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Review

Premenstrual syndrome mechanism in the brain

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ABSTRACT

Premenstrual syndrome (PMS) is a disorder in which a set of physical, emotional, and behavioral symptoms, mostly seen in the late luteal phase of the menstrual cycle, disappear with the onset of menstruation. It has a high incidence in society, and it causes problems in a person's daily life. Premenstrual dysphoric disorder is diagnosed when symptoms are clinically or socially more severe. Although the exact cause of these disorders is unknown, numerous theories have been proposed, including gonadal hormones, neurotransmitters, central nervous system (CNS) abnormalities, diet, genetic factors, and environmental factors. In this study, current studies on premenstrual disorders and the brain were compiled to shed light on the etiology of PMS. In the light of the literature, a summary of recent studies on the role of neurotransmitters related to PMS, functioning in the CNS, hormonal changes, gray matter, brain resting state, abnormalities in the limbic system, emotion processing and regulation, genetic explanations, nutrition, and alternative medicine has been presented.

Keywords: Brain, GABA, gene polymorphism, hippocampus, mood, premenstrual dysphoric disorder, premenstrual syndrome, serotonin.

From puberty until menopause, women are twice as likely as men to experience depression and anxiety.[1] Although the reasons for sex-related differences are unknown, hormonal fluctuations are likely to generate depressed states in sexually mature women, such as postpartum depression, perimenopausal depression, premenstrual syndrome (PMS), and premenstrual dysphoric disorder (PMDD).[2,3] It has an impact on women's quality of life and performance in a variety of ways. Premenstrual syndrome and brain studies are the subjects of this review.

Premenstrual syndrome is a condition in which women have psychological, physiological and behavioral symptoms in the late luteal phase of their menstrual cycle; these symptoms usually disappear once menstruation begins. It was first described by Frank in 1931.[4] In 1953, he coined the term "premenstrual syndrome" to describe the condition. It is historically first encountered in Ancient Greece, and Hippocrates' definition of hysteria, "chills, headaches, fatigue indicating the onset of menstruation,"[5] points to PMS.

Menstrual cycle

The hypothalamic-pituitary-gonadal (HPG) axis regulates hormonal variations during the menstrual cycle, which lasts 28 days. Hypothalamus secretes gonadotropin-releasing hormone (GnRH) which stimulates anterior pituitary to produce luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Both LH and FSH stimulate the production of estrogen and progesterone in the ovaries. Hormone levels then provide negative feedback to the hypothalamus and pituitary to reduce GnRH, LH, and FSH secretion.[6,7]

There are two phases in the menstrual cycle, the follicular phase, and the luteal phase. The follicular phase begins on the first day of menstruation and ends with ovulation, then the

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luteal phase continues until menstruation occurs again. Early in the follicular phase, estradiol and progesterone levels are usually low. Estradiol rises fast in the late follicular phase the following week, while LH surges just before ovulation. Estradiol drops significantly and then rises again in the luteal phase, while progesterone peaks at day 21 of a 28-day cycle. During the late luteal phase, just before menstruation, both hormone levels steadily decrease.[6,7]

Premenstrual syndrome

Breast swelling, headaches, nausea, vomiting, diarrhea, edema in the body, weakness, weight gain, decreased concentration, forgetfulness, excessive sleepiness or insomnia, change in sexual desire, feeling alone, depressed mood, irritability, tension, nervousness, anxiety, aggression, and depression-like feelings are the most common symptoms of PMS.[8-14] Symptoms worsen six days before menstruation begins and peak two days before.[9]

These symptoms are most common in women in their reproductive years, between the ages of 30 and 40.[15] Although symptoms are present in 70 to 80% of women, on average, 5% of women have clinically significant and more severe symptoms.[8] The World Health Organization (WHO) estimated that 199 million women suffer from PMS in 2010.[16] During their luteal phase, an estimated 80% of menstruating women around the world experience one or more PMS symptoms.[17] According to another study, roughly 30 to 40% of women of reproductive age suffer from PMS, with 3 to 8% of menstrual women experiencing more severe symptoms. The duration of emotional symptoms ranges from a few days to two weeks.[13] Premenstrual syndrome has a wide range of prevalence. The pooled prevalence of PMS was 47.8% in a meta-analysis study based on 17 papers, with France having the lowest prevalence at 12% and Iran having the highest at 98%.[18]

Etiology of PMS

The mental, neurological, and endocrine systems all have a role in the etiology of PMS. In the literature, various ideas for the complex pathogenesis of PMS irritability have been proposed. Premenstrual syndrome is thought to be caused by a malfunction of the hypothalamic-pituitary-adrenal (HPA) axis, which causes problems with adrenal hormone secretion and nutritional inadequacies.[19] Likewise, endocrine system assumption is used to explain the PMS physiopathological process.[20] On the other hand, in the hormonal etiology of PMDD, physiological changes in gonadal hormones are thought to trigger central neurochemical reactions that reveal symptoms.[14] There are also explanations that highlights the role of hormones. The central nervous system (CNS) sensitivity hypothesis is another possibility.[21] There are studies that indicate a hereditary component as well.[22-24]

Premenstrual dysphoric disorder is a depressive disorder that affects functionality, is less common, and is listed in the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5), which includes more severe PMS symptoms. It is well recognized that a higher score on the Daily Record of Severity of Problems (DRSP) scale, which is used to identify and diagnose symptoms, is associated with increased stress and negative outcomes in patients.[25] Premenstrual dysphoric disorder is diagnosed according to the criteria of DSM-5 and the evaluation of daily symptoms with the DRSP scale for at least two months (Table 1).[26,27]

Gonadal hormones hypothesis

Mood symptoms appear during the luteal phase and disappear immediately after menstruation, implying that gonadal steroids (estrogen and progesterone) have a role in PMS pathogenesis.[9] One view is that predisposed women overreact to normal gonadal hormone changes and develop PMS symptoms as a result of neurochemical events. Circulating ovarian steroids, particularly progesterone and its metabolite allopregnanolone, have a temporary relation.[28] Induction of mood symptoms is caused by prolonged exposure to progesterone during the luteal phase and withdrawal from progesterone during menstruation.[29] Estrogen receptors (ERα and ERβ) and progesterone receptors (PR-A and PR-B) have been found in cognition-related brain regions such as the amygdala, hippocampus (HIPP), and prefrontal cortex.[6] On the other hand, estrogen and progesterone interact with neurotransmitter systems associated with memory, learning, and executive function,

Table 1. Premenstrual dysphoric disorder[27]

A. In the majority of menstrual cycles, at least five symptoms should be present in the last week before the onset of menses, these symptoms begin to improve within a few days of the onset of menstruation and drastically decrease or disappear in the week after menstruation.

B. One (or more) of the following symptoms must be present:
   1. Marked emotional lability (e.g., mood swings; suddenly feeling sad or tearful, or increased sensitivity to not being accepted).
   2. A marked increase in anger, irritability, or interpersonal conflicts.
   3. A marked depressed mood, feelings of hopelessness, or self-deprecating thoughts.
   4. Marked anxiety, nervousness and/or being on edge or irritable.

C. One (or more) of the following additional symptoms must also be present, for a total of five symptoms when combined with the symptoms in Criterion B:
   1. Decreased interest in usual activities (e.g., work, school, friends, leisure pursuits).
   2. Subjective difficulty in focusing.
   3. Drowsiness, easy fatigue, or a marked decrease in inner strength.
   4. A marked change in food cravings; overeating or excessive cravings for certain foods.
   5. Excessive sleepiness or insomnia.
   6. Feeling overwhelmed or out of control.
   7. Bodily symptoms such as breast tenderness or swelling, joint or muscle pain, "swelling like a drum" sensation, or weight gain.

Note: Symptoms on diagnostic measures A-C should have been present for most of the previous year's menstrual cycles.

D. These symptoms resolve with clinically significant distress or impairment at work, school, usual social activities, or relationships with others (eg, avoidance of social activities; decreased productivity and efficiency at work, school, or home).

E. The disorder is not simply an exacerbation of symptoms of another disorder, such as major depressive disorder (MDD), panic disorder, persistent depressive disorder (dysthymia), or a personality disorder (although it may co-occur with any of these disorders).

F. Criterion A should be confirmed by prospective daily grading during at least two symptomatic cycles. (Note: The diagnosis may be tentatively made before such confirmation.)

G. These symptoms cannot be attributed to the physiological effects of a substance (e.g., a substance of abuse, a drug, or other treatment) or another health condition (e.g., hyperthyroidism).

including serotonergic, gamma-aminobutyric acid (GABA)-ergic, dopaminergic, and glutamatergic pathways.[30]

Combined oral contraceptives (COCs) are used in the treatment of gynecological symptoms of PMS. Increased sensitivity to the high progesterone level that occurs after ovulation, as well as ovulation suppression, has been observed to generate a variety of behavioral and physical premenstrual symptoms. Selective serotonin reuptake inhibitors (SSRIs) are effective in the treatment of nervousness and anxiety symptoms.[13] Other reproductive hormones, such as estradiol, testosterone, the adrenal hormones cortisol, and dehydroepiandrosterone sulfate, prolactin, and thyroxine, have similarly failed to differentiate women with PMD from controls in previous studies.[31]

Central nervous system hypothesis

The factors leading to CNS malfunctions in PMS have not been entirely understood. Many symptoms of PMDD, on the other hand, are comparable to psychiatric conditions involving the serotonergic system, and the links between the serotonergic system and progesterone have focused researchers' attention on serotonergic regulation.[14] Serotonin, or 5-hydroxytryptamine (5-HT), is a neurotransmitter that regulates mood, appetite, arousal, and circadian rhythms, and its depletion causes depression symptoms.[32] Studies show that women with PMS exhibit abnormal serotonergic function during the luteal phase.[32] The two best-studied neurotransmitter systems involved in the formation of symptoms are the GABAergic and serotonergic systems.[32]

Anxiety is caused by progesterone, which is produced largely in the corpus luteum (CL) of the ovaries.[14] The factor responsible for triggering PMS symptoms has been seen as progesterone produced by the CL.[33] Premenstrual syndrome is not experienced by premenarchal girls, postmenopausal women, or those who have had bilateral oophorectomy. The role of progesterone in the onset of negative symptoms is unknown. Although progesterone and estrogen levels are high, there are no symptoms of PMS during pregnancy.[32] Its metabolites allopregnanolone and pregnenolone are anxiolytics and sedatives via gamma-aminobutyric acid type A receptors

(GABAARs). Progesterone and serotonin coexist in cells in the brain's median raphe nucleus, and progesterone promotes serotonin reuptake. Progesterone suppresses estrogen receptors and increases monoamine oxidase (MAO) activity, lowering serotonin availability and resulting in a depressed mood.[14,32] Although there is compelling evidence that progesterone plays a role in the pathophysiology of PMS, studies have shown that the classical progesterone receptor is not involved in this process, and many double-blind randomized controlled trials (RCTs) have failed to demonstrate the efficacy of progesterone supplementation.[32-34]

The changing topology of the brain concerning pain is suggested to contribute to the understanding of the neurological mechanism of PMS.[35] Changes in mRNA expression of serotonin receptors 5-HT1A and 5-HT2A, GABAARs, and central monoamine neurotransmitter receptors, including ERα and ERβ, progesterone receptors, and central steroidal hormone receptors, were seen in the limbic system of a macaque model with PMS.[15] The involvement of the CNS in PMS is becoming clear due to an increase in brain imaging studies.

Genetic, psychological, and environmental hypotheses

The regulatory role of the Val158Met genotype and the investigation of the less functional variant of Val66Met were mentioned in numerous gene studies, and it was suggested that 5-HTTLPR and MAOA-uVNTR polymorphisms be investigated.[36-38] It has been proven that the vitamin D receptor (VDR) Fok1 polymorphism is significantly associated with PMS, the presence of Ff and ff genotypes increases the susceptibility to premenstrual disorders, and the FF genotype, which is common among Arab women, has a higher risk.[24] Similarly, PMS has been linked to temporal-limbic system (TLS) abnormalities that are inherited or acquired at an early age.[39] Furthermore, a study found that 56% of PMS is inherited, and women with PMDD may have distinct biological responses to ovarian steroids.[40] According to some studies, the estrogen receptor 1 (ESR1) gene promotes vulnerability to PMDD, and the ESR1 polymorphism causes sensitivity to changes in estrogen receptor signaling and other physiological gonadal hormone alterations.[41,42]

In addition to genetic factors, the individual's culture, sex education, and the mother's educational background are thought to play a role in the development of these syndromes.[43] It has been observed that there is a strong link between a lack of sex education and experiencing PMS symptoms. One study discovered a link between childhood trauma and the occurrence of PMS, particularly among women who had experienced abuse in the past.[44] The etiology of PMS is associated with cognitive and psychosocial learning theories.[14] Furthermore, recent research into the relationship between nutrition and PMS may provide insight into the underlying causes.[24,45]

PREMENSTRUAL SYNDROME-RELATED BRAIN STUDIES

Neurotransmitters in central nervous system

The fact that glutamatergic, GABAergic, cholinergic, serotonergic, noradrenergic, and dopaminergic neurotransmitter systems modulate hormonal effects on brain structure and function demands an investigation of their functions in PMS.[46] The etiology of PMDD has been linked to functional dysregulation of the CNS in numerous studies.[32,47-49]

Serotonergic system

Since the 1960s, pharmacological observations on the effects of tricyclic antidepressants, which are thought to act by increasing synaptic concentrations of serotonin and norepinephrine, on depression have led to the hypothesis that serotonin plays a role in the pathogenesis of major depressive disorder (MDD). Aggression, impulse control, anxiety, sexual behavior, pain, sleep, and eating difficulties are some of the symptoms of PMS, and these symptoms are associated with the serotonergic system. Some studies demonstrated that tryptophan, a serotonin precursor, has antidepressant properties and that acute tryptophan deficiency exacerbates premenstrual symptoms.[50,51] An integrated explanation that there may be a sensitivity to progesterone during the postovulatory phase in PMDD and that the sensitivity is probably due

to an abnormal neurotransmitter (serotonergic) makes it meaningful to understand and study the serotonergic system.[14]

First, tryptophan hydroxylase, the rate-limiting enzyme, produces 5-hydroxytryptophan, followed by the decarboxylation of 5-hydroxytryptophan to 5-HT by L-aromatic amino acid decarboxylase in the CNS. At the presynaptic terminal, 5-HT is stored in vesicles, ready to be released when nerve impulses arrive. When 5-HT is released into the synaptic cleft, it is then inactivated primarily by reuptake via the high-affinity presynaptic membrane serotonin transporter (SERT or 5-HTT). Serotonergic activity in the brain is affected by estrogen and progesterone. The role of estrogen in increasing the breakdown of MAO, the enzyme responsible for the oxidation of monoamines, and catechol-O-methyltransferase (COMT), the enzyme responsible for the breakdown of catecholamines, is instrumental in regulating the availability of free tryptophan in the CNS.[32]

Currently, the SSRIs in treatment for PMDD are administered with intermittent dosing during the luteal phase.[52,53] However, it is known that SSRIs cause problems in sexual function. Nevertheless, the first-line treatment for PMS symptoms is still serotonergic antidepressants.[10,13,53] Studies are showing that the intermittent use of SSRIs increases the effectiveness of the treatment.[54] In a case report, it was observed that SSRIs used in the treatment of a patient with PMDD after brain injury were not functional in reducing suicidal thoughts and preventing other symptoms.[55] The mechanism by which SSRIs increase central allopregnanolone levels in both rats and humans may include direct stimulation of 3α-hydroxysteroid dehydrogenase (3α-HSD), the enzyme that catalyzes the reduction of 5α-dihydroprogesterone (5α-DHP) to allopregnanolone.[41] Despite the effectiveness of SSRIs in PMDD, more research is needed to understand the underlying mechanism and to evaluate the treatment as a whole, including psychosocial therapies in addition to PMS.

Noradrenergic system

In a review made in previous years, studies thought to be related to the noradrenergic system in different patient groups were discussed. The levels of methoxy-4-hydroxyphenylglycol (MHPG), a metabolite of norepinephrine, in the cerebrospinal fluid (CSF) of PMS patients were considerably higher in the premenstrual phase than in the midcycle phase. Noradrenergic neurons originate from the locus coeruleus, and direct stimulation of this circuit produces anxiety reactions similar to panic attacks in humans.[50] This idea may be supported by a study of a norepinephrine dysfunction hypothesis in the panic disorder of a series of noradrenergic difficulties.[31] However, no research on the relationship of this system with PMS has been found in current studies.

GABAergic system

Progesterone metabolites formed in the ovary, CL, and brain bind to the GABA receptor's neurosteroid binding site on the membrane, rendering it resistant to subsequent activation.[32]

The following is the concept of how it works: GABA is derived from glutamate (Glu), which is generated by the Krebs cycle and then decarboxylated to GABA by glutamic acid decarboxylase, a rate-limiting enzyme found mostly in GABAergic neurons. Gamma-aminobutyric acid is then stored in vesicles located at the presynaptic terminal of GABAergic neurons. Three subtypes of GABA postsynaptic receptors have been identified: GABAA, GABAB, and GABAC receptors. However, endogenous agents, such as progesterone-derived neuroactive steroids or neuroactive steroids generated in the CNS, as well as exogenous agents, such as progestogens, benzodiazepines, and barbiturates, bind to the GABAA receptor.[32]

Bixo et al.[56] demonstrated that allopregnanolone is the triggering factor for negative mood symptoms in PMDD in their study on GABA active steroids in the female brain, and that isoallopregnanolone may help to reduce symptoms by antagonizing allopregnanolone's impact on the GABAA receptor. It is sedative at high concentrations and has been reported to have mood-altering adverse effects in susceptible women at levels corresponding to luteal phase concentrations.[56] Increasing allopregnanolone levels in the mid-luteal phase were linked to an increase in mood and anxiety symptoms, according to two studies.[57,58] The synthesis is first converted to allopregnanolone by the enzyme 3α-HSD, followed by enzymatic conversion of

progesterone to 5α-DHP by the 5α-reductase enzyme.[41]

Saccadic eye velocity (SEV), an objective involuntary measure of the sedative/anxiolytic effect of GABAA receptor activation in response to SEV-benzodiazepines, is measured by electrooculography to detect GABAA-mediated sedation.[56] In studies using SEV, the GABAA receptor sensitivity was found to be lowered in PMDD symptoms.[41]

Allopregnanolone is one of the few endogenous progesterone metabolites that has a substantial positive modulatory impact on the GABAA receptor in the brain and is involved in mood disorders in both men and women.[39,41,59] In general, unregulated allopregnanolone is thought to induce susceptibility to symptoms. According to a study, allopregnanolone is the triggering factor for negative mood symptoms in PMDD, and isoallopregnanolone may help to reduce symptoms by antagonizing allopregnanolone's impact on the GABAA receptor.[56] A study on an animal model suggests that women with PMS related to the cerebellum may have deficiencies in the mechanisms that regulate GABA subunits.[32] In another randomized controlled trial, PMDD symptoms were significantly reduced when the conversion of progesterone to allopregnanolone was blocked by dutasteride, an 5α-reductase inhibitor.[60]

Another research examined the putative noncompetitive antagonistic effect of allopregnanolone, a sepranolone (UC1010) isomer. The endogenous steroid isoallopregnanolone has been tested and found effective compared with placebo as a potential new treatment for PMDD.[56] Another study supports the conclusion that isoallopregnanolone antagonizes the decrease in SEV caused by allopregnanolone and self-reported sedation, possibly non-competitively.[61]

In a recent study, herbal treatment using Inochinohaha White (IHW), traditional Japanese medicine for medicine, was tried in a rodent model, and it was found to be effective in PMS treatment. It has been found that ethanol extracts of IHW (EE-IHW) increase brain-derived neurotrophic factor (BDNF) levels in a dose-dependent manner.[62]

Studies provide implications for increased cerebellar activity and decreased GABA-mediated inhibition during the symptomatic luteal phase.[32,63]

Gray matter

Gray matter (GM) morphology, as assessed by volumetric neuroimaging, is influenced by the menstrual cycle in healthy women and is directly related to the hormonal effects of estrogen due to estrogen's association with the HIPP, neurogenesis, and synaptic plasticity.[36]

A resting-state functional magnetic resonance imaging (rsfMRI) study on female brains has found that GM volume in anterior cingulate cortex (ACC) is significantly correlated with menstrual cycle.[64] In other studies, increased hippocampal GM was reported in the late follicular phase compared to the late luteal phase.[36,65] Another study investigating abnormalities in GM volumes and structural covariance patterns in PMS patients found increased GM volumes in the precuneus/posterior cingulate cortex (PCC) and decreased GM volumes in the thalamus and insula compared to healthy controls.[66]

Brain resting-state activity and connectivity

A longitudinal study between April 2014 and October 2017 examined PMDD patients and healthy controls and presented conclusions about the brain topology in PMDD.[67] Premenstrual dysphoric disorder patients exhibited hypoconnectivity in the anterior temporal lobe and hyperconnectivity of the basal ganglia and thalamus decreased network separation, increased network integration, and abnormal regional network measurements compared to healthy controls. Network changes were consistent across symptomatic and asymptomatic menstrual cycle stages, suggesting trait vulnerability markers in PMDD. These systems-level neural measures were associated with difficulties in emotion regulation and specific subsets of functional connectivity (FC) that mediate the relationship between difficulties in emotion regulation and PMDD. Essentially, PMDD patients had increased aggregation and centrality in the basal ganglia and thalamus, and decreased aggregation and centrality in the temporal

and occipital cortex.[67] It is stated that the scale used to diagnose individuals with PMDD in this study was conducted to include PMS by keeping the DRSP low. Similarly, another study showed stronger connectivity between the middle temporal gyrus and frontal-parietal lob in women with PMDD than in controls.[68] It has been reported that these topological features of brain networks are impaired in various psychiatric disorders such as schizophrenia, autism and major depression and are associated with depression severity and neuroticism.[67]

A particular gap in our knowledge of the pathophysiology of PMDD, as well as PMS, is the brain's internal network organization during a 'resting state', that is, without an external stimulus or task.[65,69] Premenstrual syndrome patients have been found to have an abnormal default mode network (DMN), including increased FC in the precentral gyrus and temporal gyrus and decreased FC in the PCC and middle frontal gyrus.[66] These areas are thought to be linked to symptoms. Women with PMS during the luteal phase showed decreased connectivity in the middle frontal gyrus and parahippocampal gyrus and increased connectivity in the left superior temporal gyrus and precentral gyrus within the DMN compared to healthy participants in a study examining the brain at rest.[70] Abnormal DMN examinations may be functional in explaining PMS pathology.

Limbic system, hippocampus, and hypothalamus

The HIPP and hypothalamus are the most studied anatomical regions in understanding the pathogenesis of PMS. Abnormalities in these regions also play a role in other mood disorders. The HIPP contains evidence of hippocampal structural and functional changes associated with menstruation changes.[65] It is thought that PMS patients may experience a range of adverse stimuli which can potentially affect the function of HIPP in the late luteal phase.[13]

Allopregnanolone is produced in the next step of 5α-reductase type I and 3α-HSD enzymes from progesterone, and these two enzymes are mostly found in the cerebral cortex, HIPP, and amygdala regions of the brain.[71] Insufficiency of allopregnanolone at the stage where it should increase causes the HPA axis to fail to maintain homeostasis after stress.

A study in rats investigating the ratio of Glu to GABA in PMS of Shu-Yu capsule (SYC), a traditional Chinese medicine formulation, showed that PMS is associated with dysregulation in the HIPP.[48] A recent study demonstrated hypoconnectivity of the anterior temporal lobe and hyperconnectivity of the basal ganglia and thalamus during the menstrual phases of PMDD patients.[67]

The fractional amplitude of low-frequency fluctuations (fALFF) is a data-driven method that is thought to reflect the intensity of spontaneous activity in the resting state of the brain. In a recent study investigating hippocampal alteration in premenstrual disorders using the FC method to identify the relationships between fALFF and neuronal activation patterns of different brain regions, PMS patients showed abnormal left HIPP compared to healthy subjects, based on brain activity and the left HIPP as the seed region. In addition, the DRSP results are correlated with FC between the left HIPP and medial prefrontal cortex (mPFC) in PMS patients.[65] The results provide the inference that hormonal fluctuations in the menstrual period are associated with hippocampal activity.

Other potential reasons for mood disorders that should be screened for an individual diagnosed with PMDD following severe traumatic brain injury (TBI), such as depression, anxiety, and HPA axis abnormalities, are reported in a case report study.[55] The precuneus, the key node of the DMN associated with emotional processing, is essential in a distributed network of cortical and subcortical regions to integrate both self-generated and external information. In a study, it was found that ReHo (regional homogeneity) values decreased in some areas of the DMN, which is a network involved in self-referential activities such as remembering the past and planning for the future.[49]

A study evaluating the neural activity pattern in PMS patients at rest in the luteal phase found decreased fALFF in the ACC and increased fALFF in the precuneus, left inferior temporal cortex, and HIPP. Additionally, the DRSP scale was performed, and a positive correlation was found.[72] Increased fALFF in the left HIPP may

explain cognitive performance and memory problems in PMS.

Unlike previous studies, new proteins were identified in an animal study of PMS using two-dimensional gel electrophoresis for proteome mapping of the hypothalamus and HIPP. The expression of Ulip2, tubulin beta chain 15, β actin, and interleukin 1 receptor helper protein was decreased; the expression of kappa-B motif-binding phosphoprotein was increased; the expression of ubiquitin carboxy, albumin, aldolase, M2 pyruvate kinase, and panthenol-cytochrome C reductase core protein I was decreased; finally, the expression of calcium-binding protein was increased.[15]

In a study examining PMDD, changes in GM volumes were reported in the HIPP/parahippocampus and cerebellum.[73]

Emotion regulation and processing

The emotions such as aggression and anxiety are processed in amygdala. Patients with premenstrual symptoms had more difficulties controlling emotion than women who did not have premenstrual symptoms, according to a PMDD study on brain topology.[67]

The HIPP plays an important role in the limbic system, encoding and recalling memory, self-reference processing, cognitive-behavioral and emotional processing.[65]

In one study, information compiled from various studies included increased follicular amygdala reactivity to emotional faces, decreased parietal reactivity during response inhibition, and different results regarding prefrontal reactivity in PMDD. It was reported that dorsolateral prefrontal activity increases during the menstrual period during a working memory task and decreases during the luteal phase during an emotion regulation task. Likewise, dorsomedial prefrontal activity in the late luteal phase in PMDD increased during anticipation of negative emotional stimuli, and ventromedial prefrontal activity in the emotional matching task decreased during the menstrual phases in PMDD.[67] In a study, FC analysis results are associated with emotional processing, behavioral and physical modulations in PMS (increased FC in the left HIPP, left mPFC, and left-PCC; decreased FC in the right midcingulate cortex, bilateral precentral gyrus, and right orbitofrontal cortex).[65]

Genetic studies

In a recent genetic study, untreated lymphoblastoid cell line (LCL) cultures from females with PMDD revealed overexpression of ESC/E(Z) complex genes via ribonucleic acid (RNA)-sequencing, and these genes, MTF2, PHF19, and SIRT1, were found to have significant effects when compared with a control group ($p<0.05$). In contrast, protein expression of the ESC/E(Z) genes was decreased in PMDD LCLs untreated with MTF2, PHF19, and SIRT1 ($p<0.05$). Lymphoblastoid cell lines from women with PMDD show a cellular difference in ESC/E(Z) complex function both in the untreated condition and in response to ovarian hormones. It is thought that the difference in the function of ESC/E(Z) complex genes may explain premenstrual disorders.[40]

In addition, single nucleotide polymorphisms in the ESR1 gene are associated with PMDD.[13] In a review, four single nucleotide polymorphisms located in the non-coding protein regions of the ESR1 gene were reported to be associated with PMDD, variations in the intron region of a gene, which may have a significant impact in regulating gene expression, and the ESR1 polymorphism, which may be associated with altered estrogen receptor signaling and sensitivity to otherwise physiological gonadal hormone levels.[41]

In a study reported for the first time in the literature, a significant relationship was observed between the VDR, VDR FokI polymorphism, and PMS expressed in many tissues, including the brain. However, in subgroup analysis by ethnicity, the FF genotype was more predominant among Arab women, with the ff mutation associated with a significantly higher risk for PMS among non-Arabs. Moreover, this study revealed differences in terms of race. A significant difference in the frequencies of the VDR polymorphism was found between the Arab and non-Arab populations.[24]

Minerals and nutritional effects

The 5-Hydroxytryptamine 3 receptor (5-HT3R) generates a non-selective cation channel through which sodium, potassium, and calcium ions can pass after being activated.[74]

In one study, it was found that people who took 400 IU or more of vitamin D daily had a reduced prevalence of PMS than those who took less vitamin D.[45] Calcium therapy is also applied as a non-drug treatments in PMDD and PMS.[13] In addition, there are significant similarities between hypocalcemia and PMS symptoms in studies showing that calcium supplementation therapy is effective.[75,76]

On the other hand, it is thought that thyroid dysfunction, fluid retention, and hypoglycemia may play a role in PMS.[14] Carbohydrate intake has been associated with serotonin levels, and low serotonin in the brain is thought to be important in the pathophysiology of PMS.[39] The fact that α-Linolenic acid deficiency causes a significant decrease in dopamine levels, which causes an increase in aldosterone level and water retention, may also explain the physiology of PMS. The role of B group vitamins in the formation of riboflavin, tryptophan, and serotonin shows the importance of nutrition in premenstrual disorders. Vitamin E inhibits arachidonic acid, causing a decrease in the GABA level, the effects of which were already mentioned in this study. Likewise, low dietary magnesium causes a decrease in dopamine levels in the brain. The association of iron, sodium, potassium, and zinc with PMS has been demonstrated.[45]

Another recent study showed that 12 weeks of zinc supplementation in women with PMS had beneficial effects on mean scores of physical and psychological symptoms, as well as serum levels of total antioxidant capacity and BDNF.[77] Studying leptin, a hormone that regulates food intake and appetite seems reasonable given the symptoms of PMS. In a study examining leptin, which is considered a prerequisite for menstrual bleeding and normal reproductive and neuroendocrine function, women with PMDD showed higher uncontrolled and emotional eating, lower cognitive restriction, higher depression and impulsivity in the long luteal phase, and the study demonstrated higher concentrations of leptin from the early luteal phase to the late luteal phase.[78] In conclusion, current brain studies were reviewed in this study to understand the etiology of PMS. Functions of the CNS, abnormal responses to normal hormonal changes, changes in GM volume in the brain, differences in activities in the resting state of the brain, abnormalities in the limbic system, causes of disturbances in emotion processing and regulation, genetic predispositions and their explanations, and the role of nutrition, mineral, and vitamin intake were presented to shed light on the mechanism. The pathophysiology of PMS has been reported to be highly complicated, involving many factors, including genetic, cultural, physiological, particularly brain physiology, and psychological explanations. Since various mechanisms are responsible for the pathophysiology of PMS, it is suggested that the etiology of PMS can be understood more clearly with a holistic perspective and interdisciplinary study.

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