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ROLE OF ESTROGEN IN DEVELOPMENT OF MIGRAINE

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ABSTRACT

Migraines are benign conditions but negatively affects the quality of life of the migraineurs. Migraines are expressed as pain associated with vasodilatation of cerebral and meningeal arteries and are classified as occurring with or without a visual aura. Migraines are 3 times more common in women than in men. They may be associated with the menstrual period, ameliorated by pregnancy, diminished at menopause and may worsen with menopausal hormone treatment. These observations indicate that fluctuations in estrogen levels may be a precipitating factor for migraines. Several polymorphisms are associated with familial migraine including genetic variation in Estrogen Receptors (ER). ER stimulates NO production in vascular endothelium this causes direct modification of migraine. Migraine is a risk factor for stroke, thus, it is concluded that the elevated estrogen level is one of the main factors responsible for the development of migraine and its preponderance in females along with the polymorphisms of estrogen receptors that affect nitric oxide production therefore causing modulation of migraines.

KEYWORDS: Estrogens, Migraines, Estrogen receptors, Nitric oxide.

INTRODUCTION

Migraines are benign conditions[1,2] but negatively affects the quality of life of the migraineurs. Neurovascular component is one of the main etiology of migraine. Migraines are expressed as pain associated with vasodilatation of cerebral and meningeal arteries and are classified as occurring with or without a visual aura, thus implicating different neuronal involvement between the two types of migraines.[1-5] Indeed, individuals who experience aura can be biochemically differentiated from those who do not.[6]

Migraines are 3 times more common in women than in men.[4,7] They may be associated with the menstrual period, ameliorated by pregnancy, diminished at menopause and may worsen with menopausal hormone treatment. These observations indicate that fluctuations in estrogen levels, may be a precipitating factor for migraines.[1,3,5] But, the differences in circulating levels of estrogen were not observed between women with and without menstrual migraine. Urinary excretion of estrone-3-glucuronide was double in women with migraine than in those who did not experience migraine, thus the ability to metabolize estrogen may be related to the development of migraine.[5] Therefore, further studies related to estrogen metabolism among women who experience migraines, with or without aura, and women who do not, need to be conducted especially related to the production of catecholestrogens that influence production and disposition of adrenergic neurotransmitters thus participating in neuronally induced cerebral vasospasm.[1,7]

Polymorphism of estrogen receptors

Several polymorphisms are associated with familial migraine including genetic variation in Estrogen Receptor alpha (ERα) (G594A polymorphism of exon 8).[8,9,10] Estrogen receptors are located within brain nuclei innervating the cerebral vasculature as well as other nuclei regulating cardiovascular function.[7] Thus, besides influencing adrenergic mechanisms, estrogen may also modulate central opioidergic tone, release of peptidergic transmitters from trigeminal nuclei, and the GABAergic system, perhaps modulating NO.[11,12,4,7,13]

Estrogen receptors and Nitric Oxide (NO)

ERα stimulates NO production in vascular endothelium, this causes direct modification of migraine. Platelet production of NO was greater in women with menstrual migraine than in those without.[4] NO released from platelets contribute to decrease cerebral vascular tone. A polymorphism E298D in eNOS results in decreased activity of the enzyme and is also associated with increased risk for cardiovascular and cerebrovascular disease. The homozygous variant is an independent risk factor for stroke in persons with migraine with aura. Females participation in the studies related to migraine is about 80% which reflects that the condition is prominent in women.[14] More studies are needed to establish the association of genetic variation in eNOS with those of

ERα in a larger population. If the genetic variant results in decreased activity of eNOS, the results are difficult to interpret within the context that increased production of NO may trigger migraine.[15] Some evidences suggest that neuronally derived NO is also involved in the etiology of migraine, but no association of migraine with genetic variation of neuronal nitric oxide synthase was found. [11,12,14] Further research is required regarding estrogenic modulation of all three isoforms of nitric oxide synthase in the cerebrovascular unit.

In addition to estrogenic modulation of neuronal transmission associated with pain and endothelial NO[17,7,16] estrogen may induce migraine through direct effects on vascular smooth muscle cells. For example, estrogen increased the efflux of magnesium from cultured cerebral smooth muscle cells.[18]

Migraine and stroke

Migraine may be a risk factor for stroke, as revealed by Atherosclerosis Risk in Communities Study, according to which there is increased incidence of ischemic stroke in young women who experience migraine with aura.[19] This observation also points to an underlying pathological condition of the neurovascular unit contributing to migraine.[17,20,21] These observations point to the need to understand and differentiate factors contributing to stroke risk.[2,22] Several chronic alterations in small arterial anatomy and function, which may not show a sex difference in frequency, predispose an individual to ischemic stroke and migraine with aura.

Migraine during women's life

The woman's reproductive cycle is regulated by the hypothalamic hypophyseal-ovarian axis through the release of estrogen and progesterone. Variations in the levels of these hormones and of their feedback control regulate the menstrual cycle, pregnancy, puerperium, and menopause.

A normal menstrual cycle lasts about 28 days and consists of two phases: the follicular or the proliferative phaseand the luteal or ovulatory phase. The first day of menstruation is considered the start of follicular phase and bleeding occurs after estrogen and progesterone levels decrease at the end of the previous cycle. At this time, the pituitary follicular stimulating hormone (FSH) level increases slightly, stimulating the development of several ovarian follicles. Each follicle contains an oocyte; only one follicle proceeds through ovulation producing increased levels of estrogens, which result in a drop of the FSH production, preventing the additional development of follicles, and in the stimulation of the hypophysis to release the luteinizing hormone (LH). Progesterone remains low during the follicular phase except for a small rise just prior to ovulation. At the time of ovulation, a mature follicle ruptures in response to a surge of LH, releasing a mature oocyte. The luteal phase starts just after ovulation and during this phase the follicle, denominated corpus luteum, secretes progesterone and estrogen, which stimulate the endometrium to prepare a thick layer of blood vessels for possible fertilization. If no pregnancy occurs, the corpus luteum persists for about 14 days and then degenerates with a fall in blood estrogen and progesterone levels and a shedding of the top layers of endometrium for the beginning of a new menstrual cycle.

When pregnancy occurs, the trophoblast releases the human chorionic gonadotropin (hCG) which allows the corpus luteum to continue to produce estrogen and progesterone until the formation of the placenta. The placenta, from that point on, produces the majority of estrogen and progesterone necessary for the pregnancy. Serum levels of estradiol and progesterone begin to rise in the mother during the 6th to 8th week of pregnancy and continue to gradually increase to their highest levels during the third trimester; serum estradiol levels during the third trimester of pregnancy are 30–40 times higher and progesterone levels are 20 times higher than their peak levels during natural menstrual cycles. The hormonal levels drop sharply during the puerperium that is defined as the time from delivery of the placenta through the first few weeks after the delivery (usually 6 weeks) and represents the phase in which the woman's body returns back to prepregnancy condition.

The transition from the reproductive to the non-reproductive phase occurs over a period of years and is the result of a reduction in female hormonal production by the ovaries. Although the perimenopausal period is characterized by considerable fluctuations of estrogen and progesterone levels, higher than during the normal phases of menstrual cycle in the fertile period, the menopause is characterized by hormonal stability due to decline of estrogen and progesterone production by the ovaries. The average age of menopause is 51 years, within an age range of 40-60 years.[6]

Migraine and the risk of vascular disease

Ischemic stroke

- Numerous studies demonstrating an association with migraine with aura
- No definite association with migraine without aura
- Association with migraine with aura confirmed by three meta-analyses

Hemorrhagic stroke

- A single large study indicating an association with migraine with auraw22; other studies providing conflicting results

Cardiac events

- Two large studies indicating an association with any migraine in men and women and with migraine with aura in women (data not available for men); conflicting results provided by other available studies
- No association with any migraine in meta-analysis of dataw30; no analysis according to migraine type due to lack of data.

Vascular death

- A meta-analysis and a large study supporting an association with migraine with aura
- No association with any migraine according to meta-analysis of data.

Other vascular diseases

- Studies indicating a possible association with any migraine and retinal disease and peripheral artery
- Disease.

CONCLUSION

Migraine represents a substantial health care burden, both clinically and economically. Individuals with migraine and their families consume substantially more health care resources than those without migraine headache. Therefore, it is imperative that standardized diagnostic criteria be consistently implemented in clinical trials and used to develop appropriate treatment algorithms and provide governmental bodies (eg, National Institutes of Health) with a rationale to support research and education for menstrual migraine.

Pharmacological studies are needed to elucidate the interplay between estrogen and serotonergic signals. Standardized diagnostic criteria would be useful to further elucidate risks for estrogen induced migraines, characterize the patterns of menstrual migraine in women, and determine its economic impact. Future clinical trials will be helpful in identifying treatment strategies for acute migraine attacks and may establish the role of short-term prevention in migraineurs. Armed with this knowledge, women and their physicians can better manage this disabling disorder through appropriate diagnosis and evidence based treatment regimens.

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