MENSTRUAL MIGRAINE, OLD AND NEW

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Summary: The Authors reviewed the connection between sexual hormones and migraine crisis. Besides other exogenous factors, the fall of estradiol blood levels in the late luteal and premenstrual phase seems a causal factor in the origin of menstrual-related headache crisis.

The behaviour of migraine crisis during the various events of female reproductive life, support this view.

The role of PRL, T, FSH and LH was also discussed.

On the other hand, menstrual migraine represents a model that fits perfectly with a neuroendocrine hypothesis which is based upon a faulty chronobiological response of the so-called antinociceptive system.

The group of primary headaches is a collection of heterogeneous diseases that even today escape precise taxonomic criteria and valid pathogenetic interpretation ([1]).

Migraine is a type of periodic headache, unilateral, throbbing, that usually begins in adolescence and presents characteristic recurrences in adult life ([2]).

Through the various forms (classic, neurological, common) the most frequent is the common type that affects 19% of the female population ([3]). Migraine presents headache attacks variable in intensity, frequency, duration, accompained by anorexia, nausea, vomiting and personality changes ([1, 2]).

In adult life the women to men ratio affected by the disease is 3/1 ([4]). The migraine worsens during the menstrual period in 60% of cases; the pain crisis is associated exclusively with menstruation in 14% of cases ([3, 4]).

The temporal link between migraine and menstruation is variable; the crisis tends to arise immediately before the flow in most cases, but also at the termination of the menstrual period or otherwise at the time of ovulation.

The headache is frequently a part (38-76% of cases) of the picture of premenstrual syndrome. In this case though, the pain crisis does not have a precise clinical characteristic. At times this headache is a migraine in origin, at other times it is a tension or tension-vascular headache ([5, 6]).

The events of female reproductive life modify the frequency and gravity of the pain crisis. Migraine diminishes in pregnancy in 78% of cases ([7]); during oral contraceptive combined pill use it might appear for the first time, worsen, or otherwise improve ([8]).

In menopause the migraine has a variable behaviour ([7]).

The cyclical hormonal fluctuations and the events of reproductive life function like a pace-maker of intensities and frequency of the crisis evoking a causal relationship between hormonal variation and the raising of pain.

THE ROLE OF SEXUAL HORMONES

The fall of estradiol and progesterone levels are the hormonal markers of the late luteal and premenstrual phase. The coincidence of this event with the period of maximal frequency and intensity of migraine crisis suggest responsibility correlating to these hormonal levels arousing the pain crisis.

First reports of Whitty *et al.* [8], suggested that menstrual migraine was a condition provoked by the fall of progesterone levels in late luteal phase.

This concept was reexamined and modified by Sommerville, who, not verifying the therapeutical effects of progesterone administration in luteal phase nor the coincidence of progesterone withdrawal and onset of migraine crisis, investigated the role of estrogens [9]. Sommerville was able to postpone and delay the classifical migraine crisis and to demonstrate the costant coincidence between physiological or therapeutical estrogen withdrawal and migraine crisis [10].

This was made possible through intramuscular administration of estradiol valerate and monitoring its levels [10, 11, 12].

These results have been confirmed successively by other investigators who utilized oral estrogens in menopause, demonstrating the parallel between withholding therapy and the increase of frequency and intensity of headache crisis [13, 14].

Premenstrual estrogen withdrawal has assumed the title of a "trigger" for migraine attack. Less frequently migraine crisis may be in connection with preovulatory estrogen withdrawal since presumably estrogen initially has only a "primer" function and successively becomes a "trigger" [11, 12].

Various reports demonstrated that basal estradiol and progesterone blood levels are constantly more elevated in migraineurs groups with respect to the control in the various phases of the cycle prevailing in premenstrual phase [7, 15].

Great importance has not been given to the absolute values of blood hormonal levels nor it has been possible to recognize the threshold values which precipitate the pain crisis, this being the moment in which hormonal levels decrease most rapidly [10, 11, 12].

The influence on frequency/intensity of migraine crisis by an estrogenic steady-state, induced through subcutaneous estradiol implants, was initially investigated by Sommerville with non-univocal results [10]. Recent reports by Al Magos *et al.* [15], show effectiveness on reduction of menstrual migraine crisis (83% of the patients completely recover) through the suppression of cyclical ovarian activity and the creation of constant blood estradiol levels by subcutaneous estradiol implants.

Pregnancy represents a particular physiological model because sexual hormonal levels, especially estrogens, reach values 100 times greater than that of the basal values of eumenorrheic women.

During gestation there is one constant reduction of the intensity: ... frequency of the crisis that is about 70%, with periods pratically free in the 3rd trimester [7, 9].

64% of women with previous medical history of menstrual migraine have pain crisis in the first post-partum week [16].

The constantly elevated levels of sexual hormones and the absence of physiological fluctuations would be responsible for the net reduction of crisis during pregnancy. Headaches reappear in the first post-partum week in association with the rapid hormonal fall [16].

The Royal College of General Practitioners reports headaches and migraine the most common symptoms in oral contraceptive combined (OC) pill users [17].

Many trials have been conducted on the link between migraine and pill usage, but the results are not univocal in relation to the various methodological bias (variation in the type and dosage of drug investigated, length of trials, failure to distinguish between headaches and migraine) [13, 17, 18].

In 18-40% of migraineurs taking OC, the migraine crisis worsens, it improved in 11-36%, and attacks can appear for the first time in 5-10% of cases [18].

Most crises appear during cyclic interruption of treatment in relation to the hormonal fall artificially induced.

Although an increase of cerebrovascular accidents in migraineurs using OC has never been demonstrated, previous history of migraine would be considered a relative contraindication to the OC use [19]. Further increase of headaches might indicate a vascular instability that would increase the risk of thromboembolic accidents [19,20],

Menopause represents a decline of cyclical ovarian function and a physiological condition in which hormonal levels are low.

Available data on the influence of menopause on migraine is limited and confused. At times the crises disappear when the menstrual cycle permanently ceases, at other times they may begin or worsen [21, 22].

Headache is a part of "minor" psychological or tension symptomatology of menopause [23].

This introduces a noteworthy bias in evaluation of the real incidence and prevalence of migraine in this period of life.

The eventual mechanism by which the fall of estrogenic hormonal levels provoke migraine crises is fully discussed [24, 25].

The classical studies of Wolf *et al.* [24] have demonstrated that migraine attacks are characterized by a preliminary cerebral vasoconstriction phase followed by painful dilation of the arteries of the scalp.

Grant [25] demonstrated typical estrogen induced arteriolar hypertrophy in the endometrium of patients with menstrual migraine.

Salvatore *et al.* [26] demonstrated uterine arteriolar vasoconstriction in premenstrual phase induced by estrogen fall. A similar model has been suggested for the scalp vessels, although histological alterations have never been demonstrated.

Sommerville [11, 12] suggest that estrogen might only have a "primer" function in the scalp vessels which respond to other stimuli as well. The studies of Curran *et al.* [27] have demonstrated the fall of serotonin blood levels during migraine attacks.

The metabolism of this neurotransmitter is influenced by estrogens. These may inhibit the activity of 5-hydroxytryptophan decarboxylase which is a pyridoxine dependent enzyme [28].

A shunt mechanism may result in a reduction of serotonin synthesis.

The deficit would be corrected by vit. B_6 supplements [28, 29].

Nevertheless 98% of blood serotonin is produced by platelets. Estrogen can favour its hyperaggregability during migraine attacks. According to a study conducted by Kemman [30] 58% of hyperprolactinemic patients (independent from pituitary adenoma) suffer from frequent (one or more per week) headache episodes whose nature has not been clarified. On the other hand in various reports [32, 33] basal prolactin levels have not resulted significantly elevated in respect to the control.

Metoclopramide, a powerful prolactinic stimulator, appears to reduce the frequency of migraine crisis [31].

Bromocriptine, a dopaminergic agonist, is a drug which reduces the frequency of migraine attacks only when they are part of the premenstrual syndrome [32].

Nader *et al.* [33] were not able to demonstrate a direct link between pain attacks precipitated by alcohol or intravenous glucose, which are characteristic factors that initiate migraine attacks, and prolactin values.

It is probable, in reality, that the supposed prolactinic alterations represent an indicator of dopaminergic disfunction.

NEUROENDOCRINOLOGICAL APPROACH. A CHRONOBIOLOGICAL HYPOTHESIS

Headaches, menstrual or not, represent periodic symptomatologic manifestations of a presumably primary condition or trait on which endogenous or exogenous factors act, precipitating pain attacks.

The pain perception is linked to the functions of the so-called antinociceptive

sensory system whose activity is variously modulated at the CNS level and its periphery ([34]).

Although a precise anatomic location of this system has not been recognized, various monoamines used as neurotransmitters modify the responses to the nociceptive stimuli (serotonine, dopamine, epinephrine).

The functions of the nociceptive system are rythmical and present oscillations in relation to various events (circadian variations, sleep/wake cycle, light/dark cycle, hormonal variations) ([35]).

Rythmical "trigger" biological events can provoke a lowering of the pain adaptive or nociceptive threshold.

This model perfectly fits the explanation of a headache because "trigger" periodic events (ovulation, menstruation, hormonal variation, seasonal variation) which are rooted in the cyclical variation of antinociceptive system, establish precise temporal patterns of the disease ([36]).

In the light of these considerations it is important to recognize the factors that characterize the "trait" or cephalalgic susceptibility, as well as the relationship existing between this and "trigger" events.

Nappi *et al.* ([37]) found that menstrual migraineurs present a prolactinic response to a stimulation test (sulpiride) or a blocking test (lisuride) clearly excessive in both cases with respect to the healthy or cephalalgic controls (daily chronic headache).

This is a classic example of a faulty dynamic response of the tuberoinfundibolar dopaminic system (TIDA).

The study undertaken with an indirect dopaminergic agonist (nomifensine) from the response of TIDA system, has led to the conclusion that the presynaptic neuron has reduced dopaminic contents since prolactinic response is scarcely inhibited ([36]).

The circadian cycle of various endocrine functions (Prl, Gh, cortisol) and of many vegetative functions (blood pressure, oral temperature) have been found varied in patients with primary headaches testifying neurotransmitter disregulation ([38]).

Periodic fluctuations of the threshold and adaptation to pain of the nociceptive system seem to be modulated by the endogenous opioids.

Blood levels of β-lipotropin (β-LPH) and β-endorphin (β-EP) have been considered the markers of endogenous analgesia level ([39]).

Besides the circadian variation, endorphinic tone varies with age and with the various events of the reproductive life (hormonal cyclical variations, pregnancy, childbirth, menopause) each one of which are characterized by typical β-LPH and β-EP levels ([40]).

The study of central opioid tone in menstrual migraine undertaken by the naloxone dynamic test, has shown a reduced response with respect to the controls in premenstrual phases verifying an opioid tone and therefore a reduced pain threshold ([41]).

This is important in the pathogenesis of headache crisis.

Peripherally a reduction of blood and CSF β-EP levels has been found in patients with daily chronic headaches ([42]).

The link exhisting between alterations in endorphinic tone and disregulation of TIDA system has been postulated, but still insufficiently investigated.

On the other hand the link existing between sexual hormones and opioid tone is sufficiently demonstrated.

A reduced P/E_2 ratio is a characteristic of premenstrual syndrome ([43]).

This reduced ratio present a mirror behaviour with respect to the fall of central opioid tone evaluated through naloxone test ([44]).

Discussions continue as to whether between the two events, a relation of cause and effect exists. Future investigations would be definitive in clarifying this topic.

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