolic hormone that suppresses estradiol levels proportionally to dose. When the dosage brought the serum estradiol under the 50 pg/ml level consistently, migraine attacks were prevented.

2. Lichten et al. [3] and Murray and Muse [4] used leuprolide acetate to lower the estradiol level below the established threshold. Due to the extreme drop in estradiol, both authors added back the estradiol patch at 0.025 mg to 0.05 mg percent. This regimen had a success rate of approximately 50 percent as both authors observed the combination medication regimen led to fluctuating serum levels due to varying absorption and therefore more migraines than the aforementioned hormonal medications listed.

3. Lichten et al. [12] illustrates in this new Case Report that the combination of nandrolone 20 mg and stanozolol 10 mg as a weekly intramuscular injection is even more effective than danazol of which it has bio-similar properties.

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