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Aims and scope

Headache and Pain Research (Headache Pain Res; pISSN: 3022-9057, eISSN: 3022-4764) publishes original articles, review articles, and short letters on all aspects of Headache and Pain Research. The main topics include migraine, cluster headache, tension-type headache, intracranial hypotension, intracranial hypertension, reversible cerebral vasoconstriction syndrome, other primary or secondary headache disorders, and issues related headache and pain such as dizziness, psychological, and cognitive problems. *Headache and Pain Research*, the official journal of Korean Headache Society, aims to rapidly spread updated advances in the headache and pain field to readers and patients, while fostering a scientifically fair and progressive relationship with researchers and reviewers. Its regional scope is currently on Korea, but it aims to grow into an international journal and welcomes outstanding editorial board members and submissions from all over the world.

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Headache and Pain Research

Migraine in Women: Inescapable Femaleness?

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The understanding of migraines as neurological conditions has significantly advanced in recent years. However, societal perceptions often attribute migraines, especially in women, to personality traits instead of acknowledging them as complex neurological conditions. Two review papers published in *Headache and Pain Research*, by Kim and Park[1] and by Seo,[2] focused on migraines in women and menstrual migraines, highlighting the importance of recognizing the influence of hormonal fluctuations and genetic susceptibility on migraines, beyond the scope of individual characteristics or traits.

The higher incidence of migraines in women has been linked to various hormonal phases and intervals during their reproductive years, including menarche, pregnancy, the postpartum period, breastfeeding, perimenopause, menopause, and the use of oral contraceptives and hormone replacement therapy. Fluctuations in estrogen, in particular, are a key factor in the pathophysiology of migraines, markedly affecting the frequency, severity, and duration of migraine episodes in women.[3]

Perimenstrual migraine attacks are typically more severe and harder to manage. Research utilizing headache and menstruation diaries has shown that these perimenstrual attacks are more disabling and tend to last longer than those not associated with the menstrual cycle.[4] Additionally, interictal plasma concentrations of calcitonin gene-related peptide are elevated in women who experience menstrually related migraines during their periods, compared to healthy women.[5] However, many women often downplay the role of menses when initially asked about a temporal relationship and do not monitor their headaches or hormonal influences. It is essential for healthcare providers to take a comprehensive history of hormonal events during the initial consultation with women who present with headaches. Pharmacological treatments must take into account potential pregnancy-related issues and their effects on fetal development. Concurrently, non-pharmacological strategies such as lifestyle adjustments, stress management, and dietary modifications are equally important, particularly during pregnancy.

Despite advancements in migraine research, significant knowledge gaps persist concerning the gender-specific aspects of its management. Further research is required to elucidate the underlying mechanisms that lead to variations in hormone levels, which in turn affect the prevalence, symptoms, and treatment responses of migraines. Moreover, investigations into the safety and efficacy of migraine treatments during pregnancy remain crucial for informing clinical practice.

In conclusion, migraines in women constitute a complex condition influenced by hormonal fluctuations and various life stages. It is essential to develop tailored management strategies that consider individual needs and potential considerations related to pregnancy in order to

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optimize outcomes. Continued research focusing on the gender-specific aspects of migraines is necessary to meet the unmet needs of women who experience this debilitating condition. Recognizing migraines as a biological disease influenced by hormonal changes will hopefully lead to more effective headache treatments that are customized to a patient's hormonal status.

AVAILABILITY OF DATA AND MATERIAL

Not applicable.

AUTHOR CONTRIBUTIONS

Conceptualization, Data curation, Formal analysis, Writing–original draft, Writing–review and editing: SKK.

CONFLICT OF INTEREST

Soo-Kyoung Kim is the Editor of *Headache and Pain Research* and was not involved in the review process of this article. Author has no other conflicts of interest to declare.

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Review Article

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Migraines in Women: A Focus on Reproductive Events and Hormonal Milestones

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Abstract

Migraine, a prevalent neurological disorder, is more common in women than in men. This sex difference is more pronounced after menarche and diminishes after menopause. Migraines in women are influenced by the menstrual cycle, pregnancy, and lactation, suggesting a connection to sex hormones, known as the estrogen withdrawal theory. Beyond endogenous hormonal changes accompanying reproductive events, exogenous hormonal factors such as contraceptives or hormone replacement therapy may also affect migraines. The hormonal influence cannot be explained simply by serum estrogen levels; instead, it involves a complex interplay of various factors. Here, we delineate aspects of migraines associated with endogenous and exogenous hormonal changes over the course of a woman's life, exploring the mechanisms and contributing factors through which sex hormones influence migraines.

Keywords: Gonadal steroid hormone, Migraine disorder, Reproductive history

INTRODUCTION

Migraines are a prevalent neurological disorder that significantly affect daily life and pose substantial socioeconomic burdens. More than 10% of the general population experiences migraines, with a higher prevalence reported among women.[1] Sexual differences in migraine prevalence become more pronounced after puberty and decrease after menopause, and sex hormones are known to play a role.[2] The well-established phenomenon of menstrual migraine, which is characterized by headaches induced by a decrease in estrogen levels during the late luteal phase, is known as the "estrogen withdrawal theory."[3] Estrogen also plays a crucial role in modulating excitatory and inhibitory pain neurotransmission.[4] These findings suggest that hormonal factors can significantly influence the sexual differences observed in migraine.

Women experience various endogenous and exogenous reproductive events, including menstruation, pregnancy, breastfeeding, menopause, contraception, and hormone replacement treatment (Figure 1). These events can induce rapid and variable changes in hormonal status, potentially influencing migraine symptoms and prevalence. Consequently, understanding the association between

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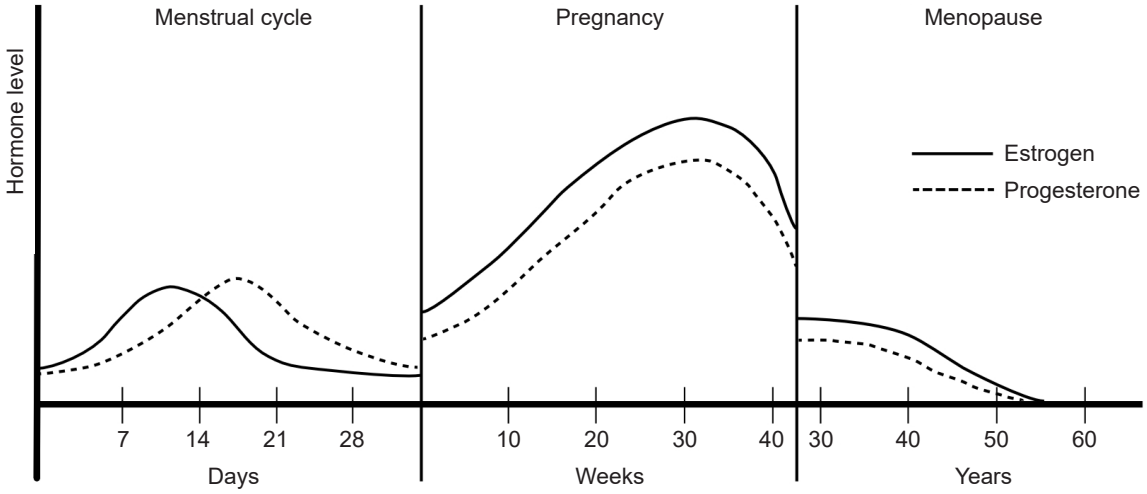

Figure 1. A fluctuations in women's sex hormones across life stages. Women experience fluctuations in sex hormones with reproductive events throughout their lives. After menarche, cyclical fluctuations in estrogen and progesterone occur with menstruation. During pregnancy, estrogen and progesterone remain elevated, normalize after childbirth, and decrease during menopause.

hormones and migraines will be essential to any investigation of the mechanisms and treatment of migraines. This review describes the intricate relationship between migraines and hormones in women. Also, this review describes the hormonal changes in response to reproductive events throughout a woman's life and how these changes contribute to patterns in migraine occurrence.

SEX DIFFERENCES IN MIGRAINE EPIDEMIOLOGY AND SYMPTOMS

The prevalence of migraines is reportedly three times higher in women than in men.[5] According to the American Migraine Prevalence and Prevention study, the overall 1-year migraine prevalence is of 11.7%, with women experiencing a prevalence of 17.1% compared with 5.6% in men. The cumulative incidence was 43% in women and 18% in men.[1,5] Another study, utilizing National Health Interview Survey data, reported a prevalence of 13.2% in the general population, with rates of 17.5% in women and 8.6% in men.[6] In a Korean nationwide cross-sectional survey, structured interviews with 1,507 subjects conducted by trained interviewers showed a 1-year migraine prevalence of 6.1% in the overall population, 9.2% in women, and 2.9% in men.[7] These findings consistently show that migraines are more common in women than in men.

Sex differences in migraine prevalence vary across age groups. Studies of pediatric migraines reported a prevalence of 4%, with no sex differences before puberty, and an increase in women older than 11 years.[8,9] The migraine prevalence was 4.0% in men and 6.4% in women aged between 12 and 17 years and it was highest among those 30–39 years of age for both sexes (24.4% in women; 7.4% in men) and lowest after the age of 60 years (5% in women; 1.6% in men). The difference in migraine prevalence between sexes was highest in the 30–39 age group.[1,5] Previous study revealed a bimodal peak in 1-year migraine prevalence at 20 and 50 years for both sexes. After the age of 10 years, migraine prevalence was consistently higher in women than in men. The difference in prevalence was greatest at age 30.2 years, with a 2.9-fold difference, and remained about 2-fold after the age of 42 years.[6]

Women with migraines tend to experience migraines for longer durations, at greater frequency, and in closer association with photophobia, phonophobia, nausea, and vomiting, compared with men.[10-13] The impact of sex on migraines becomes more significant after the age of 30 in women.[10] Although there is no significant difference in migraine medication use according to sex, women with migraines are more likely than men to take both acute and preventive medications.[14] Prognostically, a previous study reported that 23% of pediatric migraines resolve before

the age of 25, with a higher resolution rate in men (34%) than in women (15%). By the age of 50 year, 46% were migraine-free, with no significant sex difference.[8]

ROLES OF SEX HORMONES IN MIGRAINE

Sex differences in migraine prevalence emerge at puberty when women begin to menstruate and experience periodic hormonal changes during the menstrual cycle. Estrogen and progesterone are known to be related to migraine pathophysiology. Gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the secretion of luteinizing hormone (LH) and follicular stimulating hormone (FSH) from the pituitary. LH and FSH trigger ovarian maturation and ovulation, promoting the secretion of estrogen and progesterone, which are regulated by feedback mechanisms.[15] Sex hormones have low molecular weights and lipophilic properties, allowing them to passively diffuse across the blood-brain barrier. Consequently, central and peripheral levels of sexual steroid hormones are comparable, exerting an influence on migraines through neurotransmitter and pain modulation systems.[16,17] However, the effects of sexual steroid hormones on migraines are complex, with mixed effects reported depending on the site of action, duration, and concentration.

1. The impact of sex hormones on the neurotransmitter system

Several neurotransmitter systems, including serotonin (5-hydroxytryptamine [5-HT]), noradrenaline, gamma-aminobutyric acid (GABA), opioids, and glutamate have been implicated in the pathophysiology of migraines. Sexual steroid hormones play a crucial role in the regulation of these neurotransmitter systems.

Serotonin is a neurotransmitter associated with migraines, and an increased serotonin synthesis capacity has been observed in migraine patients.[17] Triptans, which are commonly used to treat migraines, are selective serotonin receptor agonists (5-HT_{1B}, 5-HT_{1D}). Tryptophan hydroxylase (TPH) is the rate-limiting enzyme for serotonin synthesis, and a previous study on oophorectomized monkeys reported that TPH mRNA activity increased nine-fold with estrogen supplementation and five-fold with an estrogen-progesterone combination.[18] The serotonin reuptake transporter (SERT) at the presynaptic area is responsible for serotonin reuptake and degradation. In oophorectomized monkeys, short-term estrogen supplementation (<28 days) decreased SERT mRNA activity.[19,20] Monoamine oxidase (MAO) is the primary enzyme that degrades serotonin. Estrogen decreases the expression of *MAO* genes in the hypothalamus and dorsal raphe nucleus.[21] These findings suggest that estrogen increases serotonergic activity and potentially promotes migraine symptoms. Progesterone may have fewer influences on the serotonin system, and the serotonergic system may respond differently based on the duration of estrogen supplementation.

The noradrenergic system plays a crucial role in modulating the signal-to-noise ratio of neurons in response to incoming afferent stimuli. Estrogen is known to increase the gene expression of tyrosine hydroxylase, the rate-limiting enzyme in noradrenaline biosynthesis.[22] In animal studies, estrogen infusion elevated noradrenaline secretion in the mediobasal hypothalamus and enhanced the gene expression of tyrosine hydroxylase in the locus coeruleus.[23] Glutamic acid, an excitatory neurotransmitter linked to pain transmission, is also influenced by estrogen. Acute exposure to estrogen increases the glutaminergic neuronal firing of hippocampal Purkinje cells, while chronic exposure enhances dendritic spine density and excitatory synapses of hippocampal glutaminergic neurons.[17]

Glutamic acid decarboxylase is responsible for converting glutamate to GABA, an inhibitory neurotransmitter, and shows increased activity with estrogen. This results in heightened GABA release and up-regulation of GABA receptors.[24] Estrogen injections can also increase enkephalin mRNA activity in the spinal cords of female rats. Both estrogen and progesterone contribute to an increased binding affinity of kappa-opioid receptors in oophorectomized rats.[25-27] These findings emphasize the intricate influence of sexual steroid hormones on various neurotransmitter systems and their potential role in modulating neuronal responses and pain pathways.

2. Calcitonin gene-related peptide and sex differences in migraines

Calcitonin gene-related peptide (CGRP) is a key pathophysiological factor in migraines. It is released in the brain and influences pain transmission within the trigeminal

nervous system. During a migraine attack, CGRP levels increase jugular blood flow, which subsequently decrease after migraine symptoms improve in response to administration of sumatriptan.[28,29] An intravenous CGRP injection can trigger migraine attacks in 65% of migraine patients but not in control groups, implying that the former may possess a lower threshold to CGRP.[30-32] Clinically, CGRP receptor antagonist and monoclonal antibodies against CGRP are employed in migraine treatment.

Several studies suggest a potential association between CGRP and sex differences in migraines. The administration of dural CGRP induces a decrease in the facial withdrawal threshold to mechanical stimuli in female rats but not in male rats. Intracisternal injections of brain-derived neurotrophic factor, and interleukin-6 decrease the facial withdrawal threshold in rats, which recover after 72 hours, and subsequent dural CGRP administration delays the recovery response only in female rats.[33] In both sexes, administration of CGRP to the trigeminal ganglion results in a decrease in the threshold of mechanical stimuli, but recovery of mechanical allodynia with minocycline and propentofylline was observed only in male rats.[34] CGRP induces vasodilation of meningeal vessels, a process linked to migraine pathophysiology.[35] A study investigating vasodilation responses in ovariectomized rats found that estradiol premedication increased vasodilation in responses to electrical stimulation. In meningeal arterial system, estradiol increases the CGRP-immunoreactive sensory innervation and promotes release of CGRP from nerve endings innervating the meningeal artery.[36]

Transient receptor potential ankyrin 1 (TRPA1), and transient receptor potential melastatin 8 (TRPM8), both of which are transient receptor potential channels of trigeminal neurons, are closely related to migraine pathophysiology. TRPA1, found on the primary afferent neurons innervating the meninges, releases CGRP when activated. Nitroglycerin increases TRPA1-mediated neuronal activity, promoting nociceptive hypersensitivity. TRPM8 attenuates migraine symptom and TRPA1-related pain. The antinociceptive action of TRPM8 is more pronounced in male rats and necessitates testosterone. Exogenous testosterone induces the recovery of mechanical hypersensitivity in female and orchiectomized male rats, implying potential sex-dependent effects of TRPM8 on migraines.[37]

Interplay between prolactin and CGRP may contribute to sex differences in migraines. Although serum prolactin levels do not differ between migraineurs and controls, prolactin increases during a migraine attack but not in tension-type headaches.[38,39] Dural prolactin administration decreases the withdrawal threshold for mechanical stimuli in female rats but not in male rats. An immunohistochemical analysis reveals a prolactin receptor in the dural afferent nerve of female rats but not in male rats. Prolactin stimulates the release of CGRP and activates the dural trigeminal ganglion neurons only in female rats.[40]

MENSTRUATION AND MIGRAINES

1. Menarche, menstruation, and hormonal dynamics

Menarche marks the onset of the first menstrual period in women, and in Korea, the mean age of menarche is reportedly 12.9±1.18 years.[41] Following menarche, approximately 10 anovulatory menstrual cycles occur per year, with a serum estrogen level ranging from 10 to 156 pg/mL. Over subsequent years, the serum estrogen level gradually aligns with that of an adult.[42] This transition period signifies the maturation of the reproductive system and involve adjustments in hormonal levels and menstrual cycle characteristics.

The menstrual cycle can be divided into two main phases: the follicular phase and the luteal phase, as determined by the occurrence of ovulation. The follicular phase spans from the onset of menstrual bleeding to just before ovulation, while the luteal phase extends from ovulation to the commencement of the next menstrual cycle. With an average duration of 28 days, a menstrual cycle is characterized by a constant luteal period of 14 days, and the entire cycle is predominantly influenced by the follicular phase. In the follicular phase, FSH and LH stimulate follicle maturation and estrogen secretion, respectively, in the ovary. The early follicular period sees low serum estrogen levels ranging from 25 to 50 pg/mL, with progesterone levels remaining below 1 ng/mL. As the follicular phase progresses, estrogen levels rise steadily, reaching a peak of 100 to 400 pg/mL during the late follicular to early luteal periods. This estrogen surge triggers the abrupt secretion of LH, leading to ovulation.

In the subsequent luteal phase, the corpus luteum, a temporary endocrine structure formed after ovulation, produces both estrogen and progesterone. During

this phase, estrogen inhibits GnRH, FSH, and LH, while progesterone plays a crucial role in maintaining the endometrium of the uterus. In the absence of fertilization, serum estrogen levels remain between 200 and 300 pg/mL throughout the luteal period, decreasing to 25–50 pg/mL before the onset of the next menstrual cycle. Concurrently, serum progesterone levels increase to 6–10 ng/mL during the mid-luteal period and decrease to 2 ng/mL in the late luteal period. These intricate hormonal dynamics orchestrate the menstrual cycle, regulating the physiological processes essential for reproductive health (Figure 2).

2. Menstrual migraine and estrogen withdrawal theory

A menstrual migraine is defined as a migraine that occurs from two days before to three days after the onset of menstruation. Previous studies have reported that menstrual migraines often peak 2 days before menstruation and are not associated with ovulation.[43,44] Additionally, there is a reported connection between serum estrogen levels and menstrual migraines. These migraines frequently occur during the late luteal and early follicular periods when serum estrogen levels decrease rapidly. In contrast, migraine attacks are less frequent when serum estrogen levels are stable.[45] For individuals with migraines, attacks during the perimenstrual period tend to be more severe and last longer compared with other phases of the menstrual cycle.[46,47] Although the mean serum estrogen level does not differ significantly between migraineurs and those without migraines, migraineurs exhibit a more rapid decline in estrogen during the luteal period compared with controls.[48]

These findings support a close relationship between estrogen decline and migraines, which underlies the estrogen withdrawal theory. In the late luteal period, estrogen supplementation has been shown to delay migraine attacks, while progesterone does not exert the same effect.[49,50] However, during the mid-follicular phase, migraines reportedly did not occur when short-acting estrogen was administered to induce a change in estrogen concentration. This suggests that priming of estrogen may be necessary before actual estrogen withdrawal triggers migraines.[51]

3. Difference in menstrual migraine between migraines with and without aura

An interesting distinction in menstrual migraine has been observed between individuals with migraine without aura (MO) and those with migraine with aura (MA). In a study examining headache patterns during the menstrual cycle in 81 women with migraines, menstrual cycles were divided into five study periods (3–7 days before menses, 1–2 days before menses, 0–1 days after menses, 3–5 days after menses, and 14–15 days before menses) and a control

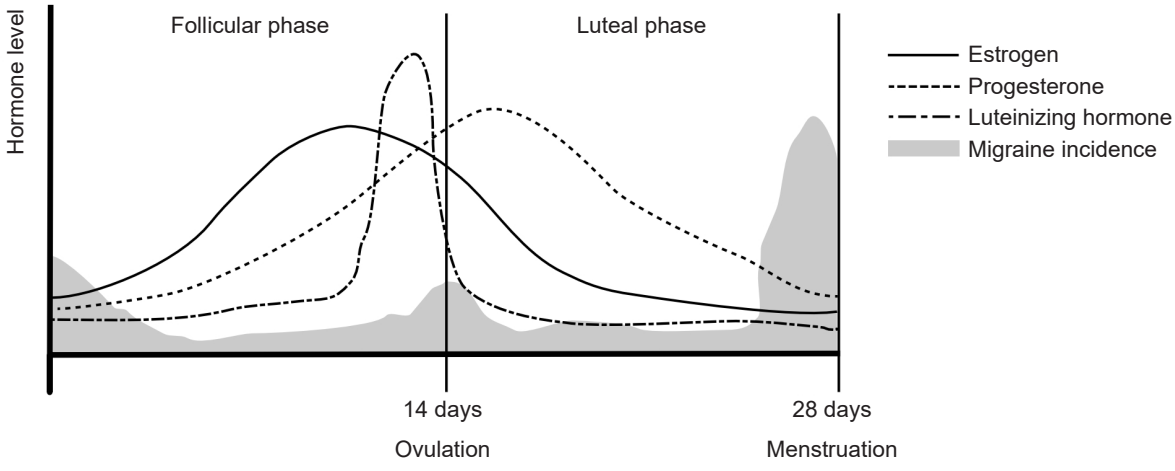

Figure 2. Hormonal changes and menstrual migraine during the menstrual cycle: The menstrual cycle can be divided into follicular and luteal phases according to ovulation. Following ovulation, the corpus luteum produces estrogen and progesterone. In the absence of fertilization, estrogen secretion decreases, leading to the initiation of menstruation. Menstrual migraines occur during the period from 2 days before to 3 days after menstruation.

period. The study found that the risk of MO increased in the period 1–2 days before menses (odds ratio [OR], 2.04; 95% confidence interval [CI], 1.49–2.81), and the period 0–1 day after menses (OR, 1.80; 95% CI, 1.40–2.30). However, the risk of MA did not differ significantly among study periods.[52] Another study investigated the differences in migraine symptoms between perimenstrual and non-perimenstrual migraines in women with migraines. Perimenstrual migraine headaches were found to have a longer duration, higher recurrence risk, increased triptan intake, higher headache intensity, and more pronounced photophobia and phonophobia compared with non-perimenstrual headaches. However, the prevalence of aura was lower in perimenstrual headaches (OR, 0.8; 95% CI, 0.6–1.0).[46] A further investigation into perimenstrual migraine differences between women diagnosed with MO and MA revealed that, while the prevalence of migraine attacks did not differ between the two groups (59% for MO versus 53% for MA, p=0.176). The risk of migraine attack without aura was significantly higher during the perimenstrual period in both MO (OR, 1.53; 95% CI, 1.44–1.62) and MA groups (OR, 1.53; 95% CI, 1.44–1.62). However, the risk of MA attacks did not show a significant change within the perimenstrual period (OR, 1.08; 95% CI, 0.93–1.26). This implies that the most common form of perimenstrual migraine is MO, even in individuals diagnosed with MA (Figure 3).[53] The cause of these differences is unclear but may be related to variations in the effects of estrogen on the trigeminal-vascular system and cortical spreading depression (CSD). In migraine patients, headache occurrence is related to the trigemino-vascular system and is caused by the short-term effects of estrogen. In CSD, the occurrence of aura is thought to be related to the long-term effects of estrogen.[54] An animal study investigating the association between estrogen and CSD found that CSD was more frequently observed in female rats than in male and ovariectomized female rats. In female rats, the risk of CSD remained unchanged during normal menstrual cycles and with long-term (3-week) estrogen supplementation. However, when the rats underwent 2 weeks of estrogen treatment followed by 1 week of withdrawal, the incidence of CSD increased.[55] This study suggests that the development of CSD is not directly linked to estrogen withdrawal during the natural menstrual cycle. Instead, it appears to be associated with withdrawal after a prolonged period of estrogen exposure.

PREGNANCY, LACTATION, AND MIGRAINES

During pregnancy, the consistent production of estrogen and progesterone by the placenta results in a stable hormonal environment free from the fluctuations of the menstrual cycle. In the third trimester, levels of serum estrogen (30–40 times) and progesterone (20 times) are significantly elevated compared with the peak levels in the menstru-

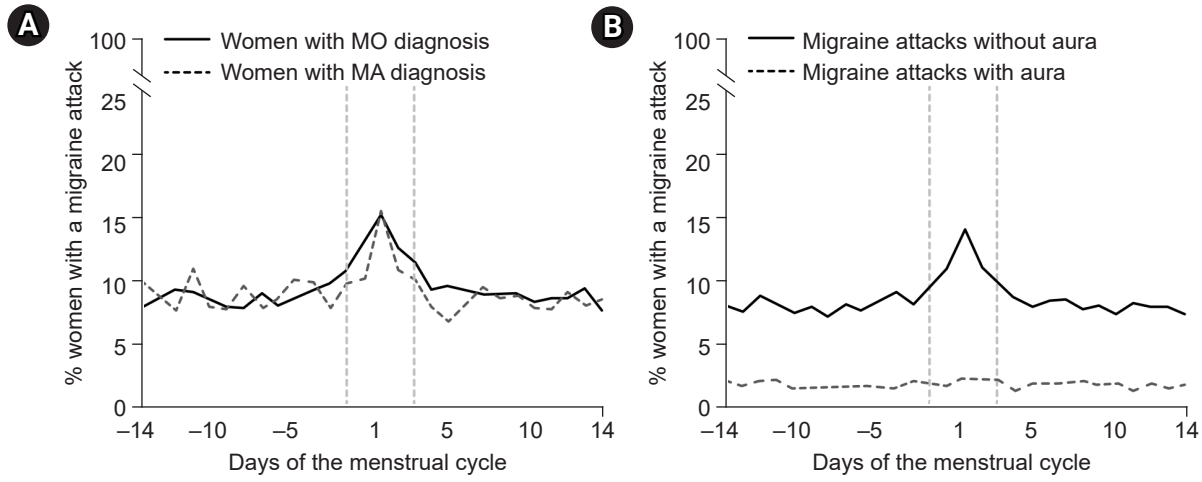

Figure 3. Differences in perimenstrual migraines between women diagnosed with migraines without aura (MO) and migraines with aura (MA): (A) The prevalence of migraine attacks did not differ between women with MO and MA. (B) The risk of MO was significantly higher during the perimenstrual period in all groups of women with migraines. Modified from Verhagen et al. (Cephalalgia 2023;43:3331024231164322).[53]

al cycle.[56] Following childbirth, the hormonal status and menstrual cycles vary depending on whether lactation occurs. Prolactin, a pituitary hormone associated with lactation, maintains a serum level of 10–25 ng/mL before pregnancy. During pregnancy, estrogen and progesterone promote mammary gland maturation while inhibiting prolactin secretion and lactation. Within 24 hours postpartum, serum estrogen and progesterone decrease, and prolactin increases, initiating lactation (Figure 4).[57]

Pregnant women with a history of migraines reportedly show significant improvement in the second and third trimesters, with improvement rates of 46.8% in the first trimester, 83% in the second trimester, and 87% in the third trimester. Some women even experience complete remission of migraines during pregnancy, with remission rates of 11% in the first trimester, 53% in the second trimester, and 73% in the third trimester. Notably, many of these changes in migraine patterns during pregnancy revert to their previous state after childbirth.[58]

These changes in migraines during pregnancy are likely associated with hormonal influences. The continuous high and steady serum estrogen levels during pregnancy align with the estrogen withdrawal theory, which posits that stable estrogen levels lead to migraine improvement. The reversion of migraine patterns after childbirth supports this hypothesis. Another potential mechanism involves the influence of pregnancy on pain transmission. Animal studies have shown[59-61] that both the nociceptive threshold and dynorphin increase in the lumbar spinal cords of pregnant rats. Simulated pregnancy in animal models using estrogen and progesterone demonstrated similar opioid analgesia in the spinal cord.[27]

However, some women without a previous history of migraines experience new-onset migraines during pregnancy, with occurrence rates of 1.3% to 18%. This phenomenon is predominantly associated with MA. It is more prevalent during the first trimester and is believed to be related to a rapid increase in estrogen levels rather than estrogen withdrawal.[58,59]

During lactation, mechanical breast stimulation enhances prolactin production. Prolactin inhibits the release of GnRH, suppressing estrogen and progesterone release and preventing ovulation.[57] Subsequently, serum estrogen levels remain consistently low without fluctuations in lactating women (Figure 4). Clinical studies have found that most women who bottle-feed their children experience migraine recurrence within 1 month after delivery compared with only 43.2% of breastfeeding women.[58] In women who bottle-feed, the decrease in prolactin restarts the menstrual cycle, leading to hormonal fluctuations that can increase the frequency of migraines.[57]

MENOPAUSE AND MIGRAINES

Menopause is the cessation of menstruation for more than 1 year without other identifiable causes. The mean age

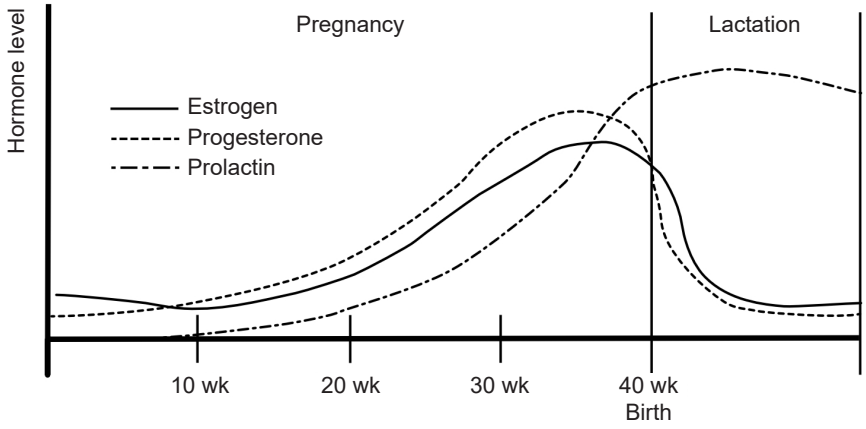

Figure 4. Sex hormones during pregnancy and lactation: During pregnancy, estrogen and progesterone remain at high levels without fluctuating. Immediately after childbirth, estrogen and progesterone decrease and prolactin increases. During lactation, prolactin is maintained at a high concentration and inhibits the secretion of estrogen and progesterone. Their concentrations remain low without fluctuations.

of menopause is approximately 50 years, with a reported mean menopausal age in Korea of 49.3±3.5 years.[62] Distinct effects on migraines have been observed between menopause and the perimenopausal period.

A woman's ovarian follicles are limited in number, with most producing approximately 400–500 ova over 40 years, after which ovarian function diminishes. Women typically experience an irregular menstrual cycle for 2–8 years before entering menopause, a stage known as perimenopause and characterized by a decline in ovarian function. During this phase, women experience hypergonadotropism, hypoestrogenism, hypoprogesteronism, and greater estrogen fluctuations.[63] The excessive stimulation of remaining follicles results in severe estrogen fluctuations. After menopause, serum estrogen and progesterone levels remain consistently low without fluctuation.[64] According to the estrogen withdrawal hypothesis, estrogen fluctuations during perimenopause can contribute to frequent migraine attacks, with an anticipated improvement in migraines after menopause.

A cross-sectional study reported an increase in migraine prevalence during perimenopause, followed by a decrease after spontaneous menopause. However, this study focused on women aged 40 to 54 years and did not comprehensively analyze postmenopausal women.[65] Another study indicated an increased risk of migraines in perimenopausal woman (OR, 1.42; 95% CI, 1.03–1.94) but not significantly in postmenopausal women (OR, 1.27; 95% CI, 0.83–1.92) compared with premenopausal women.[66] These findings support the exacerbation of migraines during the perimenopausal period, although the effect of menopause on migraines remains inconclusive.

While some studies have reported a decrease in migraine prevalence after menopause, others found no significant differences among premenopausal, perimenopausal, and postmenopausal periods.[67-69] In women with migraines, improvement after menopause ranges from 8%–36%, worsening from 9%–42%, and remaining unchanged from 27%–64%. Additionally, 8%–13% of women may experience their first migraine after menopause.[15] Other clinical factors may affect postmenopausal migraines. The risk of migraines risk in cases of early artificial menopause, such as those associated with a hysterectomy or oophorectomy, with a higher risk has been reported in surgical menopause compared with spontaneous menopause. Previous studies reported a migraine risk of 27% in surgical menopause but 7% in spontaneous menopausal women.[64,65,70] Previously, we reported that a shorter lifetime number of year of menstruation (LNYM) and hormone replacement therapy (HRT) may contribute to an increased risk of migraines in postmenopausal women.[71] The LNYM represents the cumulative duration of menstruation cycles and cumulative exposure to endogenous hormones over a women's life.[72,73] Our study suggests an elevated risk of postmenopausal migraine in women with either exogenous hormone exposure or insufficient endogenous hormone exposure.

The long-term incidence of migraines after menopause has not been fully elucidated. In a previous study utilizing the Korean National Health Insurance Service database, we reported that the risk of migraines was higher in women in longer postmenopausal groups, including those postmenopausal for ≥15 years (HR, 1.196; 95% CI, 1.169–1.224), <15 years (HR, 1.09; 95% CI, 1.069–1.111), and <10 years (HR, 1.042; 95% CI, 1.027–1.058) compared with the <5 years group. Our results suggest that an extended period after menopause may increase the risk of migraines again.[71] The mechanism is unclear, but it is possible that prolonged low estrogen levels may lower pain thresholds due to decreased GABAergic and opioidergic effects of estrogen.

EXOGENOUS HORMONAL FACTOR (CONTRACEPTION AND HORMONE REPLACEMENT THERAPY) AND MIGRAINES

In women, physiological processes such as menstruation, pregnancy, and lactation represent endogenous hormonal changes, while contraception and HRT introduce exogenous hormonal alterations. Male-to-female transsexuals taking estrogen often experience heightened and exacerbated headaches.[74] Conversely, some prior studies have indicated that continuous estrogen or HRT may alleviate headache symptoms, suggesting a potential influence of exogenous estrogen on migraine.[60,75] The impact of exogenous hormones on migraines can vary based on type, composition, timing, and route of administration.

Contraception is commonly utilized to manage menstrual cycles and prevent pregnancy, with various administration methods available. This discussion focuses on combined oral contraceptives (COCs), the most frequently

used form. The notion that COCs increase the prevalence of migraines and worsen migraine symptoms is generally accepted.[15] Approximately 70% of women who experience migraines report exacerbation of symptoms with COCs.[76] This exacerbation tends to be more pronounced in women with MA compared with those with MO, and the frequency of auras often increases.[60] These exacerbations are frequently observed during pill-free periods, with a four-fold increase in the prevalence of migraine attacks on pill-free days 3–6.[77]

Among women without a history of migraine, COC use has been associated with a significant increase in migraine prevalence (OR, 1.4; 95% CI, 1.2–1.7) compared with those who have never used COCs.[78] However, conflicting findings exist, with other studies reporting that migraine headache patterns remained unchanged in 44%–67%, worsened in 24%–36%, and improved in 5%–8% with the use of COCs.[79-81] Another study suggested that continuous estrogen administration could decrease the symptoms and frequency of migraines.[60] These discrepancies in the effects of COCs on migraines can be attributed to differences in the composition and dosage of COCs, with recent research suggesting that low-dose estrogen pills have a reduced impact on migraines.[15]

After menopause, women experience various postmenopausal symptoms, such as hot flushes, irritability, insomnia, mood changes, and osteoporosis. HRT is commonly used to alleviate menopausal symptoms and may involve estrogen alone or in combination with progesterone.[15] The effects of HRT on migraines remain inconsistent across studies. In one study investigating changes in migraine symptoms during HRT, migraine symptoms worsened in 21%, improved in 22%–23%, and remained unchanged in 57% of migraineurs.[82] Another study reported that migraine symptoms did not change in 77% of migraineurs with HRT.[80] In a population-based study, headache prevalence increased in women who did not have a history of headaches.[75] Another population-based study of 17,107 postmenopausal women reported that current HRTs significantly increase the risk of migraine (OR, 1.42; 95% CI, 1.24–1.62) compared with a non-HRT population.[83]

Differences in HRT composition and administration methods can influence its effects on migraines. Continuous estrogen administration is associated with a decrease in migraine severity and attack frequency.[60] Non-oral estrogen may have a more favorable impact on migraines compared with oral administration.[84] For example, in one study, users of transdermal estradiol patches did not experience changes in headache symptoms, while headaches worsened in those receiving oral HRT.[85] However, a population-based cross-sectional study reported that the routes of HRT administration were not associated with migraine risk, while an HRT group had a greater migraine risk compared with the non-HRT group.[86]

In summary, COCs are generally associated with migraine exacerbations, and low-estrogen pills may have a reduced impact on migraines. HRT also tends to exacerbate migraines, but the effects are influenced by composition, dose, and route of administration.

CONCLUSION

Women's migraines are profoundly influenced by hormonal changes, and the dynamic nature of hormonal fluctuations throughout their lives contributes to the complexity of this relationship. The same hormone can elicit opposite effects on migraines depending on the timing, dose, and other factors. It is therefore important to understand the fluctuations in female hormones and how they affect migraines at different times. In addition to exploring previous neurotransmitter systems, recent studies investigated CGRP as a potential mechanism underlying hormonal effects on migraines. These studies contribute valuable insights into the intricate interplay between hormonal dynamics and the manifestation of migraines. Understanding the effects of hormones on migraines is a crucial aspect of research into the mechanisms of migraines and their treatment.

AVAILABILITY OF DATA AND MATERIAL

Not applicable.

AUTHOR CONTRIBUTIONS

Conceptualization: JWP; Data curation: SK; Investigation: SK; Writing–original draft: SK; Writing–review and editing: JWP.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Headache and Pain Research

Menstrual Migraine: A Review of Current Research and Clinical Challenges

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Abstract

The term "menstrual migraine" is commonly used to describe migraines that occur in association with menstruation, as distinct from other migraine types. A significant proportion of women of reproductive age experience migraine attacks related to their menstrual cycle. Menstrual migraine is characterized by migraine attacks occurring on day 1±2 (i.e., days −2 to +3) of menstruation in at least two out of three menstrual cycles. Although the reported prevalence of menstrual migraine varies considerably, population-based studies have found that menstrual migraine affects up to 60% of women with migraines. Several hypotheses have been proposed to explain the etiology of menstrual migraine, among which the estrogen withdrawal hypothesis is the most widely accepted. Women who experience menstrual migraines often face considerable disability due to perimenstrual attacks. Studies have reported that perimenstrual attacks are more severe and more difficult to manage than nonmenstrual attacks. The principles of acute managing perimenstrual attacks are the same as those for managing nonmenstrual attacks. Short-term preventive therapy is needed to prevent menstrual migraines before they occur during the perimenstrual period. This review summarizes the prevalence, distinct clinical features, pathophysiological mechanisms, and management of menstrual migraine.

Keywords: Female, Menstrual cycle, Migraine disorders

INTRODUCTION

Migraine is a disabling neurological disease that affects 14% of the world's population at all ages.[1] Characteristic features include recurrent attacks of severe headache and accompanying symptoms such as nausea or vomiting, photophobia, and phonophobia.[2] Prevalence substantially varies with age and sex, and it affects 2–3 times more women than men. A significant number of women of reproductive age report migraine attacks related to the menstrual cycle (Figure 1).[3-6] Several mechanisms including hormonal effects have been proposed to explain menstruation-related migraine in women,[5] however, the exact underlying pathophysiological mechanisms remain poorly understood.

Many women with migraine meet the criteria for men-

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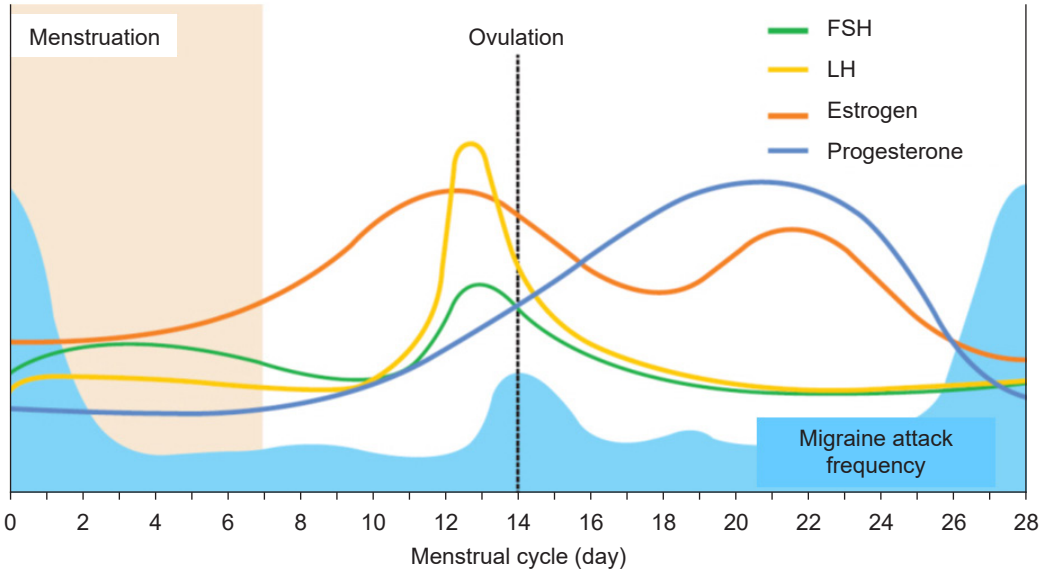

Figure 1. Relationship between menstrual cycle days and menstrual migraine.
FSH, follicle-stimulating hormone; LH, luteinizing hormone.
Modified with permission of copyright holder from the Korean Headache Society and the author, SK Kim.[6]

strually related migraine or pure menstrual migraine. Menstrual migraine can be used to describe a condition in which migraine attacks occur on day 1±2 (i.e., days –2 to +3) of menstruation in at least two out of three menstrual cycles.[7]

In women who have menstrual migraine, perimenstrual attacks are associated with considerable disability. However, in clinical practice, menstrual migraine is less well-recognized and managed. This review elucidates the prevalence, clinical features, pathophysiological mechanisms, and management of menstrual migraine.

PREVALENCE

Due to the paucity of data, and differences in the study design, population, and case definitions, there are large variations in the prevalence of menstrual migraine. Population-based studies have reported menstrual migraine affecting up to 60% of females with migraine, however, the definition of the perimenstrual period was broader than 5 days.[8,9] Another population-based studies with stricter criteria reported that 4% to 8% of all women and 18% to 25% of females with migraine have menstrual migraine without aura.[10-12] In the general population, the prevalence of menstrual migraine with aura has been estimated to be 1.7% to 8.1% of females with migraine.[10,11,13] In patients from headache clinics, the prevalence of menstrual migraine without aura is higher, varying from 22% to 70%.[14-16] The discrepancy between clinic-based and population-based studies might be a diagnostic criterion because women visiting headache clinics have a higher frequency of migraine.

A recent clinic-based study found that the accuracy of self-reported menstrual migraine is poor, compared with a diary-based diagnosis.[7] Furthermore, most clinical studies on menstrual migraine use different definitions of menstrual migraine. For example, in some studies, the perimenstrual period is extended by several days, whereas the definition of the perimenstrual period is nonexistent in others.[15,16] Clinical studies with the highest prevalence have looser definitions of menstrual migraine and extended perimenstrual windows, increasing the likelihood that a migraine will be classified as menstrual by chance. In addition, the current diagnostic criteria in the International Classification of Headache Disorders, third edition (ICHD-3) for menstrual migraine have several issues that need to be informed (Table 1).[7] First, the diagnostic criteria does not consider migraine frequency. Diagnostic misclassification of menstrually related migraine may occur in women with high frequency episodic migraine or chronic migraine, because women with 8 or more migraine days per

Table 1. Diagnostic criteria for menstrual migraine according to the International Classification of Headache Disorders 3 (ICHD-3)[26]

Pure menstrual migraine
A. Attacks, in a menstruating woman*, fulfilling criteria for migraine without/with aura and criterion B below.
B. Occurring exclusively on day 1±2 (i.e., days −2 to +3)† of menstruation in at least two out of three menstrual cycles and at no other times of the cycle.
Menstrually-related migraine
A. Attacks, in a menstruating woman*, fulfilling criteria for migraine without/with aura and criterion B below.
B. Occurring on day 1±2 (i.e., days −2 to +3)† of menstruation in at least two out of three menstrual cycles, and additionally at other times of the cycle.

*For the purposes of ICHD-3, menstruation is considered to be endometrial bleeding resulting either from the normal menstrual cycle or from the withdrawal of exogenous progestogens, as in the use of combined oral contraceptives or cyclical hormone replacement therapy. †The first day of menstruation is day 1 and the preceding day is day −1; there is no day 0.

month may have high probability of migraine attacks within 5-day perimenstrual window. Second, women with rare migraine attacks occurring exclusively at menstruation do not fulfill the diagnostic criteria because the rare migraine attack frequency does not reach 2 of 3 consecutive menstrual cycle. Third, timing of migraine attacks is currently unclear what is meant by 'occur' in the diagnostic criteria. Meaning of 'occur' is not clear whether it means migraine attacks begin and/or end on day 1±2 of menstruation. There issues have been discussed in other study.[17]

CLINICAL FEATURES

Menstrual migraine have similar clinical features compared to migraine unrelated to the menstrual cycle, but tend to be differ in the severity of symptoms or treatment response. No differences in the characteristics of perimenstrual attacks compared with attacks at other times of the cycle were reported in some studies, whereas other studies report that perimenstrual attacks are more severe and more difficult to manage than nonmenstrual attacks.[3,4,18,19] Studies using headache and menstruation diary report that perimenstrual attacks are more disabling and can persist for up to 35% longer than those unrelated to the menstrual cycle.[20-24] Moreover, perimenstrual attacks are associated with more severe pain and accentuated associated symptoms such as photophobia and phonophobia.[20]

The drug response to triptans also seems to differ between perimenstrual attacks and those unrelated to the menstrual cycle, with the former having a higher recurrence rate of attacks after acute medical treatment.[20]

DIAGNOSIS

For all types of migraine, menstrual migraine is a commonly used term occurring in association with menstruation. The diagnostic criteria of menstrual migraine have been included in the International Classification of Headache Disorders since its 2nd edition,[25] in which appendix criteria were outlined for two types of menstrual migraine without aura: "pure menstrual migraine" and "menstrually-related migraine". The ICHD-3 included the addition of criteria for menstrual migraine with or without aura.[26] Table 1 illustrates the appendix criteria for pure menstrual migraine and menstrually-related migraine, as described in the ICHD-3 from 2018.[26] A potential overestimation of perimenstrual attacks might occur by chance in all women affected by migraines, and can be mistaken for menstrual migraine. A headache and menstruation diary may help to confirm the diagnosis because studies indicate that women tend to overreport an association between migraine and menstruation.[27,28]

PATHOPHYSIOLOGY

Several hypotheses have been proposed to explain the etiology of menstrual migraine, with the estrogen withdrawal hypothesis as the most widely accepted.[29] The premenstrual phase of the menstrual cycle is characterized by declining plasma estrogen levels.[29] The estrogen withdrawal hypothesis was first introduced by Somerville[29] in 1972. The study results demonstrated that the expected onset of migraine had seemingly been delayed by a few days following the injection of estradiol. His studies suggest that a precipitous drop in estrogen shortly before menstruation increases the risk of developing a migraine attack.[29-31] In a series of small studies, a premenstrual drop in estrogen was consistently associated with migraine.[32] This hypothesis was supported by a larger study, which revealed that the incidence of migraine without aura, but not migraine with aura, was inversely associated with urinary estrogen concentrations across the menstrual cycle.[5] In general,

female sex hormones can modulate the activity of several neurotransmitter systems involved in the migraine pathophysiology and pain transmission.[33] Estrogen modulates the activity in the μ-opioid system. Late luteal low estrogen is associated with a reduced capacity to activate the μ-opioid system, resulting in a state of susceptibility to pain.[33] Estrogen can also modulate the serotonergic system activity, and a change in the serotonergic tone accompanying estrogen withdrawal has been proposed as a possible trigger of attacks.[34]

In addition to its effects on neurotransmission, estrogen can regulate the sensitization of trigeminal neurons by modulating the release of neuropeptides such as calcitonin gene-related peptide (CGRP).[35] In some in vitro animal studies, estradiol was found to reduce CGRP expression in the trigeminal ganglion.[35] The relationship between estrogen and CGRP levels in humans remains unclear, as studies have produced conflicting evidence. A study reported higher interictal plasma CGRP concentrations in women with menstrually related migraine during menstruation than in healthy women, which could explain their heightened susceptibility to migraine during the perimenstrual period.[36]

Some studies suggest that genetic factors may be involved in menstrual migraine.[37] Genetics may indeed regulate individual-level sensitivity to estrogen fluctuations, rendering some women more susceptible to menstrual migraine.[37] The current evidence is conflicting. Limited evidence exists for the role of genetics in menstrual migraine. Candidate gene association studies evaluated the role of estrogen receptor 1 gene (ESR-1),[38] which mediates estradiol activity. The COMT, CYP1A1, and CYP19A1 genes, which are involved in estradiol synthesis and metabolism, has been a further focus of research.[39] Although a British and Italian study reported no significant difference in functional polymorphisms of estrogen synthesis and metabolism genes,[39,40] an American study identified one COMT polymorphism and two tyrosine hydroxylase gene polymorphisms linked to self-reported menstrual migraine.[41] Furthermore, two ESR-1 polymorphisms were associated with menstrual migraine in the Chinese and Turkish cohorts.[42,43] Because each identified genetic variant is likely to account for modest effects in increasing the risk of menstrual migraine, further research is warranted to understand the role of genetics in menstrual migraine.

MANAGEMENT

Acute and preventive (short-term or standard) treatments were summarized in Table 2.

1. Acute treatment

The principles of managing perimenstrual attacks are the same as those for managing nonmenstrual attacks. Drugs used for the acute treatment of nonmenstrual migraine attacks are also effective for perimenstrual migraine.[28,44-51] Studies for the acute management of menstrual migraine have shown that most triptans are effective in reducing pain associated with menstrual migraine. Positive clinical evidence exists for almotriptan,[44] frovatriptan,[52] naratriptan,[45] rizatriptan,[46] sumatriptan,[48] and zolmitriptan.[50] However, some clinical trials have shown that perimenstrual attacks in women diagnosed with menstrual migraine do not respond as well to acute treatment as do their attacks outside of this period.[24,28] Perimenstrual attacks last longer than attacks at other times of the menstrual cycle,[22,23,53] therefore, treatment is usually necessary for several days. Some studies compared frovatriptan which has a long elimination half-life of 26 hours with almotriptan, rizatriptan, or zolmitriptan for the treatment of perimenstrual attacks in women diagnosed with menstrual migraine.[22,23,54] The results demonstrated similar efficacy for a 2 hours pain relief, pain-free response, and sustained pain absence at 48 hours, however, the recurrence rate (pain free at 2 hours with headache of any severity returning within 24 hours) was significantly lower with frovatriptan than with the comparators. This result suggests that frovatriptan may

Table 2. Pharmacological treatments for menstrual migraine

Acute treatment	Short-term prevention
NSAIDs[49]	NSAIDs[65]
	Ergotamine derivatives[21]
Triptans	Triptans
Frovatriptan[52]	Frovatriptan[63]
Naratriptan[45]	Naratriptan[22,23]
Sumatriptan[48]	Sumatriptan[24]
Zolmitriptan[50]	Zolmitriptan[64]
Almotriptan[44]	
Rizatriptan[46]	

NSAIDs, nonsteroidal antiinflammatory drugs.

more appropriate than other triptans for the acute treatment of perimenstrual migraine attacks. Nonsteroidal antiinflammatory drugs, alone or together with triptans,[49,55-57] and combination analgesics have also been proven effective for the acute treatment of menstrual migraine.[58] Recent study showed that lasmiditan was effective for treatment of menstrual migraine.[59]

2. Prophylactic treatment

1) Standard prophylaxis

There are no strong evidence suggesting potential efficacy in menstrual migraine. Randomized, prospective, placebo-controlled trials, assessing the efficacy of standard long-term migraine preventive therapies for menstrual migraine are clearly needed. However, in the absence of these trials, it may be helpful to try medications already established as effective for migraine prevention. Effective migraine preventive therapies include topiramate, divalproex sodium, propranolol, and timolol.[58] Hormonal preventive therapy using contraceptive was effective to reducing migraine frequency in women with menstrual migraine.[60] Recent study revealed that prophylactic use of anti-CGRP antibodies for women with menstrual migraine leads to reductions in migraine days during menstrual cycle.[61]

2) Short-term prevention of menstrual migraine.

The goal of the short-term preventive therapy is to prevent menstrual migraine headaches before they occur. Treatment is usually initiated several days before the expected onset of the perimenstrual attack to achieve a steady state of medication, although this schedule relies on the woman being able to predict the onset of menstruation, perimenstrual attacks, or both.

Clinical trial data for perimenstrual prophylaxis with nonsteroidal antiinflammatory drugs and triptans are available. Several studies have shown short-term prevention to be an effective treatment with naratriptan,[22,23] frovatriptan,[62] and oral sumatriptan.[24] Frovatripan 2.5 mg once daily and twice daily were effective in perimenstrual prophylaxis.[63] In this study, patients were treated during perimenstrual periods (start taking it 2 days before menstruation is expected and continue for 6 days).[63] Treatment began with a double-loading dose of study medication on day 1.[63] A systematic review and meta-analysis of triptans used for the prevention of perimenstrual attacks of migraine concluded that frovatriptan 2.5 mg twice daily and zolmitriptan 2.5 mg three times daily were the most effective and best tolerated perimenstrual regimens.[64] Naproxen sodium has been demonstrated to be effective for short-term prevention of migraine[65] and a number of other nonsteroidal antiinflammatory agents have been suggested to be effective when studied in smaller clinical trials.[20,58] Dihydroergotamine mesylate administered as a nasal spray for 6 days starting 2 days before the expected onset of headache in 40 women with menstrual migraine was demonstrated to reduce menstrual migraine severity.[21]

CONCLUSIONS

In women diagnosed with migraine, menstrual migraine is common and is associated with considerable disability. Although pathophysiological mechanisms remain to be explored, several mechanisms such as the estrogen withdrawal hypothesis, CGRP release, and genetic factors have been proposed to explain menstrual migraine. In women diagnosed with menstrual migraine, perimenstrual attacks differ in duration, severity, and response to treatment compared with nonmenstrual migraine attacks. If menstrual migraine persists despite standard prophylaxis, or if the response to acute treatment is inadequate, short-term perimenstrual prophylaxis should be considered. Menstrual migraine is overreported when the diagnoses are based on self-reports. Therefore, further studies are warranted to use a prospective headache and menstruation diary to confirm the diagnosis in clinical trials.

AVAILABILITY OF DATA AND MATERIAL

Not applicable.

AUTHOR CONTRIBUTIONS

Conceptualization, Data curation, Formal analysis, Writing–original draft, Writing–review and editing: JGS.

CONFLICT OF INTEREST

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COVID-19 Infection-related Headache: A Narrative Review

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Abstract

Severe acute respiratory syndrome coronavirus 2 is the virus responsible for coronavirus disease 2019 (COVID-19), which caused a global pandemic and then became an endemic condition. COVID-19 infection may be associated with clinical manifestations such as respiratory symptoms and systemic diseases, including neurological disorders, notably headaches. Headaches are a common neurological symptom in individuals infected with COVID-19. Furthermore, with the transition to endemicity, COVID-19 infection-related headaches may reportedly persist in the acute phase of COVID-19 infection and in the long term after COVID-19 infection resolves. Persistent headaches after COVID-19 infection can be a significant concern for patients, potentially leading to disability. The present review discusses the clinical characteristics and potential underlying mechanisms of COVID-19 infection-related headaches.

Keywords: COVID-19, Headache, Headache disorders, Migraine disorders, SARS-CoV-2

INTRODUCTION

In December 2019, an outbreak of a severe respiratory illness, later identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was initially reported in Wuhan, China. This outbreak rapidly escalated into a global pandemic, garnering widespread international focus due to its significant infectious potential. In February 2020, the World Health Organization officially designated this illness as coronavirus disease 2019, abbreviated as COVID-19. In populations with comorbid conditions such as atrial fibrillation, heart failure, liver disease, seizures, dementia, and insulin resistance, the prognosis following COVID-19 infection tends to be poor.[1-4] Even in the current era of endemic COVID-19, COVID-19 infection remains a major global health issue.[5-7]

In addition to the respiratory symptoms, the effects of COVID-19 are more widespread, encompassing a spectrum of neurological issues.[8] The complications associated with COVID-19 vary from mild symptoms such as headaches and dizziness to more serious conditions including strokes and seizures.[9] Findings from a comprehensive systematic review and meta-analysis showed that headache was a common symptom in COVID-19 cases, with a com-

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bined prevalence rate of approximately 25%.[10] Evidence indicates that headaches are the most frequently observed neurological symptom of COVID-19 and they can sometimes appear as the initial indication of COVID-19 infection.[11] In addition to the direct association of headaches with COVID-19, increased cases of headaches have occurred among the general population and individuals with a prior history of headaches, which may be attributed to lifestyle changes during the COVID-19 period.[12]

Because headaches are the most frequent non-respiratory symptom associated with COVID-19, recognizing their various types and underlying causes could have important clinical consequences. To date, the characteristics of COVID-19 infection-related headaches have been explored in only a few studies. Thus, in the present narrative review, clinical characteristics of COVID-19 infection-related headaches are presented, and potential pathophysiology and treatment options of COVID-19 infection-related headaches explored.

CHARACTERISTICS OF AN ACUTE HEADACHE DURING COVID-19 INFECTION

Headaches typically begin early in the course of COVID-19 symptoms and can start on the first day of the illness in approximately 40%–55% of patients, and for approximately 25% of patients, it may be the first symptom of COVID-19.[13-20] In approximately 10% of cases, a headache is the only symptom of COVID-19.[13,21,22] For 50%–80% of patients who have a history of headaches, especially primary headaches, a COVID-19 infection-related headache can show different characteristics than their usual headaches. The COVID-19 infection-related headaches typically develop gradually and are bilateral, ranging from moderate to severe intensity, and are pressing or tightening types.[23,24] The COVID-19 infection-related headaches are often accompanied by photophobia in 14%–49% of cases, phonophobia in 5%–41%, and nausea and/or vomiting in 14%–43%.[13,18,21,22] Although in most studies, tension-type headaches (TTHs) were reported the most common form, in several studies, migraines were suggested to be more frequent.[13,18,21,22] Overall, the nature of post-COVID-19 headaches can be considered as somewhere between TTHs and migraines.

As the COVID-19 pandemic progressed, various strains of the virus have been identified, each showing different characteristics and prevalence of symptoms like headache. Earlier research, which didn't include data on the Omicron variant, found a higher frequency of headache at the onset of infection in patients with the Delta variant (33%–62%) compared to the Wild-type (21%) and Alpha (12%–56%) variants.[25,26] However, not all studies support this finding.[27] Currently, the Omicron variant is the most prevalent, and there is conflicting information regarding its association with headaches.[28] Reports indicate that headaches are a common symptom of the Omicron variant, but recent findings suggest a decline in headache cases following the rise of Omicron.[29] Infections from the Omicron variant are reportedly associated with headaches more often than those from the Wild-type and Alpha variants, though the incidence is somewhat lower than with the Delta variant.[29-31]

SECONDARY HEADACHES DUE TO COVID-19 INFECTION BASED ON THE INTERNATIONAL CLASSIFICATION OF HEADACHE DISORDERS 3RD EDITION CLASSIFICATION

The most frequently observed headache disorders associated with the ongoing pandemic, classified according to the International Classification of Headache Disorders 3rd Edition (ICHD-3) codes, are discussed below.

1. Acute headache attributed to systemic viral infection

According to the ICHD-3, to diagnose an acute headache caused by a systemic infection, individuals must experience headache episodes that are diffuse and/or moderate to severe in intensity. These headaches should develop, intensify, and subside in temporal correlation with a confirmed systemic viral infection, without any signs of meningitis or encephalitis.[32] Headaches are a frequent symptom among COVID-19 patients, and those associated with the infection can exhibit characteristics of either migraine, TTH, or a combination of both. The nature of these headaches is not restricted to a single type.[33,34] With the Omicron variant of the virus, headaches are a very common symptom, ranking as the second most likely symptom following upper respiratory issues.[35]

2. Headache attributed to viral meningitis or encephalitis

Headaches attributed to viral meningitis or encephalitis typically present as either holocranial (affecting the entire head) or nuchal (in the neck area) and often occur with fever and neck stiffness. The presence and variety of neurological symptoms are dependent on the severity of the infection in individuals who have been diagnosed with meningitis or encephalitis.[32] For headaches attributed to viral encephalitis, diagnosis is established in cases where there is either multifocal or widespread brain swelling or the presence of at least one of the following symptoms: altered mentality, seizure, or focal neurologic deficit.[32]

Acute brain inflammation and encephalitis are most commonly caused by viruses such as herpes simplex virus, influenza virus, varicella-zoster virus, enterovirus, and cytomegalovirus. However, other respiratory viruses, including SARS-CoV and Middle East respiratory virus, also lead to brain swelling and inflammation.[36,37] Typically, headaches associated with these conditions are widespread, intense, and can be either throbbing or pressing, often concentrated in the frontal or retroorbital area.[32] Viral encephalitis can also present with milder symptoms such as fever and mild headache or may occur without any symptoms.[38]

In cases where individuals experience either unilateral or bilateral headaches accompanied by fever and neck stiffness, which worsen with physical activity and the Valsalva maneuver, and sometimes associated with nausea, vomiting, photophobia, then, viral meningitis or encephalitis can be suspected.[39] To confirm the diagnosis for viral meningitis or encephalitis, neuroimaging assessments may be helpful, specifically revealing the enhancement of the leptomeninges.[32] As the COVID-19 pandemic advanced, the frequency of reported encephalitis cases related to COVID-19 increased.[40] In a systematic review in which the neurological manifestations of COVID-19 were investigated, acute viral meningitis or encephalitis was the most common initial diagnosis in patients with confirmed COVID-19 infection.[41]

3. Headache attributed to other non-infectious inflammatory intracranial diseases

During a COVID-19 infection, the development of headaches is influenced by cytokine release, which also alters the pain threshold. Headaches induced by a cytokine storm, a significant immune response, typically arise between the 7th and 10th day following the onset of the disease. These headaches can be classified as headaches attributed to other non-infectious inflammatory intracranial disease according to ICHD-3 criteria.[32] In a previous cross-sectional study in which the effects of systemic inflammatory molecules in COVID-19 patients were investigated, serum levels of Nod-like receptor pyrin domain-containing 3 (NLRP3), high mobility group box-1 (HMGB1), angiotensin-converting enzyme 2 (ACE2), and interleukin (IL)-6 were significantly elevated in COVID-19 patients experiencing headaches compared with subjects without headaches.[42] In this previous study, the authors concluded that increased levels of these mediators might contribute to the sensitization of the trigeminal system, leading to headache as a secondary symptom of SARS-CoV-2 infection.[42] Furthermore, in a case-control study, cytokine and IL profiles in COVID-19 patients were assessed and compared between subjects with and without headaches. The authors found that IL-10 and IL-23 levels were significantly higher in patients suffering from headaches than in subjects without headaches among the COVID-19 cohort.[43]

4. Headache attributed to cranial or cervical vascular disorder

Increasing evidence indicates that COVID-19 may lead to an increased risk of a hypercoagulable state and thromboembolic events. The occurrence of acute stroke in COVID-19 patients is estimated to be approximately 1.5%,[44] with a potentially higher rate in severe cases requiring intensive care unit admission compared with patients treated in general wards.[45] This increased thrombosis risk is thought to be due to endothelial damage caused by cytokine release syndrome. Rare complications of COVID-19, such as cerebral venous sinus thrombosis (CVST), ischemic stroke, and hemorrhagic stroke, have been documented. Although focal neurological signs and reduced

consciousness levels are more common than headaches in many conditions, especially in ischemic and hemorrhagic strokes, headaches often serve as a primary early warning sign in CVST and subarachnoid hemorrhage. In addition, recognizing the correlation between these cerebrovascular disorders and COVID-19 infection-related headaches is crucial.

5. Headache attributed to increased cerebrospinal fluid pressure

Under the ICHD-3 diagnostic criteria, for a headache to be classified as one attributed to increased cerebrospinal fluid (CSF) pressure, the CSF pressure must be over 250 mm and the composition should be normal.[32] In addition, at least two of the following criteria must be met: presence of papilledema, the headache developing in temporal relationship with intracranial hypertension, and the headache improving in temporal relationship with reduced CSF pressure. A possibility also exists that headaches might develop due to increased CSF pressure following a COVID-19 infection. Therefore, if headaches persist after a COVID-19 infection, assessing whether they are related to increased CSF pressure is necessary.

6. Headache attributed to hypoxia and/or hypercapnia

A particular type of headache syndrome emerges and intensifies following exposure to low oxygen levels (hypoxia) and/or high carbon dioxide levels (hypercapnia), and shows significant improvement as the balance between oxygen and carbon dioxide is restored.[32] In more severe instances, SARS-CoV-2 infection can result in widespread inflammation in the alveoli and throughout the body as well as disruptions in gas exchange, leading to headaches caused by hypoxia-induced neuroinflammation.[46] In a study of hospitalized COVID-19 patients, subjects experiencing silent hypoxemia (low blood oxygen levels without respiratory distress) were more likely to report new-onset headaches.[47]

PRIMARY HEADACHE DUE TO COVID-19 INFECTION BASED ON THE INTERNATIONAL CLASSIFICATION OF HEADACHE DISORDERS 3RD EDITION CLASSIFICATION

1. Cough headache

Cough headache is an uncommon type of headache that typically emerges following coughing or other straining actions such as sneezing, bending over, or performing a Valsalva maneuver, and occurs without any abnormalities visible on imaging. A cough headache is generally bilateral and posterior, short-lived, and resolves on its own. A cough headache usually persists for a maximum of 30 minutes, although it can last up to 2 hours in some cases. In approximately 40% of cases, cough headache syndrome is symptomatic, arising as a secondary condition to other disorders.[32] This type of headache, triggered by coughing, has also been observed in COVID-19 patients.[15,48] In a cross-sectional study of hospitalized COVID-19 patients, 26% of subjects with COVID-19-related headaches reported experiencing cough headaches.[22] In addition, cough headache occurrences have been reported with frequencies ranging from 2–10%.[15,23] Some research indicates that cough headaches associated with systemic infections may be due to changes in vascular tone within the cranial vessels.[49]

POSSIBLE MECHANISM OF COVID-19 INFECTION-RELATED HEADACHES

There are several possible mechanisms of COVID-19 infection-related headaches (Figure 1).

1. Direct involvement of trigeminal nerve

ACE2, a metalloproteinase, serves as the specific entry receptor for SARS-CoV-2 in cells. In numerous studies, results indicated that SARS-CoVs can lead to damage in multiple organs by reducing ACE2 expression on cells, a mechanism also supported by research on influenza.[50] Within the central nervous system (CNS), ACE2 is primarily found in neurons but is also present in glial cells. Notably, ACE2 is located in areas, such as the brainstem and motor cortex, thalamus, caudate nucleus, putamen, raphe nucleus, tractus solitarius, rostral ventrolateral medulla, and nucleus

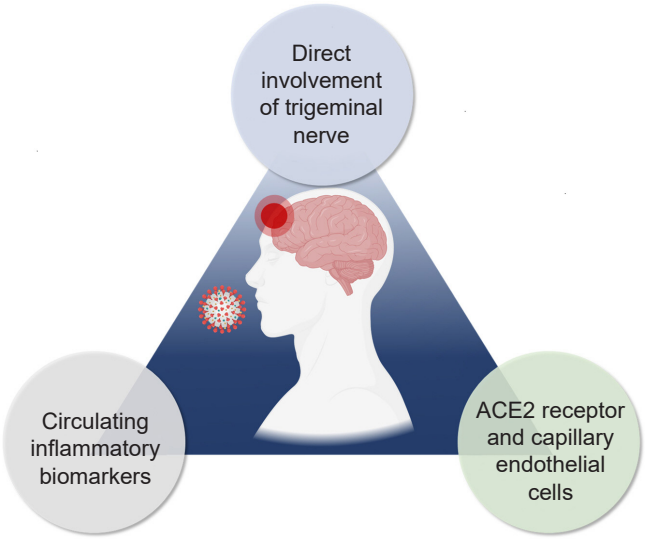

Figure 1. Possible mechanisms of COVID-19 infection-related headaches.

ambiguous.[51,52] In previous research, the renin-angiotensin system in the trigeminal ganglia was suggested to possibly facilitate the direct invasion of the trigeminal nerve endings through the nasal or oral cavities.[53,54] In in vivo studies in which the molecular mechanisms of COVID-19 were investigated, the virus was shown to enter the CNS via the olfactory bulb and then spread to other regions retrogradely through trans-synaptic routes. Pathways associated with ACE and the olfactory system are also considered potential routes for virus neuroinvasion.[55]

2. Circulating inflammatory biomarkers

An additional hypothesis for the cause of headaches associated with COVID-19 is the effect of circulating inflammatory biomarkers including cytokines.[54] Cytokines play a role in altering the pain threshold and in rendering the trigeminal nerve fibers more sensitive.[56,57] Typically, headaches in the context of COVID-19 are accompanied by other systemic infection symptoms and thought to be triggered by cytokine release syndrome. This syndrome is a result of an intense immune reaction to the infection, marked by a surge in various cytokines including tumor necrosis factor-alpha (TNF-α), IL-2, IL-6, IL-7, IL-10, granulocyte colony-stimulating factor, monocyte chemoattractant protein 1, interferon-gamma inducible protein 10, and macrophage inflammatory protein 1-alpha.[58,59] This cytokine storm is a key feature of cytokine release syndrome. The involvement of cytokines such as TNF-α in developing headaches was previously reported.[60] Evidence indicates TNF-α contributes to headache formation, including observations of elevated serum TNF-α levels during migraine episodes and the onset of headaches following TNF-α infusions.[61] Increases in inflammatory cytokines, including IL-1, which shares many functions with TNF-α, have also been reported.[58,59] In other research, patients receiving granulocyte-macrophage colony-stimulating factor treatment experienced headaches,[62] and headaches were identified as a primary side effect of IL-2 therapy.[63] Experimental models have shown that coronaviruses can infect macrophages and glial cells, leading to the release of inflammatory mediators. However, attributing the early and isolated occurrence of headaches solely to a cytokine storm remains unconvincing and more data are required to fully understand this phenomenon.

3. ACE2 receptor and capillary endothelial cells

Elevated ACE2 expression levels in the capillary endothelium indicate potential vascular damage and activation of the trigeminovascular system, which can lead to headaches.[46] The interaction of the SARS-CoV-2 spike protein with ACE2 receptors on the capillary endothelium can compromise the blood-brain barrier.[64] This activation of the trigeminovascular system results in the release of neurotransmitters known to induce pain, such as substance P and calcitonin gene-related peptide (CGRP). The headaches that result from this process may resemble migraines in their symptoms, including throbbing pain, nausea, photophobia, and phonophobia.[65]

TREATMENT FOR HEADACHES RELATED TO COVID-19 INFECTION

To date, randomized clinical trials on treating headaches related to COVID-19 infection have not been conducted. Therefore, the results of recent observational studies or expert opinions are described and summarized in this section (Table 1). The effectiveness of corticosteroids in treating headaches after COVID-19 infection has not been proven. Based on observational data from institutions that

Table 1. Summary of treatment for COVID-19-related headaches

Possible medication	Study result	Caution	Reference
Corticosteroids	There was no significant difference in the frequency or intensity of headaches that occurred after COVID-19 infection depending on whether corticosteroids were administered.	The effectiveness of corticosteroids in treating headaches after COVID-19 infection has not been proven.	20, 66
	In another study, patients receiving corticosteroids were more likely to respond well to nonsteroidal anti-inflammatory drugs (NSAIDs) for headaches that occurred after COVID-19 infection.	Corticosteroids can cause immune deficiency, which may be associated with opportunistic infections.	
Acetaminophen, NSAIDs, metamizole, triptans, or a combination of these oral medications	Several oral medications, including combination therapy, may lead to complete or partial relief (about 25% to 54%) for COVID-19-related headaches.	The effectiveness of oral medications may be insufficient, and if accompanied by nausea and vomiting, administration can be challenging.	15
Paracetamol	About 60% of patients with headaches after COVID-19 infection showed improvement after an intravenous administration of 1 g of paracetamol.	Usually, paracetamol can be prescribed as parenteral formulations.	67
Lidocaine	Lidocaine can be used to block the greater occipital nerve, leading to relief in 85% of COVID-19-related headaches that do not respond to paracetamol.	Lidocaine can be applied for occipital nerve block.	67
NSAIDs (ibuprofen)	Concerns were raised that NSAIDs, especially ibuprofen, might be associated with worse outcomes and increased infectivity of SARS-CoV-2. However, this hypothesis was not confirmed in subsequent studies.	Care should be taken regarding renal dysfunction caused by NSAIDs.	68
	Usually, NSAIDs can be prescribed as oral or parenteral formulations.	NSAID administration can mask COVID-19-related symptoms.	

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

administered corticosteroids to patients with moderate to severe COVID-19, association was not found between the administration of corticosteroids and occurrence, frequency, or intensity of headaches.[66] Conversely, in another study in which a similar hospital protocol was followed, patients with COVID-19 of moderate to severe intensity who were administered corticosteroids, subjects who responded poorly to analgesics for headaches were more often in the group that did not receive steroids.[20]

In a European study on the treatment of headaches following COVID-19 infection, the medications used were acetaminophen (75%), nonsteroidal anti-inflammatory drugs (NSAIDs), metamizole, triptans, or a combination of these (25%).[15] Complete relief of headaches was reported in 26% of all patients and 54% experienced partial improvement.[15] In another study, 59% of patients with headaches post-COVID-19 infection showed improvement after an intravenous administration of 1 g of paracetamol. For subjects who did not respond to paracetamol, lidocaine was used to block the greater occipital nerve, leading to relief in 85% of these cases.[67] Early in the COVID-19 pandemic, concerns were raised that NSAIDs, especially ibuprofen, might be associated with worse outcomes and increased infectivity of SARS-CoV-2. However, this hypothesis was not confirmed in subsequent studies.[68] However, monitoring might be necessary when using NSAIDs because the kidneys are a target organ affected by COVID-19.

PERSISTENT HEADACHE AFTER COVID-19 INFECTION

Reports vary, however, among individuals who experience headaches during the acute phase of COVID-19, 6%–45% continue to suffer from headaches beyond the initial phase of the infection (typically 2–4 weeks).[24] Factors associated with persistent headache include being younger, female, having a history of primary headaches (especially migraines), experiencing headache as the first COVID-19 symptom, and having thyroid disorders.[18,33] In studies in which persistent headaches post-COVID-19 infection were monitored, 16.5% of patients continued to experience headaches for 60 days, 10.6% for 90 days, and 8.4% for more than 180 days.[69] Therefore, the prevalence of persistent headaches apparently decreases over time. In

addition, these persistent headaches can exacerbate existing primary headaches.[69]

If serious secondary headache causes are excluded, treatment similar to that for new daily persistent headache (NDPH) can be considered. Although NDPH can be diagnosed as secondary to a systemic viral infection, the possibility of NDPH, especially following COVID-19 infection, cannot be dismissed. Viral infections can trigger NDPH and reportedly, NDPH after COVID-19 infection can occur.[70-72] Regarding treatment, because clinically proven trials have not been conducted, empirical treatment may be considered. In previous reports, treatments such as steroids and venlafaxine, as well as anticonvulsants, onabotulinum toxin, or CGRP antibody therapies were suggested.[70-72]

CONCLUSION

Headaches following COVID-19 infection are not uncommon and often improve within 3 months but can sometimes persist for a longer period, necessitating differentiation from secondary headaches. Typically, these headaches resemble TTHs or migraine headaches and can be managed with general analgesics and NSAIDs. However, in cases where headaches do not improve over a long period, various medications can be tried. The exact mechanisms underlying these headaches are poorly understood, highlighting the need for further research into their causes and the management of prolonged headaches after COVID-19 infection.

AVAILABILITY OF DATA AND MATERIAL

Not applicable.

AUTHOR CONTRIBUTIONS

Conceptualization: TJS; Data curation: TJS; Formal analysis: TJS; Investigation: TJS; Methodology: TJS; Software: TJS; Validation: TJS; Writing–original draft: YC, TJS; Writing–review and editing: YC, TJS.

CONFLICT OF INTEREST

Tae-Jin Song is the Editor of *Headache and Pain Research* and was not involved in the review process of this article. All authors have no other conflicts of interest to declare.

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Application and Effectiveness of Dietary Therapies for Pediatric Migraine

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Abstract

Migraine is a representative type of primary headache and a common chronic neurological disease that accounts for a large proportion of headaches in children, adolescents, and adults. Unlike migraine in adulthood, pediatric migraine occurs when brain development is not yet complete. This characteristic may require a new perspective for the treatment and management of pediatric migraine. Dietary therapies, mainly the ketogenic diet and its variants, can have positive effects on pediatric migraine. Several recent studies have revealed that dietary therapies, such as the classic ketogenic diet, modified Atkins diet, and low glycemic index diet, improve various neurological diseases by improving dysbiosis of microbiota, reducing proinflammatory cytokines, and increasing mitochondrial function. Nonetheless, the mechanism through which active dietary therapy affects pediatric migraine requires further research. To achieve this, an important role is played by the neuro-nutritional team, which can develop and manage tolerable diets for pediatric migraine patients through mutual collaboration among pediatric neurologists, nurses, and nutritionists.

Keywords: Diet therapy, Headache, Ketogenic diet, Migraine disorders, Pediatrics

INTRODUCTION

Children and adolescents frequently complain of headaches. Migraine is a common primary headache and a prevalent chronic neurological disease, accounting for a large portion of headaches not only in adults but also in children and adolescents.[1-3] Migraine is commonly perceived as something that occurs primarily in adults. However, beginning with puberty, the prevalence of migraine begins to increase rapidly, and this rapid change is noticeable in female adolescents.[4-6] This rapid increase in migraine prevalence in adolescent girls culminates in a high prevalence of migraine among adult women. Pediatric migraine not only affects daily academic activity, relationships with friends, school, and family life but also is associated with secondary psychological disorders.[3,5] If pediatric migraine is not managed early, it can greatly hinder the normal neurological development of children and adolescents, thus transforming it into a social problem. Therefore, early detection and management of pediatric

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migraine can reduce the prevalence and disease burden of pediatric migraine in adulthood. More attention is now being paid to the diagnosis and treatment of pediatric migraine than was done previously.[6,7]

Pediatric migraine has a slightly higher prevalence in males; however, its prevalence in females increases rapidly after puberty, thus reversing the trend. This suggests that hormonal changes may significantly affect the occurrence of pediatric migraine. Pediatric migraine is thought to have a variety of causes, with various molecular mechanisms, brain networks, genetics, and other factors having complex roles.[2,3] However, the cause of migraine remains unknown. Pediatric migraine differs from adult migraine in that it occurs at a time when brain development is not yet complete. These characteristics suggest that a new perspective is required for the treatment and management of pediatric migraine.[6-8]

TREATMENT OF PEDIATRIC MIGRAINE

Pediatric migraine treatments can be broadly divided into three categories: acute treatment, preventive medication, and non-pharmacological treatment including lifestyle modification and neuromodulation.[3,7] Acute treatment includes drugs such as acetaminophen, ibuprofen, and naproxen, as well as triptans to rapidly alleviate acute headaches in patients. However, the frequent use of acute treatment carries the risk of medication overuse headaches. Triptans are effective migraine-targeted analgesics but may have the side effect of vasoconstriction. Therefore, it is necessary to prevent migraine through appropriate preventive medications and reduce the use of acute treatment. In addition, the ditans, a group of selective 5-HT_{1F} receptor agonists, is an acute treatment that ameliorates the side effects of triptan-induced vasoconstriction. Ditans are currently undergoing a phase III clinical trial in pediatric patients with episodic migraine aged 6–17 years, and not yet widely used in the treatment of pediatric migraine.[2]

Preventive medications include antiseizure medications, antidepressants, beta blockers, calcium channel blockers, and calcitonin gene-related peptide (CGRP) monoclonal antibodies, which have recently received great attention. The CGRP monoclonal antibody is the first migraine-specific preventive medication.[4,8] CGRP is a neuropeptide secreted by the terminal of the trigeminal nerve during a migraine attack. Anti-CGRP monoclonal antibodies are a new medication that achieve migraine prevention by blocking CGRP itself or the CGRP receptor, and its safety has been confirmed. Fremanezumab, galcanezumab, and eptinezumab directly target CGRP (fremanezumab and galcanezumab are available in Republic of Korea), whereas, erenumab is a CGRP receptor antibody. Phase III clinical trials in pediatric patients are in progress.[8] Recently, the American Headache Society's Pediatric and Adolescent Headache special interest group issued an expert opinion suggesting that CGRP monoclonal antibodies could be considered for post-pubertal adolescent patients with chronic migraine who do not respond well to two or more preventive medications.[4,8,9] Additionally, there are GGRP receptor antagonists called gepants, but phase III studies on these are not yet in progress.[8]

Before the emergence of anti-CGRP monoclonal antibodies, migraine was prevented using various antiseizure medications, antidepressants, beta-blockers, and calcium channel blockers. However, these drugs are either have not completed sufficient clinical trials, not approved for use, or have side effects that make them unsuitable for use in children and adolescents. These limitations in addressing pediatric migraine render treatment more difficult and require a different approach than that for adult migraine.[4,8] In addition, the Childhood and Adolescent Migraine Prevention (CHAMP) study, conducted in 2017 targeting patients aged 8 to 17 years, found no significant difference in the headache prevention effect of amitriptyline or topiramate when compared to a placebo. Thus, the need for migraine-targeted preventive medication and other modes of treatment, such as lifestyle modification and cognitive behavior therapy was further requested through the CHAMP study.[7,8,10]

Non-pharmacological treatment, especially lifestyle modification, the third treatment for pediatric migraine, is essential in patients with migraine of all ages. This includes diet therapy, dietary habit correction, and regular, appropriate exercise and is necessary for effective long-term management of pediatric migraine. Lifestyle modifications such as establishing a healthy sleep pattern, sufficient water intake, regular living, regular exercise, and reduction of light stimulation in daily life are important parts in preventing migraine. Among them, eating habits are known to be a very powerful lifestyle modification. Recently, due to

the research on the gut microbiota-brain axis, the relationship between intestinal microorganisms and brain disease has been highlighted. In this context, attempts have been made to prevent and manage pediatric migraine through diet therapy.[11-13] The diet therapies typically implemented in pediatric migraine include ketogenic diets (KDs), the modified Atkins therapy (MAD), and the low glycemic index diet therapy (LGIT), which are currently used in the treatment of intractable epilepsy. This type of dietary therapy is based on good quality, high lipid, and low carbohydrate foods.[13-16]

TYPES OF DIET THERAPY FOR PEDIATRIC MIGRAINE MANAGEMENT

Representative diet therapies for managing pediatric migraine can be considered broad variations of the KD.

1. Classic ketogenic diet (KD) (KD 4:1, KD 3:1)

The KD creates ketone bodies and is based on a weight ratio of lipid and protein+carbohydrate of 4:1, commonly expressed as KD 4:1. KD 4:1 was designed by Dr. Russell Wilder in 1923. KD 3:1, which has a lipid-to-protein +carbohydrate ratio of 3:1, is also widely used, and KD 3:1 shows similar effects as KD 4:1. KD 4:1 and KD 3:1 are considered classic KD.[17,18] Considering the composition of the KD in terms of calories, in KD 4:1, the proportions of lipids is approximately 90% of the calories in the entire diet, carbohydrates are 4%, and proteins are 6%. KD 3:1 indicates that lipids accounted for 87% of total calories. The classic KD stabilizes the brain and exerts antioxidant effects by causing strong ketosis in the body. Additionally, because classic KD restricts overall calories, it aids in weight loss. However, due to considerably high lipid levels, there is a risk of side effects including gastrointestinal problems (nausea, vomiting, diarrhea, constipation, hyperlipidemia, and hypoglycemia), and it is not nutritionally balanced as well. Therefore, classic KD may be difficult to maintain for the long-term management of pediatric migraine. To alleviate the side effects of classic KD, diet therapies such as MAD and LGIT were developed (Figure 1).[19-21]

2. Modified Atkins therapy

Dr. Robert Atkins created the MAD in the 1970s as a diet to treat obesity. Overall, although it inherits the nutrient ratio of the classic KD, approximately 70% to 80% of the calories in the diet consist of lipids, the MAD may or may not restrict caloric intake.[19,21] Although it is not a diet aimed at ketosis, consistent ketosis can be achieved in some patients. MAD has an anti-seizure effect similar to that of classic KD. A recent study reported that the anti-seizure effect of the MAD was not inferior to that of the classic KD.[19] Nevertheless, MAD alleviates the side effects of classic KD and is attracting attention as a treatment for various neurological diseases. MAD has been used not only for epilepsy but also as a dietary therapy for migraine treatment.[18]

3. Low glycemic index diet therapy

LGIT also called as the liberalized KD, was first introduced in 2005. This is also a high-lipid diet in terms of the overall nutrient ratio, but the ratio of fat to total calories is set at 50% to 60%.[22] For reference, in a typical diet, fat accounts for about 20% to 30% of the total calories. Therefore, LGIT is still a high-lipid diet in comparison. Carbohydrates comprise approximately 10% to 15% of the total daily calories and the diet focuses on carbohydrates that are considered to have a low glycemic index (GI). Low GI ingredients raise blood glucose levels slowly. The LGIT uses ingredients with a GI of 50 or less, including most vegetables, garlic, mushrooms, tomatoes, strawberries, oatmeal, apples, oranges, cherries, dark chocolate, milk, and yogurt.[22,23] Foods classified as high GI, such as rice, bread, bagels, potatoes, and watermelons, are excluded or significantly restricted from the LGIT diet. LGIT also has a significant anti-seizure effect and contributes to brain stabilization. A recent study reported that LGIT was not inferior to the classic KD and MAD in reducing seizures by >50% in patients with drug-resistant epilepsy.[19] In addition, it is nutritionally balanced and can be included in various diets, making it suitable for long-term maintenance. Due to LGIT's tolerability, it has recently replaced the classic KD and MAD in various neurological diseases including pediatric migraine.[21-23]

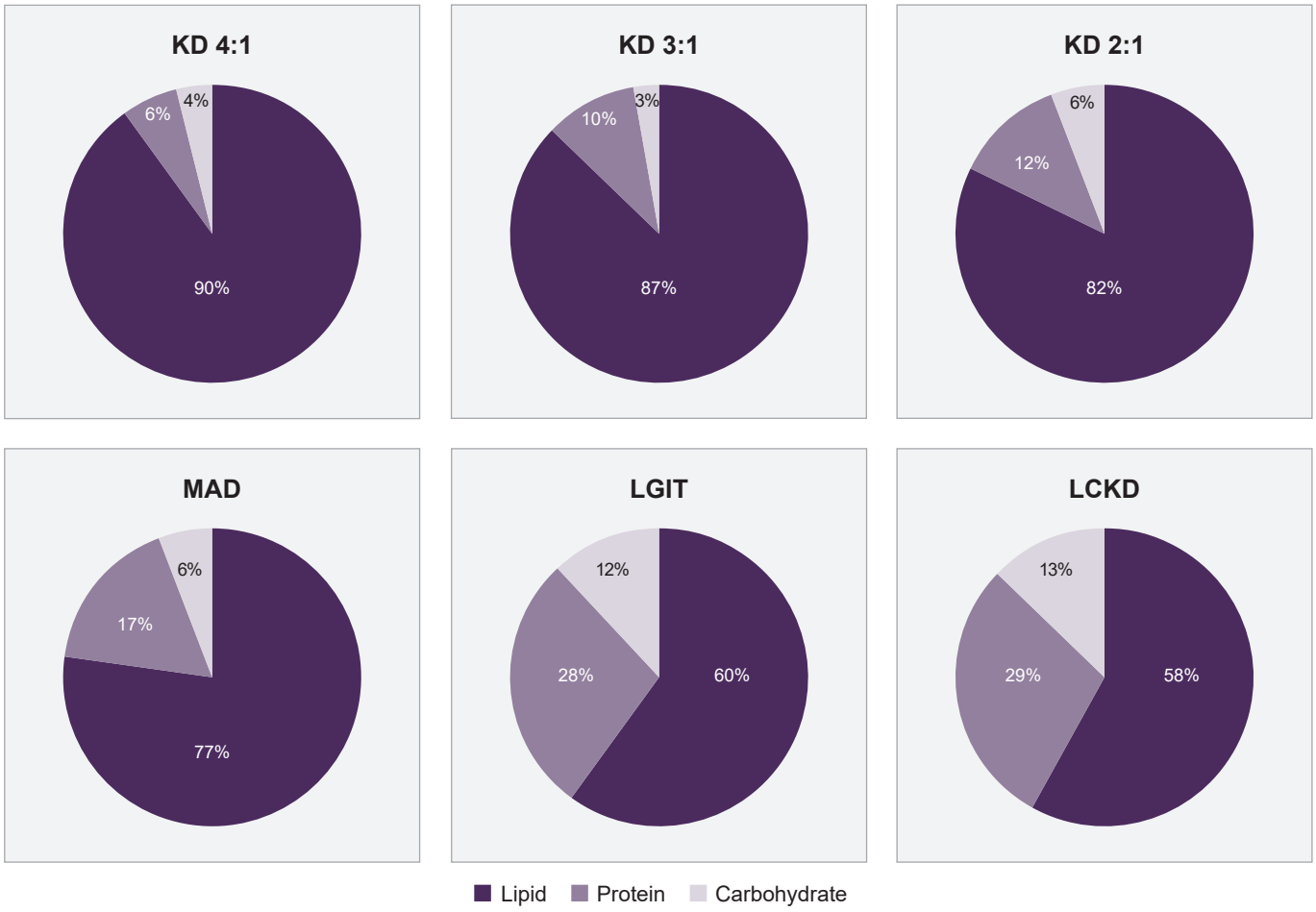

Figure 1. Types of dietary therapies and ratio of calories by nutrient for pediatric migraine.
KD, ketogenic diet; MAD, modified Atkins diet; LGIT, low glycemic index diet; LCKD, low-calorie ketogenic diet.

4. Other diet therapies for pediatric migraine management

In addition to representative KDs such as the classic KD, MAD, and LGIT and their variants, the KD 2:1, the low-calorie ketogenic diet (LCKD), the very-low-calorie ketogenic diet (VLCKD), the polyunsaturated fatty acid (PUFA)-enriched diet, and the gluten-free diet can be implemented for the management of pediatric migraine.[24,25] In KD 2:1, lipids account for 82% of total calories, and it is a KD variant that falls between KD 3:1 and MAD.[26] The LCKD sets total calories to 800–1,200 kcal/day and the proportion of lipids to approximately 58% of total calories. The VLCKD sets the total calories to 600–800 kcal/day and the lipid ratio to approximately 43% of the total calories. Both the LCKD and VLCKD are characterized by low calories, low carbohydrates, and normal protein content, and are diets that can be used for migraine patients with obesity or obstructive sleep apnea. However, in LCKD and VLCKD, electrolyte imbalance may arise from excessive calorie restriction, which may actually worsen headaches; therefore, it is necessary to implement it according to individual circumstances. The introduction of the PUFA-enriched diet was a response to the high levels of saturated or mono-unsaturated fatty acids in the KD. PUFAs are classified as omega-3 (alpha-linoleic acid and docosahexaenoic acid) and omega-6 fatty acids (linoleic acid and gamma-linolenic acid). Diet therapy using PUFA is known to have positive effects on neuronal and cardiovascular functions, and can improve the side effects associated with KD. For those

with migraine and celiac disease, a gluten-free diet can reduce the frequency of migraine.[23,27]

MECHANISM OF DIET THERAPY FOR PEDIATRIC MIGRAINE

The term 'gut-brain axis,' frequently mentioned in recent research papers, emphasizes the interaction between the brain and gastrointestinal tract. Nutrients absorbed from the gastrointestinal tract not only provide energy to operate the brain but also provide materials for organizing the brain network, and may point to the possible mechanism between migraine and diet therapy.[26] These mechanisms involve inflammation and gut microbiota profiles. Dysbiosis of microbiota can increase gut permeability and proinflammatory cytokines.[16,28] Inflammatory mediators such as interleukin (IL)-1 beta, IL-6, IL-8, tumor necrosis factor alpha, and interferon-gamma are known to induce visceral pain, and most are related to migraine attacks. CGRP may increase due to dysbiosis of the microbiota, which may disturb gastric acid secretion, causing migraine and abdominal disturbances simultaneously. The gut microbiota is involved in the production of tryptophan metabolites via the tryptophan-kynurenine pathway in the intestine. Tryptophan is the precursor of serotonin which plays a significant role in the pathophysiology of migraine in the brain.[16] In addition, studies have reported on the relationship between inflammatory cytokines and dysbiosis of microbiota in diseases including irritable bowel syndrome, celiac disease, and migraine.[29]

Several recent studies have revealed that diet therapies, such as KD, MAD, and LGIT, improve neurological diseases by alleviating the dysbiosis of microbiota, reducing proinflammatory cytokines, and increasing mitochondrial function.[26-28,30] Additionally, there is evidence that mitochondrial dysfunction plays a role in the pathophysiology of migraine, and that the KD and its variants can improve mitochondrial function by increasing adenosine triphosphate (ATP) production.[31-33] This increase in ATP production can ameliorate secondary chronic fatigue caused by migraine. Anticipated advancements in future research are expected to substantiate and augment the diverse neuroprotective functions of KD and its variants. These functions include the inhibition of neuroinflammation, reduction of CGRP levels, and improvement of serotoninergic dysfunction.[31]

CURRENT STUDIES ON DIET THERAPY FOR PEDIATRIC MIGRAINE

Existing studies on diet therapy in pediatric migraine are very rare and limited. Patients are highly resistant to strong diet therapy in the pediatric age group, so consideration is needed regarding the appropriate intensity of diet therapy.[34] However, studies of diet therapy in adults are useful as a reference for the application of diet therapy in pediatric migraine. Research on KD and its variants as therapies for neurological diseases has increased rapidly since 1995. A randomized controlled study published by Di Lorenzo et al.,[35] reported that VLCKD significantly reduced the mean number of days with migraine in overweight patients. A retrospective observational study by Valente et al.,[15] reported that monthly headache days, acute medication intake, and body mass index were all significantly reduced 3 months after starting KD. In a retrospective single-center pilot study by Tereshko et al.,[27] three diet therapies, KD 2:1, LGIT, and VLCKD implemented in 76 migraine patients significantly reduced migraine frequency and intensity. In addition, the results on Migraine Disability Questionnaire, Headache Impact Test, and fatigue severity scale were significantly reduced.[27] In a systematic review recently reported by Caminha et al.,[36] KD and its variants were summarized as migraine prevention therapy with fewer side effects in both adolescents and adults. Lelleck et al.[24] presented the possibility of individually managing LGIT using digital methods. In addition, a recent study targeting pediatric age is attracting attention. Pasca et al.[37] reported that sleep stabilization was achieved in a patient with chronic pediatric migraine through KD, and this result was confirmed by polysomnography (Table 1). Likewise, interest in the effectiveness and safety of KD and its variants as a preventive treatment for migraine is increasing, and research on their application to pediatric migraine increasing.

CONCLUSION

Although the treatment of pediatric migraine follows that for adult migraine, the available acute and preventive medications are limited when compared with those for adults. Additionally, because brain and gastrointestinal tract development is not yet complete in adolescents, active nutritional interventions such as diet therapy may be

Table 1. Current studies on dietary therapies for migraine

Study	Target patient (n)	Age (yr)	Study design	Type of diet therapy	Duration of study	Outcome
Di Lorenzo et al.[35]	35	18–65	Prospective	VLCKD	4 wk	VLCKD patients experienced −3.73 (95% CI, −5.31 to −2.15) migraine days. The 50% responder rate for migraine days was 74.28% (26/35 patients) during the VLCKD period.
Valente et al.[15]	23	47.22±15.21	Retrospective	VLCKD, KD 2:1, MAD, LGIT	3 mo	Reduction in monthly headache days (12.5±9.5 vs. 6.7±8.6; p<0.001) Reduction in days of acute medication intake (11.06±9.37 vs. 4.93±7.99; p=0.008) Reduction in patients' weight (73.8±15.2 vs. 68.4±14.6; p<0.001) and BMI (26.9±6.2 vs. 23.7±8.1; p<0.001)
Tereshko et al.[27]	76	45.90±14.77	Prospective	KD 2:1, LGIT, VLCKD	3 mo	The 50% responder rate for migraine days was 74.28% (26/35 patients) during the VLCKD period. KD protocols effectively improved migraine intensity, frequency, MIDAS, and HIT-6.
Lelleck et al.[24]	First study=49 Second study=71	First study=41±9.2 Second study=40±12.3	Prospective	LGIT	16 wk	Reduction of headache and migraine days, as well as reductions in HIT-6 and MIDAS scores. Migraine days decreased by 2.40 days (95% CI, −3.37 to −1.42), HIT-6 improved by 3.17 points (95% CI, −4.63 to −1.70), and MIDAS by 13.45 points (95% CI, −22.01 to −4.89).
Pasca et al.[37]	7	14–18	Prospective	Classic KD	3 mo	5/7 patients reported an improvement in migraine symptoms in terms of duration of the attacks, frequency, and intensity.

VLCKD, very-low-calorie ketogenic diet; CI, confidence interval; KD, ketogenic diet; MAD, modified Atkins diet; LGIT, low glycemic index diet; BMI, body mass index; MIDAS, Migraine Disability Assessment Test; HIT-6, Headache Impact Test 6.

effective. Lifestyle modification is essential for the fundamental treatment of primary headaches such as migraine. However, as with most migraine prevention medicines that have been released thus far, the mechanism by which active diet therapy affects pediatric migraine requires further research.[37,38] To achieve this, a neuro-nutritional team composed of pediatric neurologists, nurses, and nutritionists who can develop and regularly manage a tolerable diet for pediatric migraine patients is key. In the future, the importance of diet therapy will be highlighted not only as a preventive treatment for pediatric migraine but also as a lifestyle modification. Advancements in methodologies for basic research and clinical applications are expected.[39]

AVAILABILITY OF DATA AND MATERIAL

Not applicable.

AUTHOR CONTRIBUTIONS

Conceptualization, Data curation, Formal analysis, Funding acquisition, Resources, Validation, Writing–original draft, Writing–review & editing: JHN.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Headache and Pain Research

Update on Cluster Headaches: From Genetic to Novel Therapeutic Approaches

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Abstract

Cluster headaches affect 0.1% of the population and are four times more common in males than in females. Patients with this condition present with severe unilateral head pain localized in the frontotemporal lobe, accompanied by ipsilateral lacrimation, conjunctival injection, nasal congestion, diaphoresis, miosis, and eyelid edema. Recently, the first genome-wide association study of cluster headaches was conducted with the goal of aggregating data for meta-analyses, identifying genetic risk variants, and gaining biological insights. Although little is known about the pathophysiology of cluster headaches, the trigeminovascular and trigeminal autonomic reflexes and hypothalamic pathways are involved. Among anti-calcitonin gene-related peptide monoclonal antibodies, galcanezumab has been reported to be effective in preventing episodic cluster headaches.

Keywords: Calcitonin gene-related peptide, Cluster headache, Genetics

INTRODUCTION

Cluster headache (CH) is a trigeminal autonomic cephalalgia (TACs) that constitutes a primary headache disorder. Harris (1869–1960) confined the characteristics of CH in his article.[1] He marked a distinct entity of CH, separating it from migraine and documenting its unilateral nature, severity, associated autonomic characteristics, and attack frequencies. This is the comprehensive review on CH in the English medical literature and aligns with the International Classification of Headache Disorder-3 (ICHD-3).[2]

CH is an excruciating primary headache disorder that affects approximately 0.1% of the general population. It manifests itself as severe unilateral pain in the trigeminal nerve distribution, ipsilateral cranial autonomic features, and agitation during attacks.

There are several effective acute treatments, which benefit slightly more than 50% of patients with CH. Historically, it has been difficult to manage CH using preventive drugs introduced for non-headaches. However, advanced understanding based on genetic and neuroimaging studies has revealed key neuropeptides and brain structures that can

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serve as therapeutic targets for CH.

This review covers a comprehensive view of CH, including its cardinal clinical features, epidemiology, and recent pathophysiological understanding derived from neuroimaging studies. Established treatments are discussed, along with the outcomes of studies on emerging treatments.

CLINICAL FEATURE

The patient had severe unilateral cephalalgia localized to the frontotemporal region, accompanied by autonomic nervous system manifestations, including ipsilateral lacrimation, conjunctival injection, nasal congestion, diaphoresis of the forehead and face, miosis, ptosis, or eyelid edema.[3,4] These headache episodes last for varying durations, ranging from minutes to hours, with recurrent patterns that last for several days, constituting the clinical presentation of CH. This nomenclature is derived from its distinctive cyclic recurrence characterized by alternating periods of relative quiescence and clustered episodes of heightened pain intensity. This condition encompasses episodic and chronic phenotypes aligned with the taxonomy stipulated in ICHD-3.[2]

Without therapeutic intervention, CH attacks can be transient and last anywhere between 15 minutes and 3 hours, with an average of 45–90 minutes. During these episodes, patients present with ipsilateral cranial autonomic symptoms, including lacrimation, eye erythema, ocular discomfort, ptosis, aural fullness, nasal congestion, rhinorrhea, flushing, and throat swelling. These cranial autonomic symptoms occur simultaneously with pain and are caused by parasympathetic activation. Sympathetic dysfunction can manifest itself as miosis or partial Horner syndrome.[5,6]

A notable feature of CH attacks is restlessness and agitation, which distinguish them from migraines. Patients with migraine or migraine patients prefer immobility during an episode, meanwhile patients with CH engage in pacing or rocking motions, applying pressure to the affected area to mitigate pain intensity. Typically, post-attack patients remain pain-free until the onset of subsequent episodes.[4,7] In particular, there is a nocturnal predilection for attacks, with patients reporting an association with sleep disturbances. Interestingly, the attacks showed a consistent circadian pattern that occurred within a specific daily timeframe.

The temporal extent of recurrent attacks of CH is referred as a "bout" and is on average between 6 and 12 weeks in duration.[2] Patients with CH may experience bouts interspersed with periods of remission that span months or years.[4]

Episodic and chronic CH can be classified according to the duration of remission between bouts. Discrimination between episodic and chronic presentations can help guide therapeutic decisions. Patients with episodic CH may discern seasonal patterns during their bouts.

Patients with chronic CH[8] may have headaches that last more than a year without remission or may experience less than 3 months of remission.[4] Some patients with chronic CH may experience increased attacks during these seasonal transitions.[9]

EPIDEMIOLOGY

CH, the predominant entity within TACs, exhibits a relatively low incidence when juxtaposed with primary headaches, such as tension-type headaches or migraine, demonstrating an estimated prevalence of 0.1%.[10] Meta-analytical findings indicated a lifetime prevalence of 124 per 100,000 for CH.[11] Given that approximately 10% of people affected by CH transition to chronic form[11] the expected prevalence of chronic CH ranges from 10 to 15 individuals per 100,000 individuals.

1. Sex and age

CH occurs four times more frequently in males than in females. Although there was a male predominance of CH, there were no significant differences in prevalence rates between episodic and chronic CH. A sub-analysis of the sex ratio by age of onset showed that the male-to-female ratio was highest at the age of onset of 20–49 years, with 7.2:1 in episodic and 11:1 in chronic CH. The male-to-female incidence ratio was lowest in those aged >50 years, 2.3:1 in episodic CH, and 0.6:1 in chronic CH.[12] The study found that circadian rhythmicity of CH attacks was more common in female (73.6%) than male (63.3%). Female group also had a higher frequency of nocturnal attacks.[13]

2. Trigger factor

The authors suggested that the decrease in the male-to-female ratio could reflect changes in female lifestyles over several decades, potentially due to increased smoking and alcohol consumption.[11] Among the individuals who reported triggers, alcohol emerged as the most prevalent provoking factor for CH attacks, with a higher reporting rate among male participants than among their female counterparts, consistent with previous findings.

One hypothesis is that males with episodic CH may have higher alcohol consumption patterns than females with episodic CH and that this imbalance may persist during active bouts compared to female participants.[13]

Other frequently cited factors included stress and lack of sleep, which were reported more frequently in female than male participants.[14,15] Previous research has shown that female participants are more susceptible to stress-induced hyperarousal, which is characterized by heightened agitation, restlessness, and sleep disturbances. This highlights sex-specific distinctions in stress response mechanisms.

However, male participants may experience stress-induced cognitive deficits and subsequent structural and functional changes in the regions of the brain.[13] Sleep deprivation due to stress-induced arousal can trigger CH attacks in female patients. The causal relationship between attack triggers and headache still requires further elucidation.

3. Genetics

The first genome-wide association study of CHs to aggregate data for meta-analysis, identify genetic risk variants, and gain biological insights was reported in 2023.[8] This study was carried out in a total of 4,777 clinically diagnosed CH cases in 10 cohorts in Europe and one cohort in East Asia. The heritability estimate for CH was 14.5%, and the meta-analysis identified nine independent signals at seven loci (DUSP10, MERTK, FTCDNL1, FHL5, WNT2, PLCE1, and LRP1) of genome-wide significance, and one additional locus (CAPN2) in the trans-ethnic meta-analysis. Three of the identified loci (FHL5, PLCE1, and LRP1) were also associated with migraine. Furthermore, a causal effect of smoking intensity on CH was shown.

CHs are associated with the chronobiological system. Two (MERTK and FHL5) of the four loci identified in recently published genomic association studies include genes involved in circadian rhythms.[16]

PATHOPHYSIOLOGY

Although little is known about the pathophysiology of CH, trigeminovascular and trigeminal autonomic reflexes and hypothalamic pathways are involved (Figure 1). First, the trigeminovascular pathway plays a central role in the trigeminal distribution of severe unilateral pain. Second, cranial autonomic symptoms appear due to the trigeminal autonomic reflex. Finally, the hypothalamus may influence attack generation by contributing to circadian and circannual attack patterns.[17]

The trigeminovascular pathway contains neurons with cell bodies in the trigeminal ganglion, which innervate the cerebral vasculature and adjacent dura. Bipolar trigeminal ganglion neurons synapse with the trigeminocervical complex (TCC), which consists of the trigeminal nucleus caudalis of the caudal brainstem and the dorsal horn of the cervical spinal nerves C1 and C2.[18] Activated trigeminovascular pathways project from the TCC to the thalamus, resulting in the activation of cortical structures involved in pain processing, including the prefrontal cortex, subcortex, and cingulate cortex.[19] This results in the release of neuropeptides, including calcitonin gene-related peptides (CGRP), substance P, and neurokinin A.[20]

The trigeminal autonomic reflex pathway begins with the stimulation of trigeminal nerve endings, which activate secondary TCC neurons that project to the parasympathetic efferent pathway.[21,22] Parasympathetic fibers originate in the superior salivary nucleus of the pons and pass through synapses in the facial (VIIth) cranial nerve and sphenopalatine ganglion (SPG). The postganglionic parasympathetic neurons of the SPG, which express pituitary adenylate cyclase-activating polypeptide 38 (PACAP-38), nitric oxide synthase, vasoactive enteric polypeptide, and CGRP, innervate the lacrimal, nasal, and pharyngeal glands.

Finally, the hypothalamus plays an important role in regulating circadian rhythms, neuroendocrine homeostasis, the autonomic nervous system, and trigeminovascular nociceptive processing.[23] The suprachiasmatic nucleus (SCN) of the hypothalamus serves as the primary circadian pacemaker,[24] and disruption of the mechanism underlying circa-

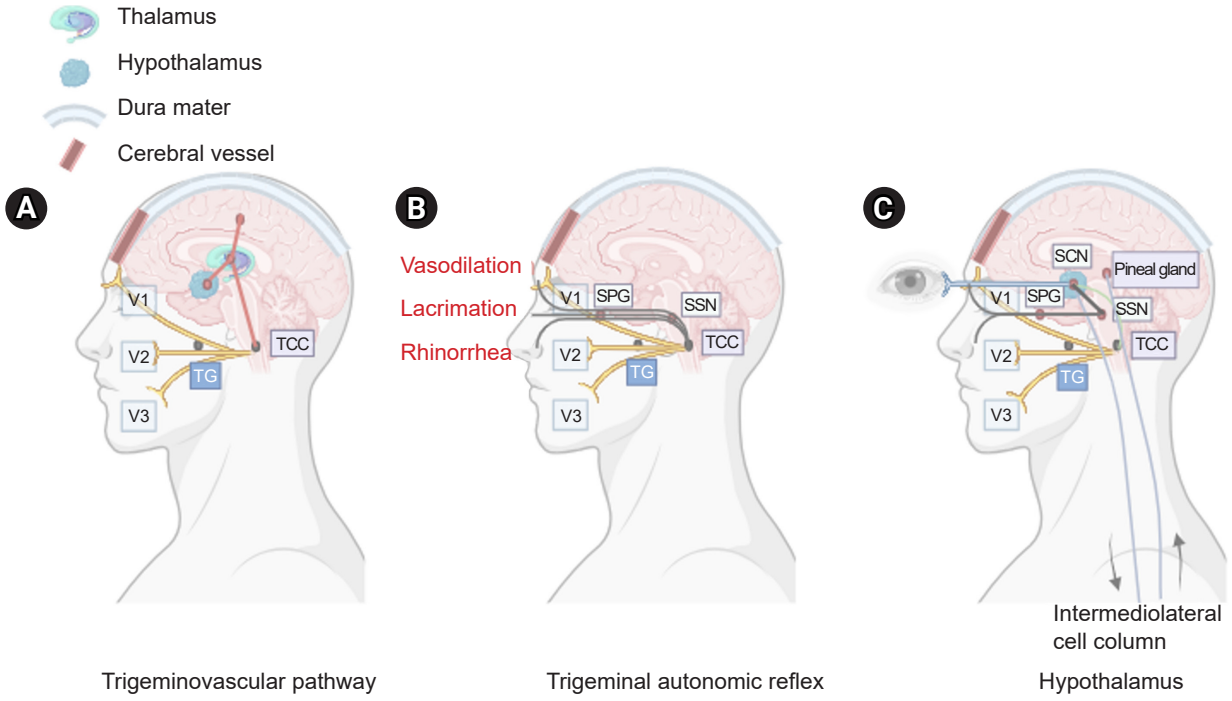

Figure 1. Three main components of cluster headache pathophysiology. (A) The trigeminal ganglion (TG) innervates the cerebral vessels and dura mater through its trigeminal branches (V1, V2, and V3) and forms synapses in the center of the trigeminocervical complex (TCC). Projections of cervical nerves from the TCC to the thalamus activate cortical structures involved in pain processing, such as the prefrontal cortex, subcortex, and cingulate cortex. (B) Trigeminal nerve terminals activate secondary TCC neurons that project to the superior salivary nucleus (SSN) of the pons and from SSN synapses to the peripheral sphenopalatine ganglion (SPG). The postganglionic parasympathetic nerves then innervate the lacrimal, nasal, and pharyngeal glands, causing autonomic symptoms. (C) The suprachiasmatic nucleus (SCN) of the hypothalamus receives light impulse input from the retina via the retinohypothalamus, and these light impulses are transmitted to the paraventricular nucleus and then to the medial and lateral nuclei of the spinal cord, supporting postganglionic sympathetic axons. The hypothalamic region projects directly to the SSN, which in turn projects to the SPG, and nerves project to the lacrimal, nasal, and pharyngeal glands.

dian regulation may contribute to the development of CH. Light input through the retinohypothalamic tract, which mediates the light-dark cycle using PACAP-38 and glutamate, increases the firing rate of neurons within the SCN core and regulates melatonin production. Low melatonin levels suggest SCN involvement in patients with CH.[25,26]

1. Neuropeptides

1) Calcitonin gene-related peptide

CGRP is an effective vasodilator that modulates nerve function. In the trigeminovascular system, CGRP is primarily localized in the sensory trigeminal ganglion. Aδ and C fibers extend to the cerebral and dural vessels, the TCC, and the spinal trigeminal tract.[27,28] Binding occurs at the CGRP receptor, which consists of a calcitonin receptor-like receptor and receptor activity-modifying protein 1 (RAMP1).[29-31] This receptor binds to the receptor component protein, increasing intracellular cAMP levels and subsequently activating protein kinase A (PKA), resulting in the phosphorylation of numerous downstream targets.

In individuals who experience CH, plasma levels of CGRP are elevated during attacks and return to baseline levels after treatment. Patients with chronic CH had lower levels of CGRP than those with remitted episodic CH, suggesting potential pathophysiological differences between episodic CH and chronic CH.[32,33]

2) Pituitary adenylate cyclase-activating polypeptide 38

PACAP-38 is a 38 amino acid neuropeptide found in the

SPG, otic ganglion, and trigeminal ganglion and plays an important role in the trigeminovascular system and trigeminal autonomic reflex systems. The activation of the retinohypothalamic tract results in the release of PACAP-38, which mediates melatonin release.[34] During spontaneous acute CH attacks, PACAP-38 levels increased. However, patients with episodic cluster, not in bouts, exhibited lower plasma levels of PACAP-38 than healthy controls. The implications of reduced inter-bout levels of PACAP-38 remain unclear, but it has been suggested that PACAP-38 is depleted during these periods, leading to decreased levels.[35] These findings support the involvement of PACAP-38 in the pathophysiology of CH.

EVALUATION

A detailed history-taking and neurological examination are necessary when evaluating patients with CHs. Patients may complain of accompanying cranial autonomic symptoms such as ptosis, lacrimation, and conjunctival injection.[36] Inter-bout examinations are usually normal; however, clinicians may perform brain imaging to rule out secondary causes that may mimic the CH phenotype. Magnetic resonance or computed tomography venography may be considered in cases where there is a concern for cerebral venous sinus thrombosis, such as in patients with papilledema, or when Horner syndrome is suspected. However, if a patient has abnormal neurological examination results beyond the typical transient ipsilateral cranial autonomic features during an attack, further examination and evaluation may be required.

1. Evolution of the diagnostic criteria for cluster headache

The term trigeminal autonomic headache (TAC) was first coined by Goadsby and Lipton. When the first edition of the ICHD was published in 1988, the term TAC had not yet been coined, but was first introduced in the second edition of the ICHD (2004). TAC includes three types of headaches: CH, chronic and episodic paroxysmal hemicrania, and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.[37]

CH has been previously reported in several other terms, such as ciliary neuralgia, histaminic cephalalgia, Horton's headache, Sluder's neuralgia, sphenopalatine neuralgia, migrainous neuralgia (of Harris), and vidian neuralgia. In ICHD-1, these terms were combined into the term "cluster headache."

In ICHD-2,[38] these short-lasting headaches with autonomic features were included in rubric 3 as "cluster headaches and other trigemino-autonomic cephalalgias." Symptoms such as restlessness or agitation were included in the diagnostic criteria. The remission period for chronic CH also changed from 14 days to 1 month.

In ICHD-3, since CH is also a trigemino-autonomic cephalalgia, the title was changed to TACs. In the 3rd edition, several additions were made to the criterion C for CH. These include forehead and facial flushing, a sensation of ear fullness, and a sense of restlessness or agitation.[2] The word "chronic" for CH continues to be used in the ICHD-3. Used to mean CH with no attack-free period. Hemicrania continua and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms are newly included in TACs (Table 1).

MANAGEMENT

The approach to CH management includes immediate treatment of acute attacks and the implementation of preventive strategies to reduce or stop the recurrence of attacks during active periods. Most treatment recommendations are based on the results of open observational studies.

1. Acute management

CH attacks typically last for a short period (15–180 minutes) and peak rapidly, requiring prompt treatment. Medication overuse headaches may occur in patients with CH, especially if they have a concurrent or family history of migraine and use less effective treatments such as oral triptans, acetaminophen, or opioid receptor agonist analgesics for acute attacks.[39]

1) Oxygen therapy

Oxygen therapy has the advantage of having fewer side effects than triptans and is an acute treatment that can be used even during pregnancy and breastfeeding. Recommendations for oxygen inhalation include inhalation of

Table 1. Evolution of the diagnostic criteria for cluster headaches

Diagnostic criteria of cluster headache (ICHD-2)	Diagnostic criteria of cluster headache (ICHD-3)
A. At least five attacks fulfilling criteria B–D	A. At least five attacks fulfilling criteria B–D
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes if untreated	B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes (when untreated)
C. Headache is accompanied by at least one of the following:	C. Either or both of the following:
1. Ipsilateral conjunctival injection and/or lacrimation	1. at least one of the following symptoms or signs, ipsilateral to the headache:
2. Ipsilateral nasal congestion and/or rhinorrhea	a) conjunctival injection and/or lacrimation
3. Ipsilateral eyelid edema	b) nasal congestion and/or rhinorrhea
4. Ipsilateral forehead and facial sweating	c) eyelid edema
5. Ipsilateral miosis and/or ptosis	d) forehead and facial sweating
6. A sense of restlessness or agitation	e) miosis and/or ptosis
D. Attacks have a frequency from one every other day to 8 per day	2. a sense of restlessness or agitation
E. Not attributed to another disorder	D. Occurring with a frequency between one every other day and eight per day
	E. Not better accounted for by another ICHD-3 diagnosis.

ICHD, International Classification of Headache Disorder.

at least 12 L/min of 100% oxygen for 15 minutes after the onset of pain, as established in randomized, double-blind trials, which showed improvement in approximately 60% of patients.[40] In some cases, flow increases of up to 15 L/min for 20 minutes using a non-rebreathing mask may be necessary, and various protocols and mask types can be used.[14,41] A systematic review and meta-analysis conducted by the Cochrane Collaboration in 2015 included three trials of normobaric oxygen therapy compared to placebo or ergotamine tartrate involving 145 patients, and a qualitative synthesis included an additional eight trials.[42] They confirmed a significant effect on attack termination and achieved a 75% response rate within 15 minutes.

2) Triptans

Subcutaneous injection of sumatriptan (6 mg) was the most effective treatment for acute cluster attacks. In an initial randomized, placebo-controlled trial of 39 patients, two cluster attacks were randomly treated with subcutaneous sumatriptan 6 mg or placebo.

The primary endpoint of this trial was defined as pain-free or almost complete relief from headache within 10–15 minutes. This was achieved in 74% of sumatriptan-treated patients and 26% of placebo-treated patients, and the success rate in reaching a pain-free state after 10 minutes was 36% for sumatriptan-treated patients and 3% for placebo-treated patients.[43]

Another study comparing subcutaneous sumatriptan 6 mg and 12 mg with placebo found that 35% of patients on placebo, 75% of patients on sumatriptan 6 mg, and 80% of patients on sumatriptan 12 mg had their headaches improved to mild or pain-free after 15 minutes.[44]

In a randomized, double-blind, placebo-controlled trial, sumatriptan nasal spray 20 mg showed positive results compared to placebo.[45] Among the 118 patients treated for cluster attacks, the sumatriptan group had significantly better response and pain-free rates after 30 minutes than the placebo group, and no serious side effects were recorded.

In two randomized, placebo-controlled clinical trials, intranasal zolmitriptan administered at doses of 5 and 10 mg was effective in alleviating pain after 30 minutes. In the first study of 92 patients, a dose of 10 mg provided 62% pain relief, compared to 40% for a dose of 5 mg and 21% for placebo. A second study of 52 patients found pain relief in 30 minutes in 63% of patients receiving 10 mg, 50% of patients receiving 5 mg, and 30% of patients receiving placebo.[46]

2. Transitional treatment

1) Corticosteroids

A 2021 multicenter, double-blind randomized controlled trial (RCT) found that prednisone 100 mg in the first week resulted in a rapid response with 7.1 attacks in the episodic CH group compared to 9.5 attacks in the placebo.[47] A pre-

vious double-blind crossover study found that a single 30 mg dose of prednisone significantly reduced the frequency of attacks in 17 of 19 patients compared to placebo.[48] In a retrospective study of 19 patients with CH, when prednisone was administered at the highest dose of 10–80 mg/day, 73% of the patients experienced more than 50% relief and 58% of the patients experienced 100% relief. However, when prednisone was tapered, typically to 10–20 mg/day, 79% of the patients experienced relapse.[49] Caution is advised when using oral corticosteroids due to possible side effects, including potential complications such as osteoporosis, metabolic disease, and opportunistic infections.

Although the mechanism of action of corticosteroids in CH remains unclear, methylprednisolone has been shown to significantly reduce plasma CGRP levels and increase urinary melatonin metabolite levels in patients with CH. This suggests that corticosteroids may control cluster attacks by reducing CGRP levels; however, more studies are needed to verify this.[49]

It is recommended to administer prednisolone 250–500 mg intravenously in the morning or oral prednisone 60–100 mg as a single dose for 5 days, then reduce the daily dose by 10 mg every 4–5 days. If the CH recurs after reaching the dosage of 10–20 mg, it has to be increased again.[50]

2) Greater occipital nerve injection

Greater occipital nerve (GON) injections for CHs are effective for an average of approximately 4 weeks.[51] A double-blind RCT examined three cortivazol injections over a 1-week period in 28 episodic and 15 chronic participants.

The results showed that 95% of the active group and 55% of the placebo group experienced two or fewer attacks per day 2– 4 days after the third injection.[52] Another double-blind RCT found that 85% of 16 intermittent and seven chronic participants were seizure-free 1 week after receiving a single dose of betamethasone.[51]

Most clinics use 2.5 mL of betamethasone and lidocaine (0.5 mL) 2% for ipsilateral pain injections. Considering the side effect of the steroid, it is generally considered safe to administer once every 3 months, and repeated nerve blocks in medically refractory patients with chronic pain have provided temporary relief in only one-third of attacks. This type of block is generally permitted in pregnant and breastfed women. It is well tolerated, but its side effects include tenderness at the injection site, temporary worsening of headache, presyncope, and alopecia at the injection site. The exact mechanism of this effect is not well known; however, it is believed to occur through a modulatory effect on the nociceptive processing of trigeminal neurons through the trigeminovascular system.[53]

3. Prevention of cluster headache

Preventive measures are necessary for people experiencing episodic CH bouts lasting more than 4–8 weeks. This is particularly applicable to patients with chronic CH. Among the available treatments, verapamil is the most effective, supported by robust scientific evidence, followed by lithium (Table 2).

1) Verapamil

Verapamil is the preferred medication for headaches. In the initial randomized, placebo-controlled trial of 30 patients, patients with episodic CHs given verapamil 120 mg three times daily for 2 weeks or placebo were found to have a significantly reduced frequency of headaches.[54] Two open clinical trials further evaluated the efficacy of verapamil, with 72 patients starting treatment at 200 mg. Complete relief from cluster attacks was observed in 49 of 52 patients with episodic CH and 10 of 18 patients with chronic CH.[55] Typically, patients are prescribed 200 to 480 mg of verapamil, but if the dose exceeds 480 mg, arrhythmias can occur; therefore, an electrocardiogram is required.[56] In clinical practice, most patients start by taking 80 mg 3 to 4 times a day and increase the dose by 80 mg every 3 to 4 days. Once the daily dose reaches 480 mg, an Electrocardiogram should be traced every 160 mg. Under regular electrocardiogram examination and supervision of a cardiologist, the dosage can finally be increased to 1,000 mg.[50]

2) Lithium

Lithium can be used as a secondary preventive agent. A meta-analysis of three published clinical trials involving 103 patients reported that 77% of the patients achieved complete remission or reduced attack frequency by more than 50% with lithium.[57-59]

Lithium has shown an efficacy similar to that of verapamil in comparative studies, but it has several side effects compared to verapamil.[60] Lithium treatment requires monitoring of plasma lithium levels (range, 0.4–0.8 mEq/L)

Table 2. Treatment of cluster headaches[39]

Treatment	Dose	Evidence	Adverse events
Treatment of acute cluster attacks			
Oxygen	12 L/min, 100%	+++	-
Sumatriptan s.c.	6 mg	+++	Feeling of pressure, warmth, heaviness, chest pain, local reaction at the injection site, drowsiness, feeling of weakness, increase or decrease in blood pressure, bradycardia, tachycardia
Sumatriptan nasal spray	20 mg	++	
Zolmitriptan nasal spray	5 mg	++	
Bridging therapy for cluster headaches			
Prednisone	100 mg tapering by 20 mg every 2–3 days	++	Depression, irritability, euphoria, stomach problems, GI ulcer, blood glucose increase, sleep disorders
Greater occipital nerve block		++	Local irritation
Preventive therapy for cluster headaches			
Verapamil	200–960 mg	++	Hypotension, fatigue, constipation, edema, bradycardia, AV block
Lithium		++	Tremor, acne, goiter, hypothyroidism, muscle weakness
Topiramate	100–150 mg	+	Cognitive dysfunction, fatigue, dizziness, paresthesia, mood swings, anxiety, weight loss, hair loss
Gabapentin	1,000–1,800 mg	(+)	Dizziness, somnolence, peripheral edema
Melatonin	10 mg	(+)	Daytime sleepiness, headache dizziness, hypothermia
Galcanezumab	120 mg s.c. once monthly	+	Local reaction, hypersensitivity, constipation

s.c., subcutaneous; GI, gastrointestinal; AV, atrioventricular; +++, a high level of evidence from studies; ++, moderate evidence from studies; +, low evidence; (+), questionable evidence.

along with regular renal and thyroid function tests.

3) Topiramate

In an open study of 36 consecutive patients, including 26 with episodic CH and 10 with chronic CH, doses of 100 to 150 mg daily were shown to reduce cluster seizures by >50%.[61] In a prospective Spanish study of 26 patients, including 12 with episodic CH and 14 with chronic CH, topiramate at a maximum dose of 200 mg alleviated cluster periods in 15 patients and reduced cluster attacks by more than 50% in six patients.[62]

4) Valproate

RCT on the effectiveness of sodium valproate for CH, 96 participants received 1,000–2,000 mg of sodium valproate or placebo daily for 2 weeks; however, there was no statistical difference between sodium valproate and placebo.[63]

5) Gabapentin

In a study of eight patients with episodic CH and four patients with chronic CH who did not respond to existing preventive medications, the administration of 1,000 mg of gabapentin significantly reduced the duration of CH.[64]

6) Melatonin

Research has been conducted on the potential effects of melatonin on the circadian rhythm of CH. A small, randomized trial of 20 patients with CH examined the effects of melatonin 10 mg or placebo administered at bedtime for 14 days in a double-blind, placebo-controlled design. Melatonin significantly reduced the number of cluster attacks, with 50% of the patients responding.[65]

4. New emerging treatment

1) Monoclonal antibodies against calcitonin gene-related peptide

Monoclonal antibodies against CGRP offer the potential for the first targeted therapy in CH. CGRP plasma concentrations increase in patients with spontaneous and induced CH attacks and decrease to baseline levels after sumatriptan and oxygen administration.[66] Among the anti-CGRP monoclonal antibodies that have recently been developed as migraine treatments and have shown good results, galcanezumab has been reported to be effective in preventing episodic CH. In a double-blind RCT, the primary endpoint was the frequency of headaches between 1 and 3 weeks after galcanezumab injection. Compared

to the placebo group, the frequency of CH per week decreased more in the galcanezumab treatment group within weeks 1 to 3, and the response rate (reduction of frequency by more than 50%) in week 3 was 71% in the treatment group, which was significantly higher than 53% in the placebo group.[67] However, a similar study of the anti-CGRP monoclonal antibody fremanezumab in patients with episodic CH has negative results.[41] Additionally, anti-CGRP monoclonal antibodies are known to have failed in clinical trials for chronic CH.[68] On this basis, galcanezumab has been approved for the treatment of episodic CH in the United States and Canada, but not in Europe. Open-label trials of eptimezumab[69] and erenumab[70] for chronic CH are currently being conducted.

2) Neuromodulation and invasive procedures

To date, invasive and non-invasive neurostimulation techniques have been attempted as new preventive treatments for chronic CH. Non-invasive calcitonin gene-related peptide (nVNS) was administered in combination with standard treatment or standard treatment alone for 4 weeks in 92 patients with chronic CH and showed improvement in the frequency of headache attacks, 50% improvement rate, and frequency of analgesic and oxygen treatment. A significant difference was observed in the 50% response rate to attack reduction (40% in the nVNS group vs. 8% in the standard treatment group). No serious side effects have been reported.[71]

A case study of deep brain stimulation (DBS) targeting the hypothalamus, based on hypothalamic activation observed during CH attacks, showed encouraging results in approximately 64% of patients with refractory chronic CH.[72] However, the only double-blind controlled study failed to demonstrate the superiority of DBS.[73]

Occipital nerve stimulation (ONS) is safer than DBS. ONS has been reported to reduce the frequency of headache attacks by approximately 60%, similar to DBS.[72]

3) OnabotulinumtoxinA

Multiple investigations into the effectiveness of onabotulinumtoxinA in managing CHs have revealed notable enhancements in headache frequency within 1 week of treatment, persisting for a duration of up to 6 months.[74] A recent study underscored the high efficacy of onabotulinumtoxinA as an adjunctive therapy in individuals with refractory chronic CH.[75] Additionally, a prospective study examining the treatment of intractable chronic CH through a singular injection of onabotulinumtoxinA into the SPG demonstrated a significant reduction in cluster attack frequency at the 24-week follow-up.[76] In an open-label, single-center study focusing on onabotulinumtoxinA as an adjunctive therapy for the prophylactic treatment of CH, improvements were noted in some patients with chronic CH, albeit without consistent benefits observed in those with episodic CH.[77]

SUMMARY

The efficacy of monoclonal antibodies against CGRP has been demonstrated only in ECH. Therefore, it is necessary to develop new and effective preventive treatments for CH. Several loci have been identified in genome-wide association studies and meta-analyses of CH. CH has a circadian rhythm, and smoking has been suggested as a causal risk factor.

AVAILABILITY OF DATA AND MATERIAL

Not applicable.

AUTHOR CONTRIBUTIONS

Conceptualization: YHK; Data curation: MK, JKY, YHK; Formal analysis: MK, JKY, YHK; Investigation: MK, JKY, YHK; Methodology: YHK; Writing–original draft: MK, JKY; Writing–review and editing: MK, JKY, YHK.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Associations of Migraine and Tension-type Headache with Glaucoma

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Abstract

Purpose: It remains unclear whether primary headaches, particularly migraine, are associated with glaucoma. We investigated potential associations between primary headaches, including migraine and tension-type headache (TTH), and primary glaucoma, including open-angle glaucoma (OAG) and closed-angle glaucoma (CAG).

Methods: We used data from the Clinical Data Warehouse collected between 2008 and 2023 to investigate whether migraine and TTH influence the risk of primary glaucoma. We compared the prevalence of primary glaucoma, including OAG, CAG, other glaucoma, and total glaucoma (TG), among patients with migraine, those with TTH, and controls.

Results: This study analyzed 46,904 patients with migraine, 48,116 patients with TTH, and 455,172 controls. Controls were selected based on propensity score matching (PSM). After adjustment for covariates and PSM, the fully adjusted odds ratios (ORs) for patients with migraine were 1.83 for OAG (95% confidence interval [95% CI], 1.33–2.51; p<0.004) and 1.55 for TG (95% CI, 1.26–1.91; p<0.004) compared to controls. Furthermore, in patients with TTH, the ORs for CAG were 2.20 (95% CI, 1.40–3.47; p<0.004) compared to controls. Additionally, patients with migraine had fully adjusted ORs of 1.71 for OAG (95% CI, 1.24–2.36; p<0.004) and 1.41 for TG (95% CI, 1.15–1.73; p<0.004) compared to those with TTH.

Conclusion: Migraine is associated with primary glaucoma, particularly OAG.

Keywords: Angle-closure glaucoma, Glaucoma, Migraine disorder, Open-angle glaucoma, Tension-type headache

INTRODUCTION

Tension-type headache (TTH) is the most common primary headache disorder, whereas migraine is more debilitating and affects 10-15% of the general population, particularly individuals of working age. Although the pathogenesis of migraine is complex and unclear, several potential mechanisms have been proposed, including vasospasm, hypercoagulability, endothelial, and vascular muscle dysfunction, and vascular changes associated with

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cortical spreading depression.[1-3] Consequently, migraine is considered a systemic vasculopathy.[1,4]

Glaucoma is a multifactorial disorder characterized by progressive optic neuropathy and visual field loss, which makes it the most common cause of irreversible blindness worldwide.[5,6] Primary glaucoma can be categorized as open-angle glaucoma (OAG) or closed-angle glaucoma (CAG), the most common types of glaucoma in Asians.[7,8] The pathogenesis of glaucoma involves vascular risk factors. Previous studies have evaluated associations between glaucoma and systemic vascular diseases (e.g., hypertension and diabetes) and ocular vascular factors (e.g., ocular blood flow and perfusion pressure).[9-11]

A previous study demonstrated a slightly increased risk of CAG in individuals with hyperlipidemia, liver diseases, peptic ulcers, and headaches. Furthermore, in a previous study, headache, but not migraine, was associated with a higher risk for CAG.[12] Recent epidemiological studies have demonstrated an association between migraine and OAG, revealing that individuals with migraine are more likely to develop OAG than those without migraine, even after adjusting for risk factors.[13,14] Conversely, another study of Chinese individuals revealed that migraine did not increase the risk of OAG.[15] Therefore, it remains unclear whether primary headaches, particularly migraine, are concomitant conditions or risk factors for glaucoma.

Here we investigated the relationships between primary glaucoma, including OAG and CAG, and migraine and TTH, the main types of primary headache.

MATERIALS AND METHODS

1. Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Clinical Research Ethics Committee of Chuncheon Sacred Heart Hospital, Hallym University (No. 2024-01-001). Because this study used only deidentified data, the review board waived the requirement for obtaining informed consent form all subjects.

2. Study participants

We analyzed clinical data from the Smart Clinical Data Warehouse (CDW), Hallym University Medical Center, collected between January 2008 and November 2023. The Smart CDW, based on the Qlik-View Elite Solution (Qlik), is used at all five Hallym University Medical Center hospitals. It enables the extraction and integrated analysis of fixed data from electronic medical records. Patients with migraine were eligible for inclusion in this study if they were aged 20-80 years, were diagnosed by a board-certified neurologist, were assigned the International Classification of Diseases tenth revision (ICD-10) code G43 in medical records, and had more than two outpatient visits or at least one admission to a neurology department. Patients with TTH were included if they were aged 20-80 years and assigned the ICD-10 code G44 in the database. The control group included patients aged 20-80 years who had undergone general health checkups at a health promotion center. Patients with a history of headache or migraine identified using a basic questionnaire administered before the health checkup were excluded.

3. Migraine, tension-type headache, glaucoma, and covariates

We compared the frequency of primary total glaucoma (TG), excluding secondary causes, among patients with migraine, TTH, and controls. Glaucoma was diagnosed based on the ICD codes in the CDW database. We excluded secondary cases using ICD codes (H40.3-6). In addition, primary glaucoma was classified as OAG (H40.1), CAG (H40.2), and other glaucoma (OG; H40.8-9). In addition, the presence of comorbidities was determined using relevant ICD-10 codes in the database, including angina (I20, I24, and I251), atrial fibrillation (I480–482 and I489), anxiety disorder (F41), cerebrovascular diseases (G45-46 and I60-69), chronic hepatitis (B18, I85, and K70-74), chronic pulmonary disease (J44), depression (F31-34, F412, and F432), diabetes mellitus (E10-14), dyslipidemia (E78), heart disease (I05-09, I21-23, I30-47, and I49-52), hypertension (I10-15), menopause (M800, M010, N924, and N95), renal failure (N03 and N18-17), and sleep disorders (F51, G258, and G47). We excluded patients with renal failure receiving concurrent dialysis prescriptions to exclude dialysis headaches.

4. Statistical analysis

Continuous data are presented as means with standard deviations, whereas categorical data are presented as frequencies with percentages. The T-test and chi-square test were used to compare continuous and categorical data among migraine, TTH, and control groups. Given the inability to randomize patients based on migraine or TTH status, we used propensity score matching (PSM) to adjust for covariates and selection bias using Python (version 3.7; Anaconda Inc.; https://www.anaconda.com) and Pymatch (version 0.3.4; https://github.com/benmiroglio/pymatch). Propensity scores ranged from 0.07 to 0.87; all matched cases had scores within 0.0001 of each other at a matching ratio of 1:1. This process resulted in 14,177 matched pairs of migraine patients and controls, 20,325 matched pairs of TTH patients and controls, and 12,808 matched pairs of migraine and TTH patients. Logistic regression was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for outcomes in the OAG, CAG, OG, and TG groups compared to their respective controls. After PSM, adjusted ORs were computed for each disorder among the three groups using covariates and propensity scores. The Bonferroni correction was applied to correct for multiple testing and p-values<0.004 were considered significant. This value was derived by dividing the p-value threshold of 0.05 by the number of tests performed, i.e., 12 (four outcome variables tested in three groups). All p-values were

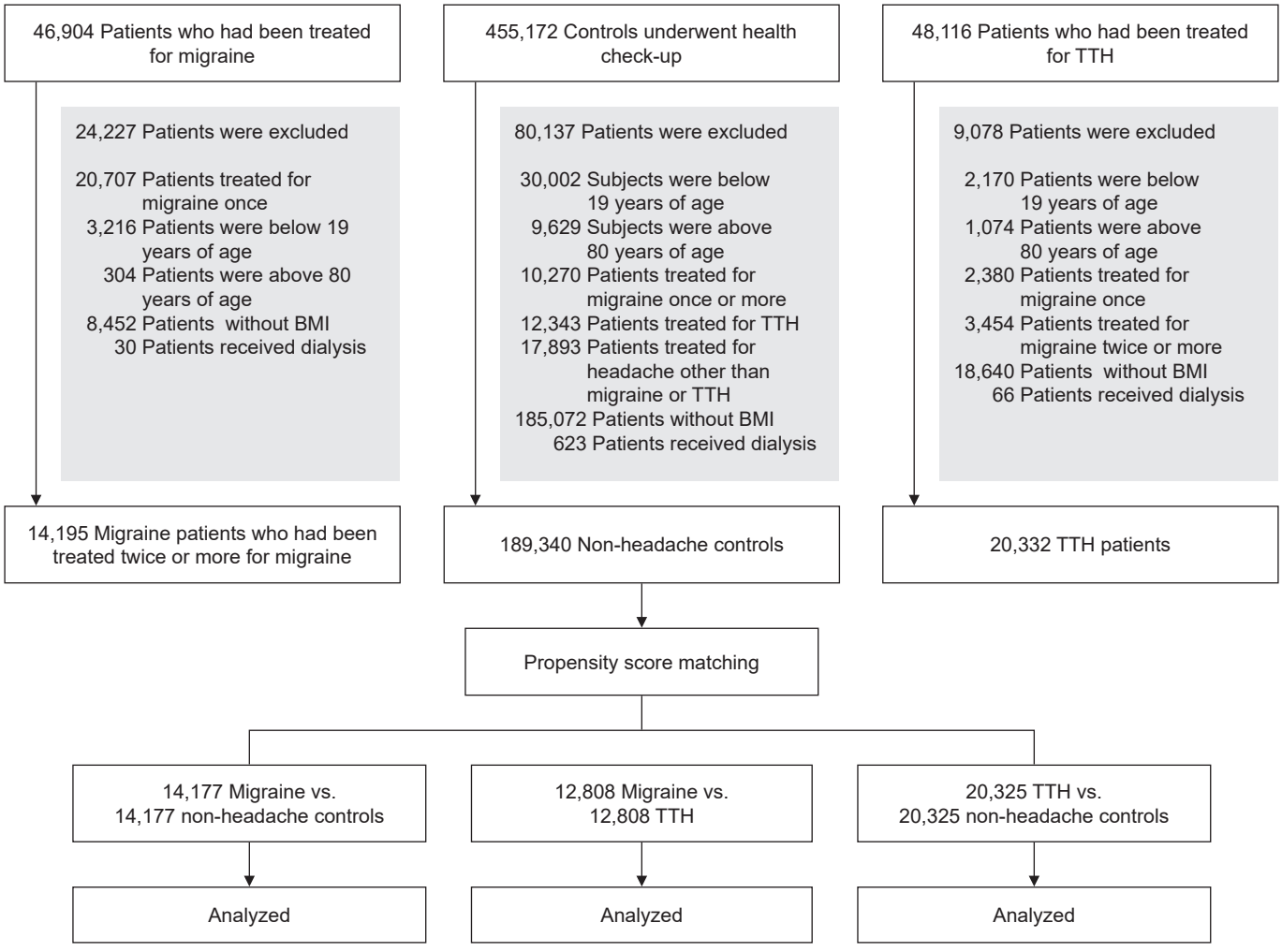

Figure 1. Flow chart of the enrollment process.
TTH, tension-type headache; BMI, body mass index.

two-sided. SPSS software (version 24.0; IBM Corp.) was used for statistical analyses.

RESULTS

1. Participant characteristics

In total, 46,904 patients with migraine, 48,116 patients with TTH, and 455,172 controls were enrolled using the ICD-10 codes. After the application of exclusion criteria, 14,195 migraine patients, 20,332 TTH patients, and 189,340 controls were included in the final analysis. Of the enrolled patients with migraine, 10,523 were females (74.1%) and the mean age was 45.6±14.4 years. In the TTH and control groups, 12,344 (60.7%) and 91,309 participants (48.2%) were females; the mean ages were 52.8±13.7 and 49.8±14.7 years, respectively. Figure 1 presents the enrollment process. After PSM, absolute standardized differences between the migraine and control groups were <0.1 (Table 1). Furthermore, no significant differences were observed between the TTH and control groups (Table 2). After PSM, no significant differences were observed between the migraine and TTH groups (Table 3).

2. Primary glaucoma in patients with migraine and controls

Prior to PSM, unadjusted ORs in individuals with migraine compared to controls were 1.74 (95% CI, 1.27-2.39; p<0.004) for OAG, 2.30 (95% CI, 1.10-4.84) for CAG, 1.03 (95% CI, 0.80-1.33) for OG, and 1.46 (95% CI, 1.19-1.79; p<0.004) for TG. After PSM, the adjusted ORs were 1.83 (95% CI, 1.33-2.51; p<0.004) for OAG, 2.55 (95% CI, 1.21-5.39) for CAG, 1.10 (95% CI, 0.85-1.43) for OG, and 1.55 (95% CI, 1.26-1.91; p<0.004) for TG in migraine patients (Table 4). Among all types of primary glaucoma, only OAG

Table 1. Characteristics of the migraine and control groups before and after propensity score matching

	Before matching			After matching		
	Migraine (n=14,195)	Control (n=189,340)	ASD	Migraine (n=14,177)	Control (n=14,177)	ASD
Female sex	10,523 (74.1)	91,309 (48.2)	0.59	10,505 (74.1)	10,619 (74.9)	0.02
Age (yr)	45.6±14.4	49.8±14.7	0.30	45.6±14.4	46.1±14.8	0.03
BMI (kg/m^2)	23.8±4.0	24.2±3.7	0.09	23.8±4.0	23.8±4.0	0.00
DM	1,045 (7.4)	19,468 (10.3)	0.11	1,043 (7.4)	985 (6.9)	0.02
HTN	2,378 (16.8)	28,802 (15.2)	0.04	2,370 (16.7)	2,378 (16.8)	0.00
Dyslipidemia	1,956 (13.8)	25,512 (13.5)	0.01	1,950 (13.8)	2,010 (14.2)	0.01
Angina	1,226 (8.6)	1,2951 (6.8)	0.06	1,218 (8.6)	1,277 (9.0)	0.01
AF	170 (1.2)	4,092 (2.2)	0.09	170 (1.2)	173 (1.2)	0.00
Heart disease	951 (6.7)	12,517 (6.6)	0.00	949 (6.7)	946 (6.7)	0.00
CVD	2,647 (18.6)	17,666 (9.3)	0.24	2,631 (18.6)	2,632 (18.6)	0.00
Chronic pulmonary disease	1,538 (10.8)	17,294 (9.1)	0.05	1,529 (10.8)	1,494 (10.5)	0.01
Renal failure	270 (1.9)	5,007 (2.6)	0.05	269 (1.9)	284 (2.0)	0.01
Chronic hepatitis	538 (3.8)	13,205 (7.0)	0.17	538 (3.8)	493 (3.5)	0.02
Anxiety	782 (5.5)	3,543 (1.9)	0.16	771 (5.4)	765 (5.4)	0.00
Depression	2,003 (14.1)	7,756 (4.1)	0.29	1,985 (14.0)	2,024 (14.3)	0.01
Sleep disorder	1,413 (10.0)	5,996 (3.2)	0.23	1,397 (9.9)	1,385 (9.8)	0.00
Menopause	834 (5.9)	7,517 (4.0)	0.08	831 (5.9)	863 (6.1)	0.01
OAG	106 (0.7)	912 (0.5)		106 (0.7)	61 (0.4)	
CAG	23 (0.2)	183 (0.1)		23 (0.2)	10 (0.1)	
OG	122 (0.9)	1,446 (0.8)		122 (0.9)	118 (0.8)	
TG	229 (1.6)	2,182 (1.2)		229 (1.6)	158 (1.1)	

Values are presented as number (%) or mean±standard deviation.
ASD, absolute standardized difference; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; AF, atrial fibrillation; CVD, cerebrovascular disease; OAG, open-angle glaucoma; CAG, closed-angle glaucoma; OG, other glaucoma; TG, total glaucoma.

Table 2. Characteristics of the TTH and control groups before and after propensity score matching

	Before matching			After matching		
	TTH (n=20,332)	Control (n=189,340)	ASD	TTH (n=20,325)	Control (n=20,325)	ASD
Female sex	12,344 (60.7)	91,309 (48.2)	0.26	12,337 (60.7)	12,416 (61.1)	0.01
Age (yr)	52.8±13.7	49.8±14.7	0.22	52.8±13.7	53.3±14.3	0.04
BMI (kg/m^2)	24.3±3.5	24.2±3.7	0.05	24.3±3.5	24.4±3.7	0.01
DM	2,420 (11.9)	19,468 (10.3)	0.05	2,419 (11.9)	2,361 (11.6)	0.01
HTN	4,996 (24.6)	28,802 (15.2)	0.22	4,990 (24.6)	5,074 (25.0)	0.01
Dyslipidemia	3,800 (18.7)	25,512 (13.5)	0.13	3,794 (18.7)	3,624 (17.8)	0.02
Angina	2,647 (13.0)	12,951 (6.8)	0.18	2,640 (13.0)	2,592 (12.8)	0.01
AF	578 (2.8)	4,092 (2.2)	0.04	578 (2.8)	575 (2.8)	0.00
Heart disease	2,017 (9.9)	12,517 (6.6)	0.11	2,015 (9.9)	1,934 (9.5)	0.01
CVD	4,322 (21.3)	17,666 (9.3)	0.29	4,315 (21.2)	4,438 (21.8)	0.01
Chronic pulmonary disease	3,100 (15.2)	17,294 (9.1)	0.17	3,095 (15.2)	3,172 (15.6)	0.01
Renal failure	644 (3.2)	5,007 (2.6)	0.03	644 (3.2)	605 (3.0)	0.01
Chronic hepatitis	1,220 (6.0)	13,205 (7.0)	0.04	1,217 (6.0)	1,200 (5.9)	0.00
Anxiety	1,326 (6.5)	3,543 (1.9)	0.19	1,319 (6.5)	1,199 (5.9)	0.02
Depression	2,374 (11.7)	7,756 (4.1)	0.24	2,368 (11.7)	2,227 (11.0)	0.02
Sleep disorder	1,574 (7.7)	5,996 (3.2)	0.17	1,567 (7.7)	1,450 (7.1)	0.02
Menopause	1,555 (7.6)	7,517 (4.0)	0.14	1,548 (7.6)	1,610 (7.9)	0.01
OAG	144 (0.7)	912 (0.5)		144 (0.7)	99 (0.5)	
CAG	58 (0.3)	183 (0.1)		58 (0.3)	28 (0.1)	
OG	215 (1.1)	1,446 (0.8)		215 (1.1)	211 (1.0)	
TG	353 (1.7)	2,182 (1.2)		353 (1.7)	294 (1.4)	

Values are presented as number (%) or mean±standard deviation.
TTH, tension-type headache; ASD, absolute standardized difference; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; AF, atrial fibrillation; CVD, cerebrovascular disease; OAG, open-angle glaucoma; CAG, closed-angle glaucoma; OG, other glaucoma; TG, total glaucoma.

was associated with migraine.

3. Primary glaucoma in patients with tension-type headache and controls

Table 5 presents the ORs for the development of primary glaucoma in TTH patients and controls. The unadjusted ORs for OAG, CAG, OG, and TG were 1.46, 2.07, 1.02, and 1.20 in TTH patients compared to controls, respectively. After adjusting for all covariates and PSM, the fully adjusted ORs in patients with TTH compared to controls were 1.53 (95% CI, 1.18-1.98) for OAG, 2.20 (95% CI, 1.40-3.47; p<0.004) for CAG, 1.08 (95% CI, 0.89-1.30) for OG, and 1.27 (95% CI, 1.08-1.48) for TG (Table 5). Among all types of primary glaucoma, only CAG was associated with TTH patients.

4. Differences in primary glaucoma between patients with migraine and tension-type headache

A comparison of patients with migraine and TTH demonstrated fully adjusted ORs of 1.71 (95% CI, 1.24-2.36; p<0.004) for OAG, 1.12 (95% CI, 0.62-2.03) for CAG, 1.19 (95% CI, 0.91-1.56) for OG, and 1.41 (95% CI, 1.15-1.73; p<0.004) for TG. Among all types of primary glaucoma, only OAG was associated with migraine (Table 6).

DISCUSSION

We investigated the risk of primary glaucoma, including each major type, among patients with migraine and TTH based on CDW data collected between 2008 and 2023. After adjusting for covariates and employing PSM, patients with migraine were at a significantly higher risk of OAG, whereas patients with TTH were at a higher risk of CAG,

Table 3. Characteristics of the migraine and TTH groups before and after propensity score matching

	Before matching			After matching		
	Migraine (n=14,195)	TTH (n=20,332)	ASD	Migraine (n=12,808)	TTH (n=12,808)	ASD
Female sex	10,523 (74.1)	12,344 (60.7)	0.31	9,192 (71.8)	8,974 (70.1)	0.04
Age (yr)	45.6±14.4	52.8±13.7	0.50	47.1±14.1	48.3±13.2	0.08
BMI (kg/m^2)	23.8±4.0	24.3±3.5	0.14	24.0±3.9	24.0±3.5	0.02
DM	1,045 (7.4)	2,420 (11.9)	0.17	1,018 (7.9)	1,100 (8.6)	0.02
HTN	2,378 (16.8)	4,996 (24.6)	0.21	2,316 (18.1)	2,416 (18.9)	0.02
Dyslipidemia	1,956 (13.8)	3,800 (18.7)	0.14	1,904 (14.9)	1,955 (15.3)	0.01
Angina	1,226 (8.6)	2,647 (13.0)	0.16	1,191 (9.3)	1,243 (9.7)	0.01
AF	170 (1.2)	578 (2.8)	0.15	170 (1.3)	189 (1.5)	0.01
Heart disease	951 (6.7)	2,017 (9.9)	0.13	915 (7.1)	929 (7.3)	0.00
CVD	2,647 (18.6)	4,322 (21.3)	0.07	2,477 (19.3)	2,528 (19.7)	0.01
Chronic pulmonary disease	1,538 (10.8)	3,100 (15.2)	0.14	1,449 (11.3)	1,475 (11.5)	0.01
Renal failure	270 (1.9)	644 (3.2)	0.09	265 (2.1)	300 (2.3)	0.02
Chronic hepatitis	538 (3.8)	1,220 (6.0)	0.12	529 (4.1)	540 (4.2)	0.00
Anxiety	782 (5.5)	1,326 (6.5)	0.04	732 (5.7)	760 (5.9)	0.01
Depression	2,003 (14.1)	2,374 (11.7)	0.07	1,759 (13.7)	1,705 (13.3)	0.01
Sleep disorder	1,413 (10.0)	1,574 (7.7)	0.07	1,197 (9.3)	1,185 (9.3)	0.00
Menopause	834 (5.9)	1,555 (7.6)	0.08	824 (6.4)	878 (6.9)	0.02
OAG	106 (0.7)	144 (0.7)		101 (0.8)	61 (0.5)	
CAG	23 (0.2)	58 (0.3)		23 (0.2)	21 (0.2)	
OG	122 (0.9)	215 (1.1)		118 (0.9)	103 (0.8)	
TG	229 (1.6)	353 (1.7)		220 (1.7)	163 (1.3)	

Values are presented as number (%) or mean±standard deviation.
TTH, tension-type headache; ASD, absolute standardized difference; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; AF, atrial fibrillation; CVD, cerebrovascular disease ; OAG, open-angle glaucoma; CAG, closed-angle glaucoma; OG, other glaucoma; TG, total glaucoma.

Table 4. ORs for primary glaucoma between migraine patients and controls

	OR (95% CI)			
	OAG	CAG	OG	TG
UA	1.74* (1.27–2.39)	2.30 (1.10–4.84)	1.03 (0.80–1.33)	1.46* (1.19–1.79)
AVA	1.83* (1.33–2.51)	2.55 (1.21–5.39)	1.10 (0.85–1.43)	1.55* (1.26–1.91)
AVPA	1.83* (1.33–2.51)	2.55 (1.21–5.39)	1.10 (0.85–1.43)	1.55* (1.26–1.91)

*Asterisk indicates a statistically significant (p<0.004).
OR, odds ratio; CI, confidence interval; UA, unadjusted; AVA, all variables adjusted; AVPA, all variables plus propensity score adjusted; OAG, open–angle glaucoma; CAG, closed–angle glaucoma; OG, other glaucoma; TG, total glaucoma.

Table 5. ORs for primary glaucoma between TTH patients and controls

	OR (95% CI)			
	OAG	CAG	OG	TG
UA	1.46 (1.13–1.88)	2.07* (1.32–3.26)	1.02 (0.84–1.23)	1.20 (1.03–1.41)
AVA	1.53 (1.18–1.98)	2.20* (1.40–3.46)	1.07 (0.89–1.30)	1.27* (1.08–1.48)
AVPA	1.53 (1.18–1.98)	2.20* (1.40–3.47)	1.08 (0.89–1.30)	1.27* (1.08–1.48)

*Asterisk indicates a statistically significant (p<0.004).
OR, odds ratio; TTH, tension-type headache; CI, confidence interval; UA, unadjusted; AVA, all variables adjusted; AVPA, all variables plus propensity score adjusted; OAG, open-angle glaucoma; CAG, closed-angle glaucoma; OG, other glaucoma; TG, total glaucoma.

Table 6. ORs for primary glaucoma between migraine and TTH patients

	OR (95% CI)			
	OAG	CAG	OG	TG
UA	1.66* (1.21–2.28)	1.10 (0.61–1.98)	1.15 (0.88–1.50)	1.36* (1.11–1.66)
AVA	1.72 (1.25–2.37)	1.12 (0.62–2.02)	1.19 (0.91–1.55)	1.40* (1.14–1.73)
AVPA	1.71* (1.24–2.36)	1.12 (0.62–2.03)	1.19 (0.91–1.56)	1.41* (1.15–1.73)

*Asterisk indicates a statistically significant (p<0.004).
OR, odds ratio; TTH, tension-type headache; CI, confidence interval; UA, unadjusted; AVA, all variables adjusted; AVPA, all variables plus propensity score adjusted; OAG, open-angle glaucoma; CAG, closed-angle glaucoma; OG, other glaucoma; TG, total glaucoma.

compared to controls without headache. Moreover, migraine was associated with a higher risk of primary glaucoma, particularly OAG, compared to TTH. Therefore, migraine may be considered a potential contributing factor for OAG.

It remains unclear whether migraine significantly increases the risk of OAG. Previous studies have demonstrated that individuals with migraine have a higher risk of developing OAG compared to those without migraine.[14] In one study, the association between OAG and migraine was significant only for individuals aged 70-79 years and those aged <50 years with no comorbidities.[16,17] Conversely, other studies have revealed that migraine does not increase the risk of OAG[15,18,19] or CAG.[15] Furthermore, in another study, no significant association was found between migraine and OAG after adjusting for confounding variables.[19]

Our retrospective study demonstrated a significantly higher prevalence of glaucoma in migraine patients than controls and TTH patients. Although the comparison with the headache-free control group aligns with previous studies, the comparison between the TTH and migraine groups was considered meaningful due to the divergence from previous studies. A meta-analysis suggested that migraine may significantly increase the risk of developing OAG.[20] However, some cohort studies have failed to confirm this association. As a result, it remains unclear whether migraine increases the risk of OAG.

Glaucoma is characterized by progressive degeneration of retinal ganglion cells and optic nerve axons. Based on pathophysiological and anatomical features, glaucoma is categorized into OAG and CAG. The pathogenesis of glaucoma involves factors such as oxidative stress, excitotoxicity, altered immunity, and impaired microcirculation.[21] Although the exact pathophysiology of migraine is unclear, it is associated with neurovascular dysfunction resulting from vascular changes, impaired hypoperfusion, and microembolism.[22] Several epidemiological studies have demonstrated the role of vascular risk factors in the pathogenesis and progression of glaucomatous optic neuropathy.[11,16,23-27] A pooled analysis of the associations between systemic vascular risk factors and OAG revealed that hypertension is the most significant risk factor for OAG. However, the relationships between OAG, type 2 diabetes mellitus, and migraine require further evaluation.[11]

In the present study, patients with TTH had a higher risk of CAG compared to controls. Furthermore, migraine was associated with primary glaucoma, particular OAG, compared to TTH. A population-based retrospective cohort study based on the Taiwan Health Insurance Database revealed that headaches were associated with a 1.13-fold higher risk of CAG; however, there was no significant association between migraine and CAG.[12] Patients with CAG can experience headache due to increased intraocular pressure, which may lead to a diagnosis of CAG. CAG should be considered among individuals older than 40 years with late-onset headaches.[28,29] TTH is the most common type of primary headache and has non-characteristic features, which may explain the high prevalence of CAG in patients with TTH. Further studies are needed to explore the associations between primary headaches other than migraine and glaucoma.

Our study had several limitations. First, the retrospective collection of clinical data from individuals presenting to a university medical center with five affiliated hospitals may limit the generalizability of our results. Therefore, we cannot establish a causal relationship, and the possibility of an inverse correlation cannot be ruled out. Second, we did not account for potential sources of selection bias and confounding variables. Third, our retrospective design did not allow for the collection of clinical data on headache

characteristics (e.g., frequency) or medication history (e.g., triptan use). In addition, the diagnoses of glaucoma, and other comorbid diseases were determined based on the ICD codes recorded in the CDW database. Thus, detailed clinical information regarding glaucoma was not collected. Future prospective, population-based studies are needed to investigate the association between primary headaches and glaucoma.

In conclusion, our analysis of CDW database data revealed a significant association between migraine and OAG, whereas TTH was significantly associated with CAG, compared to controls without headache. Moreover, a significant association was observed between migraine and primary glaucoma, particularly OAG, compared to TTH. Future prospective studies are needed to fully investigate the associations of glaucoma with migraine and TTH.

AVAILABILITY OF DATA AND MATERIAL

The data presented in this study are available upon reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

Conceptualization: SHL, JHS; Data curation: JHK, YSK; Formal analysis: JHK; Investigation: JHK, JHS; Methodology: JHK, JHS; Software: JHK, JHS; Validation: JHK, JHS; Writing–original draft: JHK, JHS; Writing–review and editing: all authors.

All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

Jong-Hee Sohn is the Editor of *Headache and Pain Research* and was not involved in the review process of this article. All authors have no other conflicts of interest to declare.

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Headache and Pain Research

Cluster Headache Characteristics and the Severity of Obstructive Sleep Apnea: Insights from Polysomnography Analysis

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Abstract

Purpose: Cluster headache (CH) is characterized by circadian rhythmicity of the attacks, and it is known to respond exceptionally well to oxygen therapy. Furthermore, obstructive sleep apnea (OSA) frequently co-occurs with CH, and both conditions may be parallel outcomes of hypothalamic dysfunction rather than being causally related. The aim of this study was to analyze the association between CH characteristics and polysomnographic factors stratified by the severity of OSA in patients diagnosed with CH and OSA.

Methods: We retrospectively analyzed the data of OSA patients with CH who were enrolled in the Korean Cluster Headache Registry and underwent polysomnography due to clinical suspicion of OSA. Basic demographic data, headache-related parameters, and polysomnographic parameters were analyzed according to the severity of OSA (apnea-hypopnea index: <15 or ≥15 per hour).

Results: Twelve CH patients with OSA were evaluated. The onset age of CH was higher (38.5 years vs. 19.0 years, p=0.010), and the maximal duration of cluster bouts was longer (156.5 days vs. 47.0 days, p=0.037) in the moderate-to-severe OSA group than in the mild OSA group. Unlike other polysomnographic parameters, the apnea-hypopnea index and respiratory arousal index during rapid eye movement (REM) sleep were comparable across different OSA severity levels.

Conclusion: The onset age and duration of cluster bouts were associated with the severity of OSA in CH patients. Additionally, the relatively high susceptibility to hypoxia during REM sleep in patients with mild OSA implies that interventions may be potentially advantageous, even in CH patients with mild OSA.

Keywords: Age of onset, Cluster headache, Obstructive sleep apnea, Polysomnography, REM sleep

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INTRODUCTION

Cluster headache (CH) is a rare and severely disabling trigeminal autonomic cephalalgia with strong chronobiological traits.[1] CH, characterized by bouts and remission periods, can be classified as episodic or chronic. Distinguishing from other headache disorders, oxygen therapy has proven effective for rescuing CH attack.[2]

CH is considered one of the primary headache disorders most closely associated with sleep.[3] In general, headaches and sleep are intertwined in various aspects, including clinical, physiological, epidemiological, and anatomical aspects.[4] Evidence supports that CH attacks are more prevalent and severe during the night compared to daytime attacks in patients with periodicity (occurring at specific times during day or seasons).[5-7] Initial studies suggested that CH attacks are associated with rapid eye movement (REM) sleep, coinciding with the onset of the first REM sleep phase within 90 minutes of falling sleep. However, recent several studies have shown that CH attacks are not significantly associated with REM sleep.[8-10]

Obstructive sleep apnea (OSA) is one of the most common sleep disorder that causes recurrent hypoxia and frequent arousal due to repeated airway collapse.[11] CH has been linked with sleep disordered breathing, particularly OSA. The higher prevalence of OSA (from 58%–80%) among CH patients compared to healthy controls, coupled with the increased frequency of CH attacks at night, led to the hypothesis of a potential causal relationship between these two conditions.[12-14] Studies conducted on CH patients showed an increased prevalence of OSA syndrome and a higher respiratory distress index during CH attack compared to healthy controls.[15] However, the true relationship between CH and OSA is complex and has not been clarified yet. Currently, OSA and CH may be considered as parallel outcomes of hypothalamic dysfunction rather than a causal relationship.[16]

In this complex relationship between CH and sleep, our study analyzed the association of CH characteristics and polysomnographic factors stratified by OSA severity in patients with CH and diagnosed with OSA. The aim was to explore the correlation between CH and sleep, specifically focusing on their association with OSA.

MATERIALS AND METHODS

1. Ethics approval and consent to participate

All participants provided written informed consent when they enrolled in the KCHR (No. 2016-09-396). The study design was approved by the Institutional Review Board of Dongtan Sacred Heart Hospital of Hallym University and allowed of additional written informed consent to be waived due to retrospective data collection and fully anonymity (No. 2022-12-003-001). All methods were performed in accordance with the relevant guidelines and regulations.

2. Participants

This retrospective, observational single-center study included participants with CH who underwent polysomnography (PSG) on clinical suspicion of OSA at the headache clinic in the Department of Neurology of the Hallym University Dongtan Sacred Hospital (Hwaseong, Korea) between January 2020 and October 2022. CH was diagnosed by two neurologists (SJ Cho and HJ Im) based on individual interviews and the diagnostic criteria of the 3rd edition of the International Classification of Headache Disorder.[1] PSG was conducted as a level 1 sleep study (i.e., an overnight stay in a sleep laboratory with a technician in attendance)[17] at the Sleep Center of Hallym University Dongtan Sacred Hospital.

The inclusion criteria for participants were as follows: 1) participation in the Korean Cluster Headache Registry (KCHR), a prospective observational study of CH,[18] 2) being over 19 years of age, 3) and having undergone PSG between January 2020 and October 2022 on suspicion of OSA. The exclusion criteria were as follows: 1) PSG conducted more than 2 years after the last cluster bout, 2) failure to be diagnosed with OSA by PSG. In the 3rd edition of the International Classification of Headache Disorders,[1] CH is classified as episodic (i.e., bouts lasting from 7 days to 1 year, separated by out-of-bout periods lasting at least 3 months) or chronic (i.e., bouts lasting 1 year or longer without remission, or with out-of-bout periods lasting less than 3 months) CH, and our study investigated both episodic and chronic CH. All participants were interviewed and evaluated by trained personnel using a self-reported ques-

tionnaire.

3. Assessment of cluster headache

All participants in the KCHR completed a structured questionnaire designed for the evaluation of CH. The KCHR protocol evaluated sociodemographic variables, including sex, ages at onset and presentation, body mass index (BMI), and history of smoking and alcohol consumption. We collected the following clinical data regarding current and previous cluster bout including headache characteristics, disease duration, headache frequency (headache attacks per day), headache intensity, headache duration, diurnal rhythmicity, total number of bouts that was independent of disease duration, and presence of premorbid migraine. The following evaluations were also conducted: the Headache Impact Test-6 used for measuring the impact of a headache,[19] and the visual analog scale (VAS) used for measuring the pain intensity of a headache.[20] The VAS score is determined by measuring the distance (mm) on the 10-cm line between the "no pain" anchor and the patient's mark. A higher score indicates greater pain intensity.

4. Assessment of sleep factors and polysomnography data

All participants underwent laboratory nocturnal PSG (Embla®; Natus), which entails electroencephalogram, electrooculogram, electromyogram, electrocardiogram, respiratory flow and effort, oximetry, pulse, and body position recordings. PSG data were reviewed and scored by sleep experts using the Embla RemLogic PSG Software using 30-second epochs according to the standard criteria by the American Academy of Sleep Medicine. Standard sleep indexes including total sleep time, sleep efficiency, wake after sleep onset, sleep latency, percentage of each sleep stage over total sleep time, apnea-hypopnea index (AHI, total number of apneas plus hypopneas per hour of sleep), mean oxygen saturation, lowest oxygen saturation, total arousals, and an arousal index were calculated. OSA has been defined and quantified primarily by the frequency of apneas and hypopneas during sleep. According to the International Classification of Sleep Disorders 3rd edition criteria, the severity of OSA by AHI is divided into mild (≥5 to 15 per hour), moderate (≥15 to 30 per hour), and severe (≥30 per hour).[21] In this study, the participants were divided into two groups according to the score of AHI: a mild OSA group (AHI≥5 to 15 per hour) and a moderate to severe OSA group (AHI≥15 per hour). Sleep parameters were evaluated using a self-reported questionnaire booklet. Excessive daytime sleepiness was defined as an Epworth Sleepiness Scale score≥11.[22] The likelihood of OSA was assessed by the STOP-Bang questionnaire. A score over 3 reflected a moderate risk of apnea during sleep.[23] And, insomnia symptoms were assessed using the Insomnia Severity Index, with a score>14 indicating moderate-to-severe insomnia.[24] Sleep quality was evaluated using the Pittsburgh Sleep Quality Index with a score>5 indicating poor sleep quality.[25]

5. Statistical analysis

Categorical data were presented as frequencies and percentages. Continuous data, such as age, daily headache frequency, and headache intensity were presented as the median with data range (minimum to maximum). Nonparametric tests were used to establish statistical significance at $p<0.05$ when the normality assumption was not met. In our study, due to the small sample size and non-normal distribution of the data, group comparisons according to OSA severity were performed using nonparametric methods. Specifically, the Mann-Whitney test was used for continuous variables, and Fisher's exact test was used for categorical variables. Data analysis was performed using SPSS version 24 (IBM Corp.).

RESULTS

1. Participants

Among 105 participants in the KCHR for 34 months, 14 participants who were clinically suspicious of OSA with CH underwent PSG. However, two participants were excluded due to being undiagnosed with OSA (AHI<5 per hour) and no cluster bout for 2 years after PSG. Ultimately, a total of 12 participants were included in our analysis (Figure 1). All participants were male, and the median age was 42 years (range, 24–62 years). The median BMI was 26.1 kg/m^2 (range, 21.0–32.9 kg/m^2). There were 10 participants (83.3%) with episodic CH and two participants (16.7%) with chronic

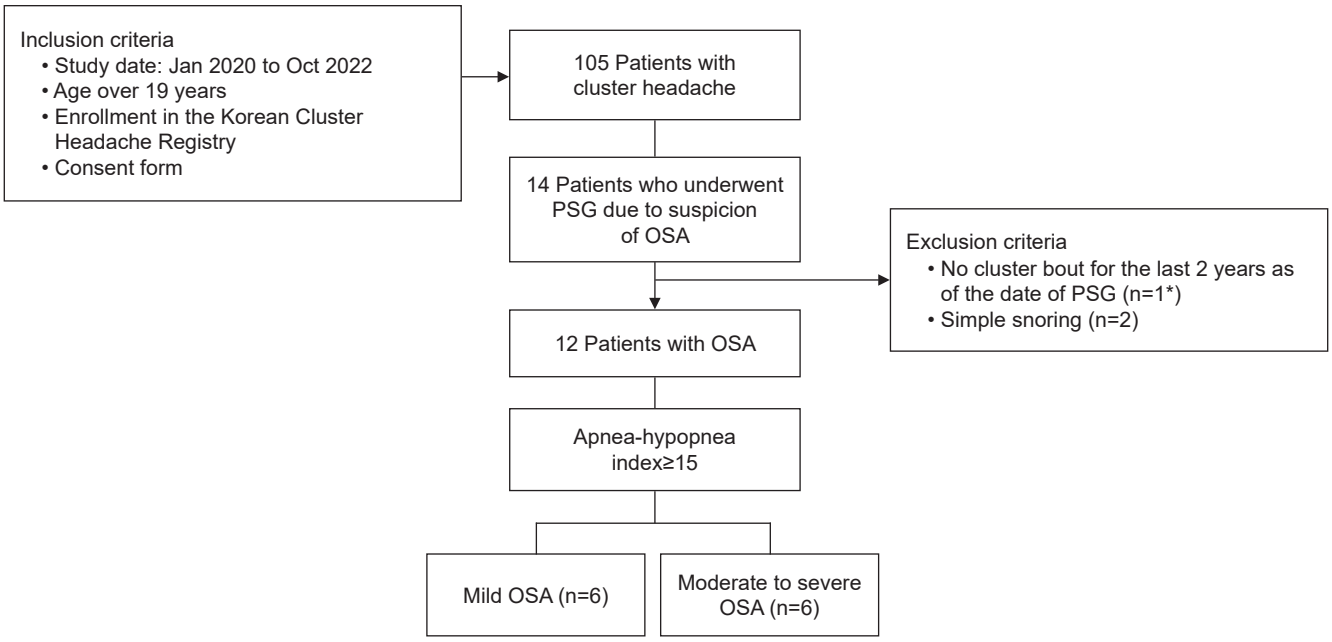

Figure 1. Flowchart of patient selection and evaluation.
*One patient met both exclusion criteria.
PSG, polysomnography; OSA, obstructive sleep apnea.

CH. Nine participants (75.0%) had undergone PSG during the cluster bout, and three participants had undergone PSG during the remission period. Six participants were classified for mild OSA, and the remaining participants were for moderate to severe OSA (AHI≥15 per hour). Two patients with chronic CH were classified as having moderate to severe OSA.

2. Clinical characteristics of cluster headache according to obstructive sleep apnea severity

The median disease duration of CH in all participants was 6 years (range, 1–16 years), and the median onset age of CH was 29 years (range, 15–55 years). The age at onset of CH in the moderate to severe OSA group was higher than in the mild OSA group (median, 38.5 years vs. 19.0 years; p=0.010). The maximal duration of cluster bout in the moderate to severe group (median, 156.5 days) was longer than that in the mild OSA group (median, 47.0 days; p=0.037). Other clinical features of cluster attacks including intensity, duration, and frequency did not show significant differences and were comparable between CH patients with moderate to severe OSA and those with mild OSA (Table 1). A total of 10 participants (83.3%) reported diurnal periodicity. There were no statistically significant differences in age, sex, BMI, and cardiovascular risk factors including hypertension, diabetes, hyperlipidemia, and smoking between the two groups.

3. Sleep parameters and polysomnography data features according to obstructive sleep apnea severity in cluster headache patients

In this study, most participants (n=9, 75.0%) had undergone a PSG during the cluster bout (ictal phase of CH) and no cluster attack was observed during PSG. As for the difference of OSA severity between two groups, the median value of mean oxygen saturation was 96.2% (range, 95.3%–97.4%) in the mild OSA group and 94.6% (range, 93.2%–96.2%) in the moderate to severe OSA group. There was a significant difference in AHI scores between the two groups during non-rapid eye movement (NREM) sleep, as well (4.3 vs. 19.0, p=0.004). However, there was no significant difference in AHI during REM sleep according to OSA severity (23.5 vs. 24.6, p=0.688). As a result, the REM-AHI/NREM-AHI ratio was higher in the mild group than in

Table 1. Clinical characteristics of cluster headache patients (n=12) according to OSA severity

Characteristic	Mild OSA (n=6)	Moderate to severe OSA (n=6)	p-value
Age (yr)	40.5 (24.0–42.0)	43.5 (34.0–62.0)	0.076
Male sex	6 (100.0)	6 (100.0)	>0.99
BMI (kg/m^2)	26.6 (23.8–31.4)	26.0 (21.0–32.9)	0.631
Hypertension	1 (16.7)	3 (50.0)	0.545
Diabetes	1 (16.7)	0 (0.0)	>0.99
Hyperlipidemia	4 (66.7)	4 (66.7)	>0.99
Current smoking	3 (50.0)	5 (83.3)	0.105
Age at diagnosis of CH (yr)	28.0 (23.0–40.0)	41.5 (27.0–55.0)	0.044*
Age at onset of CH (yr)	19.0 (15.0–31.0)	38.5 (25.0–55.0)	0.010*
HIT-6 score	68.5 (63.0–78.0)	70.0 (48.0–78.0)	0.872
Maximal duration of cluster bouts (day)	47.0 (33.0–128.0)	156.5 (67.0–1,247.0)	0.037*
VAS score (headache severity)	9.0 (7.0–10.0)	9.0 (5.0–10.0)	0.672
Duration of CH attacks (min)	110.0 (30.0–180.0)	35.0 (20.0–120.0)	0.319
Frequency of CH attacks (day)	1.0 (0.5–2.5)	1.8 (1.0–2.0)	0.360
Location of CH attacks (right/left)	4 (66.7)/2 (33.3)	1 (16.7)/5 (83.3)	0.242
Presence of circadian rhythm in CH attacks	5 (83.3)	5 (83.3)	>0.99
CH attacks only at night	1 (16.7)	3 (50.0)	0.545
Presence of morning headache	1 (16.7)	1 (16.7)	>0.99
Improvement in response to oxygen therapy	1 (16.7)	4 (66.7)	0.143
Improvement in response to triptan therapy	5 (83.3)	4 (66.7)	0.211
PSG during cluster bouts	4 (66.7)	5 (83.3)	>0.99

Values are presented as median (range) or number (%).
These p-values are based on the Mann-Whitney or Fisher exact test; *Asterisk indicates a statistically significant (p<0.05).
OSA, obstructive sleep apnea; BMI, body mass index; CH, cluster headache; HIT-6, Headache Impact Test-6; VAS, visual analog scale; PSG, polysomnography.

the moderate to severe group with borderline significance (5.8 vs. 0.9, p=0.054). Lowest saturation and longest apnea showed no significant differences between the two groups. As shown in Table 2, there was a significant difference in respiratory arousal index according to OSA severity during NREM sleep (13.4 vs. 20.9, p=0.037). During REM sleep stage, however, respiratory arousal index between two groups were comparable (14.3 vs. 14.4, p=0.872). And these results were also demonstrated in an analysis for patients who undergone PSG during the cluster bout (Figure 2). As shown in Table 2, there was no significant difference between the two groups in moderate to severe insomnia and poor sleep quality. Among the 12 patients included in the final analysis, only three patients were diagnosed with moderate to severe insomnia.

DISCUSSION

This is the first study that evaluated the characteristics of CH and polysomnographic parameters according to OSA severity in daily clinical practice using a prospective CH registry. We used single hospital data of patients with CH from the past 34 months. In the dataset 13.3% of the CH patients had undergone PSG, and 85.7% had been diagnosed with OSA. In previous study, OSA were reported to be diagnosed with PSG in 29% among the patients with CH compared to 7% among age–sex-matched healthy controls.[15] Compared to the prevalence (6%–17%) of OSA in the general population, the CH population has a relatively higher prevalence in OSA, so active screen for OSA is recommended in CH patients.[13,26]

Moderate to severe OSA accounted for half of the diagnosed OSA in participants with CH in our study, which is slightly lower than the 60% reported in previous studies of CH.[27] Interestingly, the median onset age of CH was significantly higher in CH patients with moderate to severe OSA group than in those with mild OSA group (38.5 years vs. 19.0 years), while in the multicenter data in Korea, the

Table 2. Polysomnographic data and sleep parameters of cluster headache patients (n=12) according to OSA severity

Variable	Mild OSA (n=6)	Moderate to severe OSA (n=6)	p-value
Excessive sleep sleepiness	5.0 (2.0–11.0)	5.0 (2.0–15.0)	0.421
Insomnia Severity Index	10.5 (4.0–23.0)	8.5 (5.0–17.0)	0.345
Moderate to severe insomnia	2 (33.3)	1 (16.7)	0.500
Pittsburgh Sleep Quality Index	8.0 (8.0–16.0)	9.5 (8.0–14.0)	0.809
Total sleep time (min)	375.7 (350.6–420.7)	367.1 (317.5–383.3)	0.423
REM sleep (min)†	28.8 (7.8)	30.5 (9.3)	0.423
NREM sleep (min)†	351.3 (92.3)	328.0 (90.8)	0.423
Sleep efficiency (%)	94.4 (81.9–98.9)	95.8 (81.9–98.2)	0.936
WASO (min)	12.1 (4.0–83.0)	12.5 (6.5–70.0)	0.873
Total AHI (events/hr)	5.7 (5.0–9.4)	22.3 (16.1–53.3)	0.004*
AHI in REM (events/hr)	23.5 (0.0–30.7)	24.6 (5.3–58.5)	0.688
AHI in NREM (events/hr)	4.3 (3.4–9.4)	19.0 (14.6–56.1)	0.004*
REM/NREM-AHI ratio	5.8 (0.0–6.8)	0.9 (0.2–4.0)	0.054
Mean SpO_2 (%)	96.2 (95.3–97.4)	94.6 (93.2–96.2)	0.036*
Minimum SpO_2 (%)	90.5 (70.0–92.0)	86.5 (69.0–89.0)	0.091
Total ArI	14.1 (6.4–33.4)	21.3 (18.8–51.4)	0.037*
Resp ArI	4.6 (1.6–8.9)	14.6 (8.0–50.1)	0.004*
Total ArI in REM	16.6 (0.0–26.2)	20.0 (0.0–66.0)	0.688
Resp ArI in REM	14.3 (0.0–21.4)	14.4 (0.0–45.9)	0.872
Total ArI in NREM	13.4 (5.7–33.4)	20.9 (17.9–53.2)	0.037*
Resp ArI in NREM	3.4 (0.8–8.9)	13.4 (8.6–51.7)	0.006*

Values are presented as median (range) or number (%) unless otherwise specified.
These p-values are based on the Mann-Whitney or Fisher exact test; *Asterisk indicates a statistically significant (p<0.05). †These data represent the median (%).
OSA, obstructive sleep apnea; REM, rapid eye movement; NREM, non-rapid eye movement; WASO, wakefulness after sleep onset; AHI, apnea-hypopnea index; SpO_2, oxygen saturation; ArI, arousal index; Resp, respiratory.

mean onset age of CH was 29.3 years[28] and the peak onset age was around 30 years.[29] Because the severity of OSA depends on increasing age,[26] this association can be consequential a coincidence, but detrimental effect of moderate to severe OSA might have a role for occurrence of CH.[30,31]

In addition, the maximal duration of cluster bout during the follow-up period was significantly longer in CH patients with moderate to severe OSA than in those with mild OSA. Two patients with chronic CH were classified as having moderate to severe OSA. These results support the previously reported association between moderate to severe OSA and refractory or chronic CH, which was not present in mild OSA.[32,33] Therefore, the findings that the older onset age and the longer duration of cluster bout, the higher severity of OSA, which means that there is relationship and comorbidity, at least, between CH and OSA.

In this study, there were no differences in AHI and respiratory arousal index during the REM sleep stage according to OSA severity (Table 2, Figure 2). This indicates an increased susceptibility to hypoxia during REM sleep, especially among those with mild OSA, resulting in REM-related OSA marked by respiratory difficulties during this phase of sleep. Particularly, REM sleep in OSA patients is associated with more frequent and prolonged obstructive events, often accompanied by severe oxyhemoglobin desaturation.[34] This increased vulnerability during REM sleep is attributed to reduced pharyngeal muscle activity due to withdrawal of excitatory inputs to upper airway motor neurons.[34] Consequently, the upper airway is more prone to collapse during REM sleep in OSA patients compared to NREM sleep. Even in cases of mild OSA, REM sleep can contribute to a cycle of heightened respiratory distress and frequent arousals in patients with CH. Therefore, interventions such as positive airway pressure (PAP) therapy may be beneficial for CH patients experiencing OSA symptoms, such as excessive daytime sleepiness, snoring, or stopped breathing during sleep. Case reports[35,36] have demonstrated symptom improvement in CH patients following PAP

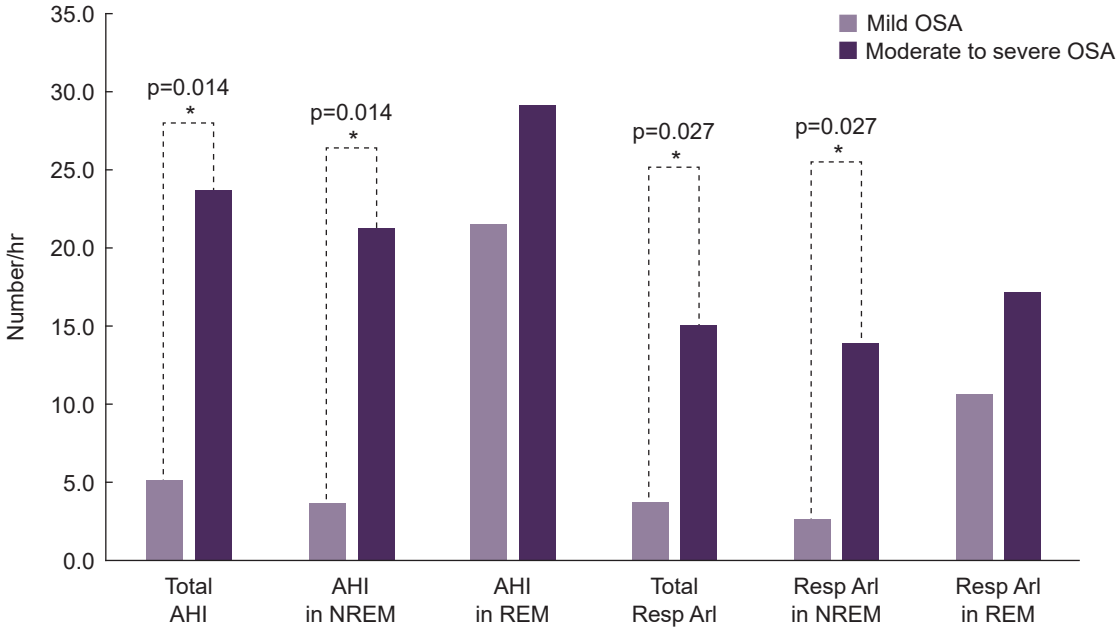

Figure 2. Comparison of polysomnographic respiratory parameters according to OSA severity in patients during cluster bouts.
*Asterisk indicates a statistically significant ($p<0.05$).
AHI, apnea-hypopnea index; NREM, non-rapid eye movement; REM, rapid eye movement; Resp, respiratory; Arl, arousal index; OSA, obstructive sleep apnea.

therapy, suggesting its potential benefits in managing CH when OSA coexists. This underscores the importance of considering sleep-related factors in CH management.

Our study has certain limitations. First, the details about CH were collected via self-reports from the participants, which could have resulted in an over or underestimation of the true clinical characteristics of the CH attacks. Second, the sample size of this single-center study was small, so selection bias and type I or type II errors might have been committed. It is difficult to obtain large sample sized as CH patients presents with disabling pain when they visit the hospital, making it difficult to evaluate a sleep disorder and conduct laboratory PSG, especially during the cluster bout. Third, the low prevalence (11.4%) of OSA in our CH registry could have been influenced by the low performance of PSG.

It was difficult to perform sleep study for the patient, especially those during cluster bout with severe pain. However, it may have also reflected the real-world proportion of OSA evaluation by PSG among consecutive CH patients. Future studies on the appropriate indications for PSG and intervention of OSA in patients with CH are warranted. Therefore, a multicenter prospective randomized study regarding impacts on CH in patients currently using PAP as treatment of OSA is needed.

In conclusion, onset age of CH and maximal duration of cluster bout were both associated with severity of OSA in CH patients. And the relatively high susceptibility of sleep apnea during REM sleep in patients with mild OSA suggests the potential benefits of intervention even in mild severity of OSA, for CH patients. Although the relationship of OSA and CH is not causal, considering PSG examinations for comorbid OSA and can be beneficial for further management, especially in patients with CH who are elderly, experience prolonged cluster bouts, or exhibit unresponsiveness to drug treatment.

AVAILABILITY OF DATA AND MATERIAL

Anonymized data supporting the findings presented in the current study will be shared upon reasonable request from a qualified investigator.

AUTHOR CONTRIBUTIONS

Conceptualization: SJC, HJI; Data curation: YH, MKK, SJC, HJI; Formal analysis: YH, SJC, HJI; Investigation: YH, MKK, SJC, HJI; Methodology: MKC, SJC, HJI; Software: YH, SJC; Validation: MKC, SJC, HJI; Writing–original draft: YH, MKK, HJI; Writing–review and editing: YH, MKK, MKC, SJC, HJI.

CONFLICT OF INTEREST

Soo-Jin Cho is the Editor-in-Chief of *Headache and Pain Research* and was not involved in the review process of this article.
Soo-Kyoung Kim is the Editor of *Headache and Pain Research*and was not involved in the review process of this article.
Mi-Kyoung Kang is the Editor of *Headache and Pain Research* and was not involved in the review process of this article.
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- Reference citations should not be used in the abstract. Abbreviations should be minimized and, if used, must be defined within the abstract by the full term followed by its abbreviation in parentheses.
- The abstract should be concise, less than 250 words, and describe the subject of research concisely, in a paragraph. The abstract for an original article must be structured to include a Purpose, Methods, Results, and Conclusion as follows:

  Purpose: In one or two sentences, the specific purpose of the article and why it is worthy of attention should be indicated. The purpose stated here should be identical to the one given in the title of the paper and the introduction.

  Methods: The methods used to achieve the purpose explained in the first paragraph should be described succinctly, stating what was done and how bias was controlled, what

data were collected, and how the data were analyzed.

Results: The findings of the methods described in the preceding paragraph are to be presented here, with specific data. All results should flow logically from the methods described.

Conclusion: In one or two sentences, the conclusion of the study should be stated. This should relate directly to the purpose of the paper, as defined in the first paragraph of the abstract.

- Unlike that for an Original Article, the abstract for review/case report consist of a single paragraph without separate sections. The most recently published articles should be consulted for style.
- Three to five keywords (index terms) should appear after the abstract. For the selection of keywords, refer to the list of Medical Subject Headings (MeSH, https://www.ncbi.nlm.nih.gov/mesh).

2.3. Main Body

2.3.1. Original Article

Original articles are papers containing results of basic and clinical investigations, which are sufficiently well documented to be acceptable to critical readers. The maximum length of a manuscript is 5,000 words (exclusive of the title page and abstract), 50 references (if the references exceed 50, authors can consult with the Editorial Office). A total of 8 figures or tables are allowed; additional tables and figures may be provided using the online data supplement system.

Introduction

- The introduction provides the research background and specific purpose or objectives, generally enough to inform the readers of the topic, and relevant findings of others are described. The hypothesis tested can be stated. The references should be as few and pertinent as possible.

Materials and Methods

- The first paragraph should address whether the study was conducted under an approval by the Institutional Review Board (with or without patient informed consent) and Institutional Animal Care and Use Committee of the institution where the study took place for any investigation involving humans and animals, respectively.
- The materials (or subjects), inclusion and exclusion criteria, research plan, and the methods used should all be described.
- Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance.
- How the disease was confirmed and how subjectivity in observations was controlled should be explained in detail, if relevant.
- When experimental methodology is the main issue of the paper, the experimental process should be described in detail so as to make it possible for the reader to recreate the experiment as closely as possible.
- The methods of statistical analysis and criteria for statistical significance should be described.
- If the study includes reuse/overlap of materials previously published or under consideration for publication elsewhere, the reuse/overlap of study materials should be clearly stated.

Results

- The results of the paper should be described logically according to the Methods section.
- Tables and figures are recommended when they can present data more succinctly and clearly. Do not duplicate the content of tables or figures in the Results section.
- Briefly describe the core results related to the conclusion in the text when data are provided in tables or in figures.
- In the Results section, audio or video files are also welcomed. Supplementary results can be placed in the Appendix.

Discussion

- In the first part of the discussion, the main findings should be briefly summarized, then possible explanations for these findings should be explored, and these results should be compared and contrasted with the findings of other relevant studies.
- The results of previous relevant studies should not be mentioned repeatedly, but any concordance or discordance should be noted.
- The core findings and the conclusions derived from them

should be emphasized according to the best available evidence.
- In the last part of the discussion, the limitations of the study, future research suggestions or plans, and the conclusion should all be described. If there was a research hypothesis in the introduction section, whether it was supported should be stated.

Conflict of Interest
- State any potential conflict of interest that could influence the authors' interpretation of the data, such as financial support from or connections to pharmaceutical companies, political pressure from interest groups, or academically related issues.

Acknowledgments and Author Contribution
- All persons who have made substantial contributions but have not met the criteria for author- ship are acknowledged here. All sources of funding applicable to the study should be explicitly stated here.
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- Conference paper
  Mark MH, Dickson DW, Schwarz KO, et al. Familial diffuse Lewy body disease. Presented at the 10th International Symposium on Parkinson's Disease; October 19, 1991.

- Forthcoming
  Tian D, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. Proc Natl Acad Sci USA. Forthcomming 2002.

- Book
  Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology, 4th ed. Mosby; 2002.
  Gilstrap LC 3rd, Cunningham FG, VanDorsten JP, editors. Operative obstetrics, 2nd ed. McGraw-Hill; 2002.
  Meltzer PS, Kallioniemi A, Trent JM. Chromosome Alterations in Human Solid Tumors. In: Vogelstein B, Kinzler KW, editors. The Genetic Basis of Human Cancer. McGraw-Hill; 2002. p. 93-113.

- Online book or Website
  Foley KM, Gelband H, editors. Improving palliative care for cancer [Internet]. National Academy Press; 2001 [cited

2002 Jul 9]. Available from: https://www.nap.edu/catalog/10149/improving-palliative-care-for-cancer

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- The tables should start on a separate page. The tables should be numbered using Arabic numerals in the order in which they are cited in the text.
- The title of the table should be not sentences, but phrases or clauses, without periods.
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Figures

- Multiple figures mentioned in the text should be described as follows, e.g., Figures 1, 3.
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- All names and all other identifiers of the patient, authors, and authors' institutions should be removed from the figures.
- Color figures should be in RGB color mode and line drawings should be black on a white background.
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- Video clips can be submitted for placement on the journal website. All videos are subject to peer review and can be uploaded as supplementary materials.
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Supplementary Data

- Supplementary data: If there are complementary materials that help the understanding of readers or if there is a large amount of data, these may be used as supplementary data. Supplementary data should be as concise as possible and must be related to the main conclusion of the paper. Supplementary data can include electronic files of high resolution images, background datasets, video materials, animations, and more. Supplementary data will be published online alongside the electronic version of the article. Video data files can be submitted in the same way as a figure or table by referring to the video or animation content. Since video and animation cannot be embedded in the print version, authors have to provide text for both the electronic and the print version for the portions of the article that refer to this content.

2.3.2. Review Article

- A review is generally published as a commissioned paper at the request of the editor(s).
- Review articles contain an Abstract, Introduction, Main text, and Summary (or Conclusion) followed by references, tables, and figure legends.
- A review article is a comprehensive scholarly review on a specific topic. It is not an exhibit of a series of cases.
- Neither new information nor personal opinions are to be included.
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the data necessary to convey that message. The approximate length should be less than 5,000 words. There should be an unstructured abstract equal to or less than 250 words. References should not exceed 200 references.
- The most recent Review articles published in *Headache and Pain Research* should be consulted for further details on formatting.

2.3.3. Case Reports

- Case reports will be published only in exceptional circumstances, if they illustrate a rare occurrence of clinical importance. These manuscripts should be organized in the following sequence: title page, abstract and keywords, introduction, case report(s), discussion, acknowledgments, references, tables, figure legends, and figures. Case reports are limited to 2,000 words (excluding the abstract, references, tables, and legends), and references should not exceed 30. A maximum of 5 figures or tables are allowed.

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- Constructive criticism of a specific thesis published by *Headache and Pain Research* is welcome.
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- Editorials are invited by the editor and should be commentaries on articles in the current issue. Editorial topics could include active areas of research, fresh insights, and debates in all fields considered to be of interest to *Headache and Pain Research* readers. Editorials should not exceed 1,000 words, excluding references, tables, and figures. References should not exceed 5. A maximum of 3 figures including tables is allowed.

2.3.6. Perspective

- A perspective is a report of the authors' viewpoint on a specific subject of interest to our readers as a commissioned paper at the request of the editor(s).
- Little or no new original information is included, and there is limited literature analysis. A perspective is a report of the authors' viewpoint on a specific subject of interest to our readers as a commissioned paper at the request of the editor(s).

Table 1. Specification for publication types

Type of article	Abstract (word)	Text (word)[a)]	Reference	Table & figure
Original article	Structured, 250	5,000	50	8
Review article	250	5,000	200	Not limited
Case report	250	2,000	30	5
Letter to the editor	Not required	1,000	5	2
Editorial	Not required	1,000	5	3
Perspective	Not required	1,500	5	3

[a)]Excluding the title page, abstract, references, tables, and legends.

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- The submitted manuscript will first be evaluated at the editorial office regarding the completeness of the submitted materials and their suitability to *Headache and Pain Research*. Modifications/corrections may be requested from the authors at this stage before starting the peer review.
- Submitted manuscripts will generally be reviewed by the editors, as well as two peer reviewers who are experts in the submitted subject matter and the peer reviewers will make suggestions to the editor(s).
- Authors may suggest preferred and non-preferred reviewers during manuscript submission. However, the ultimate selection of the reviewers will be determined by the editor(s).
- The authors can monitor the progress of the manuscript throughout the review process at the submission site (https://submit.e-hpr.org).
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Accept: The manuscript is accepted for publication.

Minor Revisions: A revision needs to be submitted within the due date. Otherwise, the manuscript will be treated as a new submission.

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Reject, Resubmission allowed: The authors are allowed to resubmit their work. However, it is effective only when they are able to respond to the various reviewer comments and make substantial changes to the study. The resubmitted manuscript will be treated as a new submission.

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	성인	15세 이상의 청소년
효능·효과	전조증상을 수반하거나 수반하지 않는 편두통의 급성치료.	조증상을 수반하거나 수반하지 않고, 치료없이 4시간 이상 지속되는 편두통의 통증 급성치료. * 단, 편두통 관련 증상(눈부심, 소리공포증, 구역)에 대한 이 약의 유효성은 확립되지 않았음
용법·용량	편두통 발현시 1정 복용. 24시간내 재발시 1정을 재투여할 수 있으며, 재투약은 초회 투여와 최소 2시간 이상의 간격을 둠. 1일 총 투여량으로 25밀리그램(2정)을 초과해서는 안됨.	편두통 발현시 1정 복용
	- 식사와 관계없이 복용 가능. - 편두통 예방의 목적으로는 복용하지 않음. - 만약 일차 투여 후 치료반응이 없다면, 같은 증상 발현 시 재투여해서는 안됨. - 30일 동안 평균 4회 이상의 편두통 치료에 대한 안전성은 확립되지 않았음.	

알모그란®정 제품요약정보 전문의약품

[원료약품 및 분량] 1정 중 •유효성분 : 알모트립탄말산염(별규) - 17.5mg (알모트립탄으로서 12.5mg) •첨가제 : 만니톨, 미결정셀룰로오스, 포비돈, 전분글리콜산나트륨, 푸마르산스테아릴나트륨, 오파드라이화이트(Y-1-7000), 카르나우바납 **[효능·효과]** 성인: 전조증상을 수반하거나 수반하지 않는 편두통의 급성치료. 15세 이상의 청소년: 전조증상을 수반하거나 수반하지 않고, 치료없이 4시간 이상 지속되는 편두통의 통증 급성치료. 단, 편두통 관련 증상(눈부심, 소리공포증, 구역)에 대한 이 약의 유효성은 확립되지 않았다. **[용법·용량]** 성인: 편두통 발현시 이 약 1정을 복용한다. 24시간 내 재발시 1정을 재투여할 수 있다. 재투약은 초회 투여와 최소 2시간 이상의 간격을 둔다. 1일 총 투여량으로 25밀리그램(2정)을 초과해서는 안된다. 15세 이상의 청소년: 편두통 발현시 이 약 1정을 복용한다. **[사용상의 주의사항]** 금기 1) 이 약이 함유한 성분에 대한 과민증의 병력이 있는 환자 2) 허혈성 심질환(협심증, 심근경색의 병력, 또는 무증상 허혈성 심질환(silent ischemia)으로 진단된 경우) 환자 또는 허혈성 심질환 또는 변형협심증(Prinzmetal's variant Angina)을 포함한 관상동맥경축 또는 기타 심혈관질환의 증상 및 징후를 나타내는 환자 3) 뇌혈관사고(CVA) 또는 일과성 허혈발작(TIA)의 병력이 있는 환자 4) 중등도 내지 중증의 고혈압 환자, 치료받지 않은 고혈압 환자 또는 조절되지 않은 고혈압 환자('1. 경고' 항 참조). 5) 말초혈관 질환자 6) 다른 5HT1 수용체 효능약, 에르고타민함유제제 또는 디히드로에르고타민 또는 메티세르지드 등의 맥각유도체를 투여받고 있는 환자(이 약을 24시간 이내에 병용하지 않는다.) 7) 중증 간장애 환자 8) 편측마비성, 안근 마비성 또는 기저성 편두통 환자 **[저장방법]** 기밀용기, 실온(1~30°C)보관 **[사용기한]** 제조일로부터 60개월 **[포장단위]** 4정 **[개정년월일]** 2017년 8월 9일 ※ 제품에 대한 자세한 내용은 최신의 제품설명서를 참고하시기 바라며, 식약처 의약품통합정보시스템 홈페이지(https://nedrug.mfds.go.kr/)에서 확인하실 수 있습니다.

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AML-A1.0-111-201905

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프레탈이 걸어온 길,

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Safety

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The 1st & Original Cilostazol PLETAAL

PLETAAL® SR cap. (cilostazol)

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[효능·효과] 1. 만성동맥폐색증(버거씨병, 폐색성 동맥경화증, 당뇨병성 말초혈관병증 등)에 따른 궤양, 통통 및 냉감 등 허혈성 제증상의 개선 2. 뇌경색(심인성뇌색전증 제외) 발증 후 재발억제

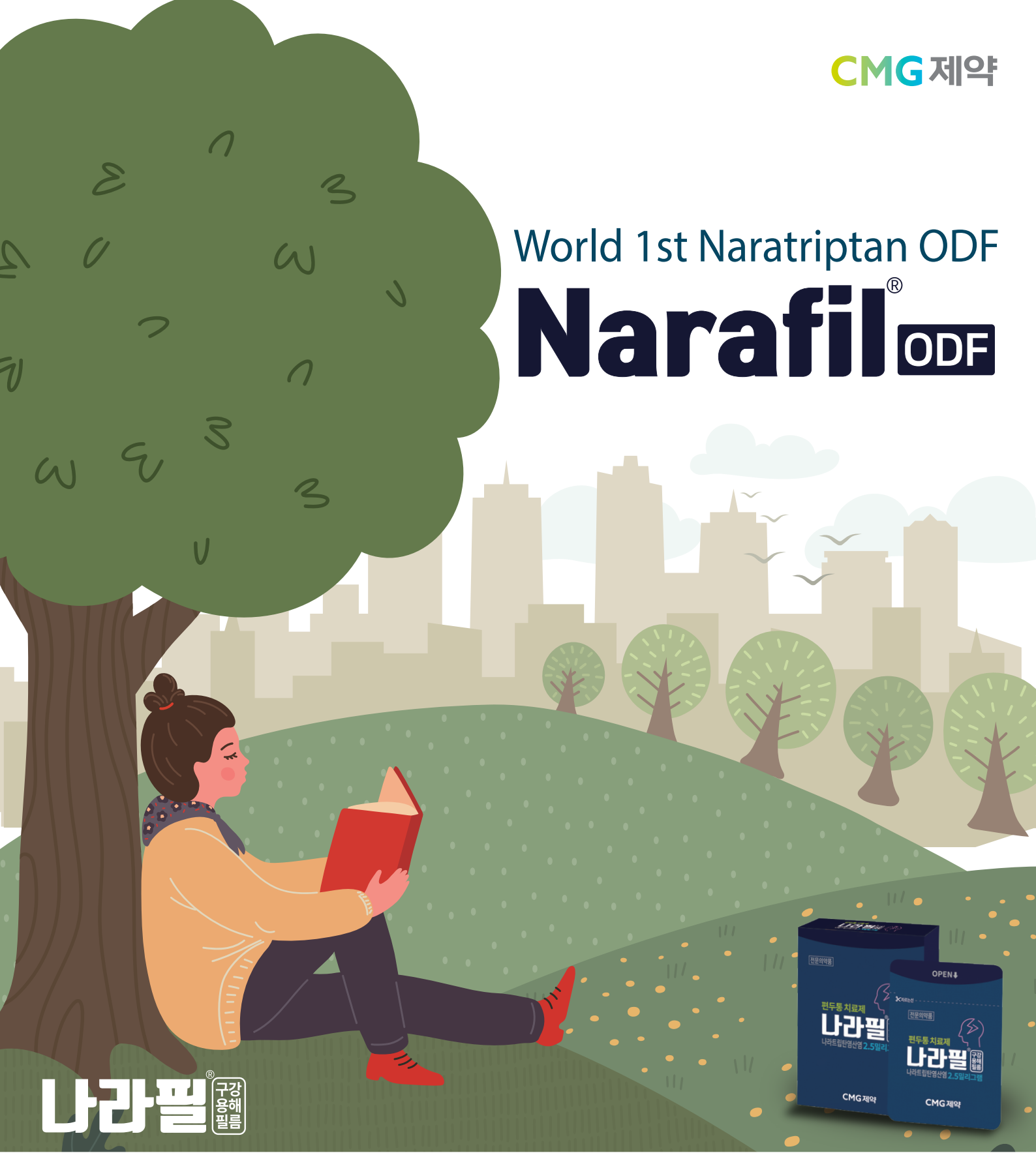
[용법·용량] **프레탈®정**은 성인 1회 100mg을 1일 2회 경구 투여합니다. 단, 연령, 증상에 따라 적절히 증감합니다. **프레탈®서방캡슐**은 성인 1회 200mg을 1일 1회 경구 투여합니다. 이 약은 식사를 피하여 공복 상태에서 복용합니다.

PLT-23-001 | 20230116 approved

CMG 제약

World 1st Naratriptan ODF

Narafil® ODF



[제품정보] 나라필구강용해필름 2.5mg **[유효성분]** 나라트립탄 **[효능·효과]** 전조증이 수반되거나 수반되지 않는 편두통의 조속한 완화 **[용법·용량]** 이 약을 평소에 예방 목적으로 사용해서는 안되며, 다른 편두통 치료약물과 병용하지 않고 단독요법으로 투여하는 것이 바람직하다. 이 약은 구강붕해정으로 혀 위에 놓고 타액으로 녹여 삼키며, 씹거나 부수어서는 안된다. 1. 성인 나라트립탄으로서 권장 투여량은 2.5 mg, 1회 투여이다. 24시간동안 총투여량이 5.0 mg을 초과하지 않아야 한다. 이 약 2.5 mg 1회 투여 후 편두통이 재발하면, 최소 4시간의 간격을 두고 2.5 mg을 재투여한다. 이 약 투여 후 반응하지 않는 환자에게는 치료상의 이익이 없다면 동일발작에 대하여 재투여해서는 안되나 연이은 발작에는 투여할 수 있다. 2. 청소년을 대상으로 한 위약대조 시험에서 나라트립탄 0.25 mg, 1.0 mg과 2.5 mg 1회 투여가 위약보다 유효함이 입증되지 않았다. 그러므로 18세 미만의 환자에게 나라트립탄 투여는 권장되지 않는다. 12세 미만의 소아에 나라트립탄을 사용한 임상자료는 충분하지 않으므로 나라트립탄 투여는 권장되지 않는다. 3. 66세 이상의 고령자에 대한 나라트립탄의 안전성·유효성은 확립되지 않았으므로, 투여가 권장되지 않는다. 약물동력학 자료에 의하면 연령에 따라 소실율이 감소했다. 4. 신장애 환자에 투여시 주의해야 한다. 24시간 동안 최대 투여량이 2.5 mg을 초과하지 않는다. 중증의 신장애 환자(크레아티닌청소율<10 mL/분)에는 투여하지 않는다. 5. 간장애 환자에 투여시 주의해야 한다. 24시간동안 최대 투여량이 2.5 mg을 초과하지 않는다. 중증의 간장애 환자(Child Pugh grade C)에는 투여하지 않는다. **[사용상의 주의사항]** 1.경고 이 약에 함유되어 있는 인공감미제 아스파탐은 체내에서 분해되어 페닐알라닌으로 대사되므로, 페닐알라닌의 섭취를 규제할 필요가 있는 유전성질환인 페닐케톤뇨증 환자에는 투여하지 말 것. - 1일 허용량 제한 : 아스파탐 함량을 WHO권장량(40mg/kg/1일)이하로 조정(가능한 한 최소량 사용)할 것. 60 kg 성인 : 1일 최대복용량 2.4 g 2. 다음 환자에는 투여하지 말 것. 1) 이 약에 과민반응의 병력이 있는 환자 2) 허혈심장병 환자 3) 심근경색증 병력이 있는 환자 4) 프린츠메탈협심증/관상혈관경련 환자 5) 말초혈관병 또는 허혈심장병과 일치하는 증상/증후를 보이는 환자 6) 뇌혈관사고(CVA) 또는 일과성허혈발작(TIA)의 병력이 있는 환자 7) 조절되지 않는 고혈압 환자 8) 중증의 신장애(크레아티닌 청소율<15 mL/분)또는 간장애(Child-Pugh grade C)환자 9) 다른 5-HT1 효능제 투여 후 24시간 이내인 환자 10) 편마비, 뇌기저 또는 안근마비 편두통 환자

※ 제품에 대한 자세한 정보는 나라필구강용해필름 제품설명서 또는 식약처 의약품통합정보시스템(http://nedrug.mfds.go.kr)을 확인하여 주세요.

CMG 제약 경기도 성남시 분당구 판교로 335 CHA Bio Complex 사무동 6층
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3B
- Broad - 가장 많은 임상 Data를 확보한 Statin[1]
- Better - 한국인 대상 임상에서 효과 및 안전성을 입증한 Statin[2,3]
- Benefit - 고용량 Statin 단일제 대비 빠른 목표 달성 및 복약순응도 개선[4,5]

LDL-C 강하의 확실한 선택

아토반듀오정

10/5mg
10/10mg
10/20mg
10/40mg

[Ezetimibe + Atorvastatin]

Ref. 1) Lancet. 2003 Apr 5;361(9364):1149-58. / N Engl J Med 2005; 352:1425-1435 / Lancet 2004;364:685-96. 등 2) J Diabetes Investig. 2013 Sep 13; 4(5): 466-474. 3) Cardiovasc Drugs Ther. 2010 Apr;24(2):181-8 4) Circulation. 2003 May 20;107(19):2409-15. 5) Am J Cardiol. 2013 Dec 15;112(12):1885-95.

Azilect® – extend the now

- Azilect® helps patients with PD regain control throughout the day and night[1,2]
- Azilect® provides a good start to the day[2]
- Azilect® improves patient's quality of life[3]

AZIL-KR-00270 08/2023

Prescribing Information

AZILECT is a potent, irreversible MAO-B selective inhibitor, which may cause an increase in extracellular levels of dopamine in the striatum. This selective enhancement of dopamine activity leads to beneficial effects in patients with idiopathic Parkinson's disease. AZILECT is indicated for the treatment of idiopathic Parkinson's disease (PD) as initial monotherapy or as adjunct therapy with levodopa or dopamine agonists.

■ **Qualitative and Quantitative Composition**

Azilect tablets 0.5mg
Each tablet (105mg) contains
- Active ingredient: Rasagiline mesylate (in-house) 0.78mg (equivalent to 0.5mg rasagiline base)
- Excipients: Mannitol, Maize starch, Pregelatinised maize starch, Colloidal anhydrous silica, Stearic acid, Talc

Azilect tablets 1mg
Each tablet (210mg) contains
- Active ingredient: Rasagiline mesylate (in-house) 1.56mg (equivalent to 1mg rasagiline base)
- Excipients: Mannitol, Maize starch, Pregelatinised maize starch, Colloidal anhydrous silica, Stearic acid, Talc

■ **Pharmaceutical Form**

Azilect tablets 0.5mg
White to off-white, round, flat, bevelled tablets, debossed with "GIL" and "0.5" underneath on one side and plain on the other side.

Azilect tablets 1mg
White to off-white, round, flat, bevelled tablets, debossed with "GIL" and "1" underneath on one side and plain on the other side.

■ **Therapeutic Indication**

Treatment of idiopathic Parkinson's disease:
1) Initial monotherapy or adjunct therapy with dopamine agonists
2) Adjunct therapy with levodopa in patients with end of dose fluctuations.

■ **Dosage and Administration**

Rasagiline is administered orally, once daily as monotherapy or as adjunct therapy.
1) Monotherapy or adjunct therapy with dopamine agonists: Rasagiline is administered orally, at a dose of 1 mg once daily.
2) Adjunct therapy with levodopa: In patients taking levodopa, the recommended initial dose of rasagiline is 0.5 mg once daily. If the patient tolerates the dose, but a sufficient clinical response is not achieved, the dose may be increased to 1 mg once daily.
It may be taken with or without food.

■ **Warnings and precautions for use**

Contraindications
1) Hypersensitivity to the active substance or to any of the excipients.
2) Concomitant treatment with other monoamine oxidase (MAO) inhibitors (including medicinal and natural products without prescription e.g. St. John's Wort). At least 14 days must elapse between discontinuation of rasagiline and initiation of treatment with MAO inhibitors.
3) Concomitant treatment with pethidine. At least 14 days must elapse between discontinuation of rasagiline and initiation of treatment with pethidine.
4) Concomitant use of tramadol
5) Concomitant use of dextromethorphan
6) Rasagiline is contraindicated in patients with moderate or severe hepatic impairment.

■ **Storage Condition :** Tight container, Store at room temperature (1-25ºC)
■ **Shelf Life :** 36 months after manufacturing
■ **How Supplied :** 30 Tablets
■ **Local Importer & Distributor :** Lundbeck Korea Co., Ltd.
19F KOBACO Building, 137, Olympic-ro 35-gil, Songpa-gu, Seoul, Korea
■ **Co-promotion :** Teva Handok Co., Ltd.
132, Teheran-ro, Gangnam-gu, Seoul, Republic of Korea
■ **Manufactured by request of** Teva Pharma GmbH.
Graf-Arco-Str. 3, 89079 UIM, Germany
■ **Manufacturer :** Teva Pharmaceutical Industries Ltd.
18, Eli Hurvitz Street, Industrial Zone, Kfar Saba 4410202, Israel
■ **For Further Information :** please contact us at (02) 431-6600 (Tel)
※ Latest updated information after the revision date will be available at the Lundbeck Korea website (http://www.lundbeck.com/kr).
※ Please refer to the prescribing information for more details.

Latest Leaflet revised: 2020. 09. 16

Ref. 1) Rascol et al. Lancet. 2005;365:947-954 **2)** Stocchi and Rabey. Eur J Neurol. 2011;18:1373-1378 **3)** Reichmann and Jost. Eur J Neurol. 2010;17:1164-1171

Lundbeck TEVA HANDOK

Once-Daily AZILECT® rasagiline

수벡스정

수마트립탄 + 나프록센

하나로![1]

더 강력하게[2,3] – 수벡스정

† **SUMATRIPTAN**, SUMATRIPTAN SUCCINATE;
§ **NAPROXEN**, NAPROXEN SODIUM

REFERENCES 1. 의약품안전나라. 의약품등 정보검색(검색어: 수벡스정). Available at https://nedrug.mfds.go.kr/searchDrug. Accessed on 27 of Feb, 2024, **2.** 대한두통학회. 편두통 진료지침 제2판, 2009 Nov, Available from: https://www.headache.or.kr/bbs/board.php?bo_table=3_5_1_1&wr_id=1, **3.** Brandes JL *et al.* Sumatriptan–naproxen for acute treatment of migraine: a randomized trial. *JAMA.* 2007 Apr 4;297(13):1443–54.

수벡스정 제품요약정보

[제품명] 수벡스정 **[원료약품 및 그 분량]** 이 약 1정 중 유효성분: 수마트립탄숙신산염+19mg (수마트립탄으로서 85mg), 나프록센나트륨+500mg **[효능·효과]** 18세 이상의 성인 환자에서 전조증상을 수반하거나 수반하지 않는 편두통의 급성 치료 **[용법용량]** 이 약은 쪼개거나 씹거나 또는 부수지 말고 물과 함께 그대로 삼켜서 복용한다. 이 약은 편두통 예방 목적으로는 복용하지 않는다. ○ 성인 : 이 약의 권장 복용량은 1일 1정(수마트립탄 85mg/나프록센나트륨500mg)이다. 24시간 동안 최대 권장 용량은 2정을 초과해서는 안된다. 이 때, 투여 간격은 최소 2시간 간격을 두고 복용해야 한다. 최초 1정 투여 후 재투여에 대한 효과는 체계적으로 평가되지 않았다. 초기 투여가 효과가 없는 경우 재투여에 대한 효과는 확립되지 않았다. 30일 동안 평균 5회 이상의 편두통에 대한 이 약의 안전성은 확립되지 않았다. 이 약은 수마트립탄숙신산염의 최소 유효용량보다 높은 용량을 포함하고 있으므로 환자별로 높은 용량의 수마트립탄에 대한 유익성과 더 높은 이상반응의 위험성을 고려하여 이 약의 사용하여야 한다. 개별 환자 치료목적에 맞게 최소 유효용량을 최단기간 동안 사용해야 한다. ○ 신 장애 환자 : 이 약은 신부전 환자와 중증의 신 장애(크레아티닌 청소율 < 30 mL/min) 환자에게 투여해서는 안된다. 이 약은 경증~중등증의 신 장애 환자에서의 투여는 권장되지 않는다. ○ 간 장애 환자 : 이 약은 중등도~중증(Child-Pugh B and C) 간 장애 환자에게 투여해서는 안된다. 이 약은 경증의 간장애 환자에서의 투여는 권장되지 않는다. **[사용상의 주의사항]** 1. 다음 환자에는 투여하지 말 것 : 1) 수마트립탄, 나프록센 및 이 약의 구성성분에 과민증이 있는 환자 2) 설폰아미드에 과민반응 병력이 있는 환자(중략) 3) 아스피린이나 기타 비스테로이드성 소염진통제의 투여에 의하여 천식, 비염, 코의 용종, 두드러기, 알레르기 반응 또는 그 병력이 있는 환자 (중략) 4) 허혈성 관상동맥질환(중략), 심근막질환, 부정맥(특히 빈맥)의 증상, 징후 또는 그 병력이 있는 환자 또는 프린즈메탈 협심증을 포함한 관상동맥연축 병력이 있는 환자 5) 잠재적인 심혈관 질환 환자(중략) 6) 관상동맥 우회로술(CABG)을 받기 전후의 환자 7) Wolff-Parkinson-White 증후군 또는 기타 심장 부전도 경로 장애가 있는 환자 8) 조절되지 않는 고혈압 환자, 중등도 또는 중증 고혈압 환자 9) 심한 심기능부전 환자 10) 뇌혈관성 우발증상(CVA), 뇌졸중, 일시적인 허혈성 발작(TIA) 병력이 있는 환자 11) 편마비, 경련, 눈근육 경련 및 마비, 시각 장애를 동반한 편두통 또는 뇌저성 편두통 병력이 있는 환자 12) 말초혈관 질환 환자 13) 허혈성 장 질환, 염증성 장 질환 환자 14) 활동성 소화성 궤양, 활동성 장출혈 환자 15) 뇌혈관 출혈, 기타 출혈 질환 또는 심한 혈액이상 환자 16) 중등증 또는 중증 간장애 환자 17) 중증 신장애 환자 18) 고칼륨혈증 환자 19) 임부 또는 임신하고 있을 가능성이 있는 여성, 수유부 20) 18세 미만의 소아 및 청소년 21) 에르고타민 및 그 유도체 함유제제(methysergide 포함) 또는 다른 트립탄, 5-HT1 수용체 효능제를 복용하는 환자 22) MAO 억제제를 투여 중이거나 투여 중단 후 2주 이내의 환자, 선택성 5-HT 재흡수 억제제, 클로미프라민 또는 리튬을 투여 받고 있는 환자 **[제조자]** Halo Pharmaceutical Incorporated, 미국, 30 North Jefferson Road, Whippany, New Jersey 07981, USA **[소분제조자]** 에스케이케미칼(주) 충청북도 청주시 흥덕구 산단로 149 **[판매자]** 에스케이케미칼(주) 경기도 성남시 분당구 판교로 310

2023.10.30 개정

※처방하시기 전 제품설명서 전문을 참고하십시오. 최신 허가사항에 대한 정보는 '식품의약품안전처 의약품안전나라 (https://nedrug.mfds.go.kr/index)'에서 확인할 수 있습니다.

SVX-HA03-202402-01

SK 케미칼 Life Science Biz.

편두통 치료제[1]

미가드 정 2.5mg

Frovatriptan succinate monohydrate

미가드는 국내 임상 연구를 통해서
유효성 및 안전성 Profile이 확인된 편두통 치료제입니다.[1,2]

- 트립탄계 약물 중 가장 긴 반감기[3] 미가드
- 타 트립탄계 약물 대비 긴 지속시간, 낮은 재발률[3-5] 미가드
- 국내 임상 연구로 확인된 유효성과 안전성 Profile[2] 미가드

Long Lasting Action
Lower Rate of Recurrence[3-5]

제품 요약 정보[1]

전문의약품 **분류번호 :** 114[해열·진통·소염제]

【제품명】 미가드정 2.5mg 프로바트립탄숙신산염일수화물 **【원료약품 및 그 분량】** 프로바트립탄숙신산염일수화물(별규) 3.91mg (프로바트립탄으로서 2.5mg) **【성상】** 양면이 볼록한 흰색 원형 필름코팅정 **【효능·효과】** 전조증상을 수반하거나 수반하지 않는 편두통의 급성치료 **【용법·용량】** 이 약은 편두통 예방 목적으로는 복용하지 않는다. 만약 프로바트립탄의 일차 투여 후에 치료반응이 없다면, 같은 증상 발현 시 이 약을 재투여해서는 안된다. - 성인(18~65세) 이 약의 권장 투여용량은 프로바트립탄으로서 2.5mg(1정)이다. 만약 편두통이 초기 진정 후 재발한다면, 2시간 이상의 간격을 두고 재투여할 수 있다. 1일 총 투여량으로 5mg(2정)을 초과해서는 안된다. - 신장애환자 신장애 환자들에게 용량을 조절할 필요가 없다. - 간장애환자 경증 또는 중등증의 간장애 환자들에게는 용량을 조절할 필요가 없다. 중증의 간장애 환자에게는 투여하지 않는다(사용상의 주의사항 1. 다음환자에게는 투여하지 말 것 항 참조). **【제조자】** Almac Pharma Services Limited, Almac House, 20 Seagoe Industrial Estate, Craigavon, Co Armagh, BT63 5QD, United Kingdom **【소분제조자】** 에스케이케미칼(주) 충청북도 청주시 흥덕구 산단로 149 **【판매자】** 에스케이케미칼(주) 경기도 성남시 분당구 판교로 310(삼평동)

2016. 7. 1 개정

※처방하시기 전 제품설명서 전문을 참고하십시오. 최신 허가사항에 대한 정보는'온라인의약도서관(http://drug.mfds.go.kr)'에서 확인할 수 있습니다.

References 1. 미가드정 허가사항, 온라인의약도서관. [Cited 2018 Feb 12] Available from : http://drug.mfds.go.kr 2. Moon HS et al. J Clin Neurol. 2010 Mar;6(1):27-32 3. Geraud G et al.Headache 2003;43(4):376-388. 4. Evers S et al. J Headache Pain. 2015;16:514. 5. Cortelli P et al. Neurol Sci. 2011 May;32 Suppl 1:S95-8.

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경기도 성남시 분당구 판교로 310(삼평동) Tel 080-021-3131 www.skchemicals.com/ls

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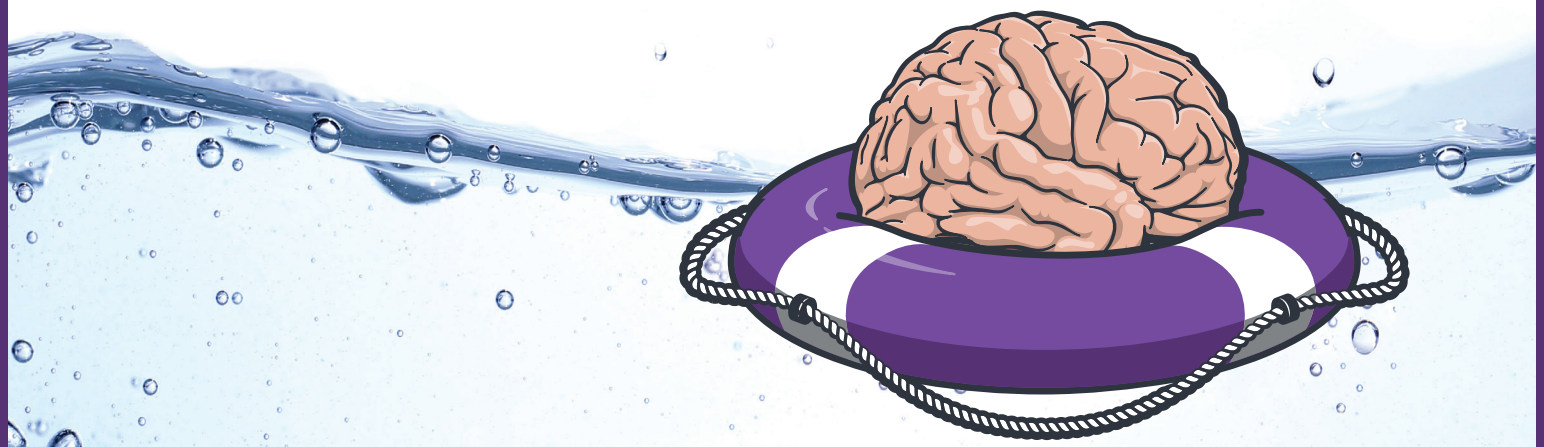
Easy to swallow without water and
fast absorption for treatment of acute migraine

NAGRAN

ODT 2.5mg **Naratriptan Hydrochloride**

나그란®구강붕해정 2.5mg



[제품명] 나그란®구강붕해정 2.5mg [성분명] 나라트립탄염산염 **[효능 · 효과]** 전조증이 수반되거나 수반되지 않는 편두통의 조속한 완화 **[용법 · 용량]** 이 약을 평소에 예방 목적으로 사용해서는 안되며, 다른 편두통 치료약물과 병용하지 않고 단독요법으로 투여하는 것이 바람직하다. 이 약은 구강붕해정으로 혀 위에 놓고 타액으로 녹여 삼키며, 씹거나 부수어서는 안된다. 성인(18 ~ 65세) : 나라트립탄으로서 권장 투여량은 2.5 mg, 1회 투여이다. 24시간동안 총투여량이 5.0 mg을 초과하지 않아야 한다. 이 약 2.5 mg 1회 투여 후 편투통이 재발하면, 최소 4시간의 간격을 두고 2.5 mg을 재투여한다. 이 약 투여 후 반응하지 않는 환자에게는 치료상의 이익이 없다면 동일발작에 대하여 재투여해서는 안되나 연이은 발작에는 투여할 수 있다.

* 제품에 대한 자세한 정보는 제품설명서 또는 식품의약품안전처 의약품 통합정보시스템(http://nedrug.mfds.go.kr)을 확인해주시기 바랍니다.

Yuyu Pharma

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아조비®
(fremanezumab)
injection 225 mg/1.5 mL

More migraine-free days with only 4 injection days per year[1,2]

Reference 1. 의약품통합정보시스템 (http:\\nedrug.mfds.go.kr) 아조비 제품정보 **2.** Goadsby PJ, *et al. Neurology* 2020;95:e2487-2499

아조비프리필드시린지주(프레마네주맙, 유전자재조합) 아조비오토인젝터주(프레마네주맙, 유전자재조합) 전문의약품

[유효성분] 1프리필드시린지/1오토인젝터(1.5 밀리리터) 중 프레마네주맙(별규) 225밀리그램 **[효능효과]** 성인에서의 편두통의 예방 **[용법용량]** 이 약은 1회 225mg을 1개월 간격 또는 1회 675mg(225mg 3회 연속)을 3개월 간격으로 피하 주사한다. 투여간격을 변경할 경우 다음 예정일부터 새로운 투여 일정으로 투여한다. 이 약의 투여를 잊은 경우 가능한 한 빨리 투여한다. 이후 최종 투여 일자를 기준으로 이 약의 투여 일정을 정할 수 있다. **[수입자]** ㈜한독테바, 서울시 강남구 테헤란로 132 **자세한 품목허가 사항은 식품의약품안전처 의약품통합정보시스템 (http://nedrug.mfds.go.kr) 또는 제품의 첨부문서를 확인하여 주시기 바랍니다.** ☎소비자 상담전화(02-527-5506)

AJO-KR-001 80 05/29/2025

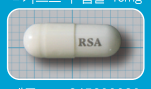
가스트릭 캡슐

(Roxatidine acetate HCl 37.5mg/75mg)

■가스트릭 캡슐 37.5mg

제품코드:645602410

■가스트릭 캡슐 75mg



제품코드:645600030

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WE CARE

【원료약품 및 그 분량】 1캡슐 중 ■가스트릭 캡슐 37.5mg : 록사티딘아세테이트염산염(별규)…37.5mg ■가스트릭 캡슐 75mg : 록사티딘아세테이트염산염(별규)…75mg

【효능·효과】 · 주효능 · 효과 – 1) 위 · 십이지장 궤양 2) 역류성 식도염 3) 졸링거엘리슨 증후군 4) 위산이 흡인될 위험(Mendelson's syndrome)이 있는 환자의 마취전 투여, 특히 분만중인 환자의 마취전 투여, 5) 다음 질환의 위점막 병변(미란, 출혈, 발적, 부종)의 개선: 급성위염, 만성위염의 급성악화 **【용법·용량】** · 성인 1) 위 · 십이지장궤양, 역류성 식도염, 졸링거엘리슨 증후군 : 록사티딘아세테이트염산염으로서 1회 75mg 1일 2회 아침, 저녁 식후에 경구투여한다. –위 · 십이지장궤양의 경우 1회 150mg 1일 1회 저녁에 투여할 수도 있다. –위 · 십이지장궤양의 경우 대개 4주 이내에 치료가 되지만, 증상소실은 수일 내에 나타난다. –치료를 시작한지 4주 후에도 완치가 되지 않는 환자의 경우에는 동일용량을 2주간 더 투여해야 한다. –크레아티닌 청소율이 20–50mL/분 정도로 신기능이 손상된 환자의 경우에는 1회 75mg 1일 1회 저녁에 투여한다. –크레아티닌 청소율이 20mL/분 이하의 경우에는 1회 75mg 2일 1회 저녁에 투여한다. 2) 급성위염, 만성위염의 급성악화기 : 1회 75mg 1일 1회 저녁식후 또는 취침시에 투여한다. 3) 마취전투여 : 1회 75mg을 2회(수술전일 취침시 및 수술당일 마취도입 2시간 전) 투여한다. · 연령, 증상에 따라 적절히 증감한다.

※기타 자세한 사항은 대화제약(주) 마케팅팀(080-855-0114, 02-586-6451)로 문의하시기 바랍니다.

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