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Contents

Dear colleagues,

Primary headache disorders and especially migraine remain a challenging topic for physicians and neurologists. Many things have changed in the new era of preventive (anti-CGRP/r) treatment, but there is still a lack in the diagnosis and management of headache and their complications. In this new special issue of the journal "*Archives of Clinical Neurology*", with four high quality articles, we try to cover some (headache) issues that concern the clinical practice of the neurologists.

First, in the review of Constantinidis, the diagnosis, the genetic polymorphisms, the neurophysiologic and imaging alterations, the comorbidities, the environmental or lifestyle factors and the multidimensional management of Medication Overuse Headache (MOH) are discussed, in line with the recent guidelines of the European Academy of Neurology.

Xifaras did a narrative review to synthesize current evidence on the connection between patent foramen ovale (PFO) and migraine, exploring epidemiological data, pathophysiological mechanisms, and clinical and therapeutic implications.

In a non-systematic review Spingos and Vikelis selected studies about personality traits and medication adherence in migraine patients in way to understand the highly burdensome problem of non-adherence to migraine preventive treatments.

Liapi et al., investigated the subjective experience of migraine, as well as at the perceived consequences that occur on the quality of life of 14 migraineurs, women and men. In this work, it was sought to enable sufferers to express their personal experience of migraine, which is often treated as an "invisible" disease.

On behalf of the Headache Scientific Panel of the Hellenic Neurological Society we would like to thank all authors.

Manolis Dermitzakis, MD, PhD

Neurologist

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Άρθρα...

MEDICATION OVERUSE HEADACHE

Theodoros S. Constantinidis
Korinthos, Greece

Abstract
Medication overuse headache (MOH) is a secondary headache type caused by the overuse of acute headache medications, occurring only on a pre-existing headache. The current definition has removed the two main causative factors included in previous classifications: a substantial increase in frequency and/or intensity of pain, and the reversal of the deteriorated headache after medication withdrawal. This change makes diagnosing MOH at the individual level challenging, and the concept remains a matter of debate. However, there is compelling evidence for the harmful effects of medication overuse in both human and animal studies. A susceptible brain is a necessary prerequisite for medications to exert their deleterious effects. Genetic polymorphisms, neurophysiologic and imaging alterations, comorbidities, environmental or lifestyle factors, and even demographic and socioeconomic factors may affect the brain's susceptibility in headache sufferers. Some of these factors might result from MOH after its establishment. The management of MOH is multidimensional. The first important step is prevention. Following diagnosis, management begins with educational advice and extends to outpatient or inpatient withdrawal of the overused drugs, whether abrupt or gradual. This process may include the use of adjunctive pharmacotherapy for withdrawal symptoms, the addition of preventative treatment, and, if needed, non-pharmacological interventions. All these topics are discussed in the current review, in line with the recent guidelines of the European Academy of Neurology.

Keywords: headache, migraine, medication overuse, analgesics, withdrawal

ΚΕΦΑΛΑΛΓΙΑ ΑΠΟ ΚΑΤΑΧΡΗΣΗ ΦΑΡΜΑΚΩΝ

Θεόδωρος Σ. Κωνσταντινίδης
Νευρολόγος, Κόρινθος, Ελλάδα

Περίληψη
Η κεφαλαλγία από κατάχρηση φαρμάκων (ΚΚΦ) είναι μια δευτερογενής κεφαλαλγία, που προκαλείται από την κατάχρηση φαρμάκων για την αντιμετώπιση της οξείας κεφαλαλγίας και εμφανίζεται μόνο σε έδαφος προϋπάρχουσας κεφαλαλγίας. Ο τρέχων ορισμός της αφαίρεσε τους δύο κύριους αιτιολογικούς παράγοντες, οι οποίοι περιλαμβάνονταν στις προηγούμενες ταξινομήσεις: σημαντική αύξηση στη συχνότητα ή/και την ένταση του πόνου και την αποκατάσταση της επιδεινωθείσας κεφαλαλγίας μετά τη διακοπή των φαρμάκων. Αυτό καθιστά δύσκολη τη διάγνωση της ΚΚΦ σε ατομικό επίπεδο και η έννοια στο σύνολό της παραμένει επί του παρόντος θέμα αντιπαράθεσης. Ωστόσο, υπάρχουν αδιάσειστα στοιχεία για τις βλαβερές συνέπειες της υπερβολικής χρήσης φαρμάκων, τόσο σε μελέτες σε ανθρώπους όσο και σε πειραματόζωα. Ένας επιδεκτικός στην ΚΚΦ εγκέφαλος είναι η απαραίτητη προϋπόθεση για να ασκήσουν τα φάρμακα τα αρνητικά αποτελέσματά τους. Γενετικοί πολυμορφισμοί, νευροφυσιολογικές και απεικονιστικές αλλοιώσεις, συννοσηρότητες, περιβαλλοντικοί παράγοντες ή παράγοντες του τρόπου ζωής ή ακόμη και δημογραφικοί και κοινωνικοοικονομικοί παράγοντες, μπορεί να επηρεάσουν την επιδεκτικότητα του εγκεφάλου του κεφαλαλγικού ασθενούς. Κάποια από τα παραπάνω μπορεί να είναι αποτέλεσμα της ΚΚΦ, μετά την εγκατάστασή της. Η διαχείριση της ΚΚΦ είναι πολυδιάστατη. Το πρώτο σημαντικό βήμα είναι η πρόληψη. Το επόμενο βήμα, μετά τη διάγνωση, ξεκινά με εκπαιδευτικές συμβουλές και επεκτείνεται στην εξωνοσοκομειακή ή ενδονοσοκομειακή απόσυρση των φαρμάκων κατάχρησης, είτε απότομη είτε σταδιακή, με χρήση ή όχι συμπληρωματικής φαρμακοθεραπείας για τα συμπτώματα στέρησης, με προσθήκη προφυλακτικής αγωγής και εάν χρειάζεται, μη φαρμακολογικές παρεμβάσεις. Όλα αυτά τα θέματα συζητούνται στην τρέχουσα ανασκόπηση, σύμφωνα με τις πρόσφατες οδηγίες της Ευρωπαϊκής Ακαδημίας Νευρολογίας.

Λέξεις κλειδιά: κεφαλαλγία, ημικρανία, αναλγητικά, κατάχρηση φαρμάκων, απόσυρση

Introduction

Many drugs prescribed for various medical conditions may cause headaches as an adverse drug reaction. This can occur under the ordinary use of the prescribed drugs, meaning within the range of dosages and duration of treatment as instructed by the patients' doctors. For several drugs, this adverse reaction is frequent, and the same is true for other non-medicinal substances like alcohol, carbon monoxide, or nitric oxide.

Under the current diagnostic criteria of the International Classification of Headache Disorders, 3rd edition (ICHD-3),[1] all these headache-provoking drugs and substances are grouped under the heading "headache attributed to a substance or its withdrawal" (coded as 8). People susceptible to this headache type may or may not have a pre-existing headache disorder. In the latter group, the phenomenology of their headache may resemble the pre-existing one.

Given that headache is a common symptom, how can we diagnose whether a headache is caused by the drug or substance used rather than merely occurring by chance? According to the current criteria of the International Headache Society (IHS),[1] the following rules should be fulfilled:

- The usage or withdrawal of a substance known to cause the observed type of headache.
- The causation between headache and substance use is decided by at least two of the following:
  - Close temporal relation between the exposure to or withdrawal from the substance and the subsequent headache.
  - Cessation of the usage or exposure to the substance results in a close temporal sequence of either pain freedom or pain relief, or the same occurs within a defined period in the case of headache after substance withdrawal.
- The characteristics of the headache are typical for withdrawal from or exposure to the substance.
- There is evidence of some other type of causation.
- There is no better explanation from any other ICHD-3 diagnosis.

A subcategory of this general category, "headache attributed to a substance or its withdrawal," is medication overuse headache (MOH), coded 8.2. The distinguishing characteristic of MOH from the rest of this category (code 8) is that the substances causing the headache are medications used by patients for the acute treatment of their headaches. MOH occurs only if these medications are overused, which is defined as usage above a cutoff of days per month (d/m), determined separately for each class of medications. It is surprising that MOH has been described almost exclusively in headache patients and not in other medical disorders, despite the overuse of analgesic medications for these disorders. A question raised about the concept of MOH is how a clinician can determine the causation between medication overuse (MO) and MOH. Are the current diagnostic criteria sufficient to guarantee MO as the causative factor for the resulting headache, namely MOH?

The concept of MOH through the history of ICHD revisions

The first clinical observation of a new headache type provoked by the excessive use of ergotamine preparations was published in 1951 by Peters and Horton.[2] In the following years, these initial clinical observations were verified and expanded. Eventually, this headache type was included as a distinct category of secondary headache disorder in ICHD-1, under the heading "Headache induced by chronic substance use or exposure".[3]

In each subsequent revision of ICHD-1, several amendments have been made concerning the diagnostic criteria of MOH (see Table 1). The result of these successive modifications are the current criteria, summarized as follows[1]:

- The patient has a pre-existing headache disorder (not only a primary headache disorder) occurring on ≥ 15 d/m.
- Usage of common analgesics and NSAIDs on ≥ 15 d/m, and the rest (triptans, opioids, combinations of substances in one preparation, and combined overuse of different drug classes and preparations, but not each individual drug class) on ≥ 10 d/m. The duration of overuse should be more than 3 months, in a roughly regular manner, e.g. 3 or 4 times per week.
- No other ICHD-3 diagnosis may better explain the headache.

Table 1. Diagnostic criteria of MOH through ICHD revisions

MOH	ICHD-1 1988[3]	ICHD-2 2004[4]	ICHD-2R 2005[5,6]	ICHD-3b 2013[7,8]	ICHD-3 2018[1]
Occurs in patients with a pre-existing headache disorder	Included in all ICHD versions, either in the main body of the diagnostic criteria or in the following notes or comments				
Frequency of headache	≥ 15 d/m for >3m	≥ 15 d/m for >3m	≥ 15 d/m for >3m	≥ 15 d/m for >3m	≥ 15 d/m for >3m
Headache developed or markedly worsened	Included as criterion	Included as criterion	Included as criterion	*Removed*	*Removed*
Pain freedom or notable relief after discontinuation	Within 1 month	Within 2 months	Within 2 months	*Removed*	*Removed*
Clinical characteristics	Described for ergotamine overuse (diffuse, pulsating)	Described as variable with peculiar shifting pattern	Removed	*Removed*	*Removed*
Definition of medication overuse	Dosages per month (e.g. >50 gr aspirin or >100 combined analgesics tablets)	>15 d/m for NSAIDs and common analgesics >10 days for triptans, opioids, and combinations in one preparation	>15 d/m for NSAIDs and common analgesics >10 days for triptans, opioids, and combinations in one preparation >10 d/m for combinations of different drug classes and each one of them used for <10 d/m	>15 d/m for NSAIDs and common analgesics >10 days for triptans, opioids, and combinations in one preparation >10 d/m for combinations of different drug classes and each one of them used for <10 d/m	>15 d/m for NSAIDs and common analgesics >10 days for triptans, opioids, and combinations in one preparation >10 d/m for combinations of different drug classes and each one of them used for <10 d/m
Probable/Definite headache definition	Not included	Introduced	Remained	Removed	Removed
Not explained by another ICHD diagnosis	Not mentioned explicitly	Not mentioned explicitly	Not mentioned explicitly	Stated explicitly	Stated explicitly

Obviously, the two major factors establishing causation between MO and MOH, are absent from the current criteria. These factors, written in italicized in Table 1, are:

The development of a new type of headache or the marked worsening of a pre-existing one.

The resolution of MOH after medication withdrawal.

Both factors were included in the diagnostic criteria of ICHD-1 and ICHD-2 but were removed in ICHD-3 (both beta and final versions). Nevertheless, these causation factors remain in the general diagnostic criteria for the category coded 8 ("Headache attributed to a substance or its withdrawal") , indicating that while they do not apply to each headache disorder in this category, they serve as a guideline for most.

Thus, with the removal of the previously recognized causation factors, we might envision the following scenario:

a migraineur fulfilling the diagnostic criteria for chronic migraine, without MO, begins overusing triptans (> 10 days/month) for the last 6 months. There is no change in the frequency or the intensity of her headaches-only the overuse of triptans. Does such a patient fulfill the current MOH criteria?

The answer is clearly yes, based purely on the criteria. Thus, a new headache type, MOH, is diagnosed without any change from the pre-existing one. In this and many similar cases diagnosed as MOH, the headache may develop in the future, making it a probable headache (pMOH).[9] However, a diagnosis of probable MOH is not defined in the ICHD-3 diagnostic criteria. The comments section of ICHD-3 acknowledges that the term pMOH is reasonable, especially in epidemiological research.[1]

These conceptual modifications of the MOH definition make its nosological entity highly controversial.[10] Additionally, a review of six observational clinical trials published between 2006-2016, which examined the proportion of MOH patients whose headaches improved solely after the withdrawal of overused medications, found that only about 30% showed improvement on average.[11] Such findings cast further doubt on the existence of MOH, even when applying the causation criterion of headache resolution after medication withdrawal.

An argument presented by Jes Olesen,[8] supporting his proposed modifications of MOH in ICHD-2, was that a notable group of chronic migraineurs with MO, despite being unresponsive to prophylactic treatment, became responsive just after withdrawing the overused medications. This clinical observation was based on his personal unpublished data. However, this observation suggests the broad spectrum of harmful effects of MO but does not support the addition of a new headache type to a pre-existing one, namely MOH.

Epidemiology, Risk Factors, Comorbidities

The worldwide median prevalence of MOH is estimated at 1-2%, with studies from different countries ranging between 0.5% and 7.2%, and a female-to-male ratio of 4:1.[12-13] Peak prevalence occurs in the sixth decade of life and is more frequent in lower socioeconomic statuses.[12]

In Greece, the prevalence is estimated at 0.7% (95% CI: 0.5-0.9), with a female-to-male ratio of 4:1, peak prevalence in the 35-54 age group, and higher prevalence in the C2 socioeconomic class, corresponding to skilled manual labor.[14] The prevalence of MO alone without MOH is 2.0% (95% CI: 1.75–2.30).

The incidence of MOH was estimated in a longitudinal population-based cohort study in Norway with 26,197 participants.[15] The incidence was 0.72 per 1000 person-years (95% CI: 0.62–0.81). Risk factors identified by multivariate analysis in this study are illustrated in Table 2. A separate clinic-based study with 142 female migraineurs found the odds ratio of metabolic syndrome as a risk factor for MOH to be 5.3[16] (Table 2).

Most of these risk factors are psychiatric disorders, which are common comorbidities of MOH. The Eurolight project, a cross-sectional survey of 10 European Union countries, reported that depression was five times more prevalent in patients with probable MOH than in healthy subjects (OR: 5.5 for both males and females), and anxiety was ten times more prevalent in males (OR: 10.4) and seven times in females (OR: 7.1).[17] Similarly, 57.7% of MOH patients were reported to suffer from anxiety and 40% from depression in the COMOESTAS cohort, a multicenter study with six months follow-up.[18] A more detailed investigation of psychiatric comorbidities has been reported by Radat et al.[19] (Table 3).

Substance abuse involving substances other than those defined in MO, such as nicotine or caffeine, has been reported repeatedly.[15,19] Could the overused medications for headaches not only be overused but also abused? If they are abused, might a diagnosis of dependence disorder also apply to the patient? This line of thinking is reinforced by the ICHD-3 recommendation to use the Severity of Dependence Scale

Table 2. Risk factors for MOH[15]

Risk factors	Odds Ratio
Headache 7-14 d/m	19.4
Migrainous headache	8.1
Any headache	5.9
Metabolic syndrome	5.3[16]
Use of tranquilizers	5.2
Non-migrainous headache	4.9

Combination of chronic musculoskeletal complaints, gastrointestinal complaints, and Hospital Anxiety and Depression Scale score ≥ 11	4.7
Use of analgesics (for any condition)	3.0
Physical inactivity	2.7
Use of sleep-inducing medication	2.5
Hospital Anxiety and Depression Scale/ Depression (≥11)	2.6
Sick leave (>2 weeks previous year vs no)	2.5
Self-reported whiplash	2.2
Hospital Anxiety and Depression Scale/ Anxiety (≥11)	2.0
Insomnia	1.9
Chronic musculoskeletal complaints	1.9
Female gender	1.9
Low education	1.9
Age >50 y.o.	1.8
Smoking	1.8
Gastrointestinal complaints	1.6
Daily caffeine (≥540mg)	1.4

(SDS) in MOH patients [1]. Is MOH ultimately an addiction disorder? Applying the DSM-IV diagnostic criteria [20-21], a cluster randomized pragmatic, double-blind trial [22] classified 50% of MOH patients as substance dependent. Another multicenter, cross-sectional study found that 66.8% of MOH patients met the same DSM-IV criteria for substance dependence [23-24]. However, the DSM-V diagnostic criteria, published in 2013, introduced the term "substance use disorder" (SUD), combining the previously separate diagnoses of substance abuse and dependence . A conceptual analysis of the symptoms and behavioral changes of patients with SUD, according to DSM-V, concluded that they do not apply to the diagnosis of MOH [26]. Thus, the issue of addiction in MOH patients remains controversial.

Other medical conditions reported to be comorbid with MOH include musculoskeletal and gastrointestinal disorders,[15] as well as metabolic syndrome. [16] However, there is no robust evidence for other specific disorders that may be comorbid with MOH.

Pathophysiology

MOH results from the action of MO on a brain susceptible to developing it, rather than solely from the drug action (MO).[9,12] This susceptibility occurs only in the brains of headache patients, which is why MOH does not present in other medical disorders. However, the duration of MO leading to the presentation of MOH varies depending on the specific overused drug (Table 4).[27] Despite the shorter duration for MOH presentation after triptan overuse, the percentage of MO patients developing MOH may be smaller compared to those overusing analgesics and opioids.[28]

Table 3. Psychiatric comorbidities with MOH, compared to migraine (according to ICHD-2, 2004)

Psychiatric disorder	Odds Ratio
Major depression	21.8
Panic disorder	12.1
Substance abuse	7.6
Generalized anxiety disorder	6.0
All mood disorders	4.5
Social phobia	4.3
All anxiety disorders	3.5

Table 4. Mean duration (years) of MO for the development of MO per used drug class and drug[27]

Analgesics		4.8
	Common analgesics	5.2
	Analgesics + Caffeine	5.4
	Analgesics + Codeine	5.5
	Opioids	2.2
Triptans		1.7
	Sumatriptan	2.4
	Zolmitriptan	1.7
	Naratriptan	0.7
	Rizatriptan	0.3
Ergots		2.7

Genetic susceptibility

A large systematic review analyzed 17 gene polymorphism association studies in MOH, encompassing an overall analysis of 50 polymorphisms in 33 genes.[29] The genes identified with a potential relation to MOH included polymorphic variants of dopaminergic genes (SLC6A3, DRD2, DRD4), which affect susceptibility to MOH, and genes associated

with drug dependence (ACE, BDNF, HDAC3, WSF1), which affect the frequency (in days/month) of drug use. Specifically, the ACE D/D polymorphism severely decreased habituation after somatosensory stimulation, while the ACE I/D genotype exhibited a milder decrease.[9] Similarly, the common single-nucleotide polymorphism 196G>A of BDNF results in decreased activity through Val66Met substitution, ultimately reinforcing substance abuse behavior.[9] However, the lack of replication studies and various methodological issues in the published studies make these results inconclusive.[29]

Central sensitization

Common symptoms in migraineurs include increased sensitivity to light (photophobia) and sound (phonophobia), as well as the perception of innocuous stimuli as painful (allodynia). The underlying neurophysiological basis of these symptoms is the well-known phenomenon of sensitization, which involves neural mechanisms such as lowering the depolarization threshold, increased temporal summation, and expansion of receptive fields.[9,12-13] Due to the sensitization process, repeatedly administered sensory stimuli result in long-lasting, high-amplitude evoked potentials, as recorded using neurophysiological techniques, without the reduction observed in normal controls. This phenomenon is known as non-habituation. In MOH patients overusing analgesics and triptans, the sensitization process and the subsequent lack of habituation are further amplified, as shown by somatic and trigeminal pain-related cortical potentials.[30] Similar results have been recorded using different sensory modalities, such as somatosensory evoked potentials,[31] CO2 laser-evoked potentials,[32] and the cold pressor test.[33] The amplification of the sensitization process in MOH has also been confirmed in animal experiments.[34-35] Additionally, animal studies have shown that perturbations in serotoninergic and endocannabinoid metabolism result in increased sensitization.[9]

All these human cortical alterations, observed using clinical neurophysiological methods, were reversed after the complete withdrawal of the overused drugs.[30,36]

Structural, functional and metabolic imaging alterations

Since MOH is defined as a chronic (≥15 days/month) headache occurring on a pre-existing one, any structural alteration compared to healthy controls might be attributed to the pre-existing headache type rather than MOH itself. Similarly, if the control group comprises episodic rather than chronic headache sufferers, any structural imaging differences may result from the chronicity of the pre-existing headache, which is part of the concept of MOH, rather than medication overuse. Therefore, methodologically, the most valid comparison should be between the MOH group and the chronic type of pre-existing headache. However, several studies on MOH have been performed in comparison to healthy controls[37-38] or episodic migraineurs.[39-40] A voxel-based morphometry study (VBM)[41] compared a group of 66 chronic migraineurs, 33 of whom had MOH, with the rest being without MOH, and another group of 33 healthy controls. The comparison between the two groups of chronic migraineurs showed a decrease in gray matter volume (GMV) in the rectal gyrus of the orbitofrontal cortex bilaterally, as well as a decrease in GMV in the left middle occipital gyrus. Conversely, an increase in GMV was observed in the left temporal pole/parahippocampus. These GMV alterations accounted for 31.1% variance in the frequency of analgesic use. Additionally, the VBM analysis of both MO and non-MO chronic migraineurs compared to healthy controls revealed decreased GMV in the precuneus, cerebellum, and multiple areas of the frontal, temporal, and occipital lobes.

Structural imaging alterations related to MOH involve:

- The orbitofrontal cortex, a key node of the mesocorticolimbic dopaminergic system (including also nucleus accumbens, striatum and ventral tegmental area)
- The left middle occipital gyrus and left temporal pole/parahippocampus, both parts of the reward system.[42-43]

In contrast to gray matter, white matter lesions have been less studied in MOH. One study with 38 chronic migraineurs, 58 MOH and 45 healthy controls, found significantly fewer periventricular white matter lesions in MOH patients compared to chronic migraineurs without MOH. The authors hypothesized a possible anti-inflammatory role of NSAIDs, commonly used by MOH patients, in the pathogenesis of these lesions.[44-45]

A functional MRI study tested decision-making under risk in four groups: MOH patients, MOH patients six months after detoxification, chronic migraineurs without MOH, and healthy controls.[46] The comparison between MOH patients and chronic migraineurs without MOH demonstrated reduced activity in the substantia nigra/ventral tegmental area complex and increased activity in the ventromedial prefrontal cortex compared to MOH patients at six months after detoxification. Another fMRI study examined brain activity under noxious mechanical stimuli to fingers, comparing MOH patients to healthy controls.[47]

Resting-state fMRI studies have tested functional connectivity (FC)[39] or FC plus diffusion tensor im-

aging.[48] Both compared MOH patients to healthy controls, with one study differentiating the control group as episodic migraineurs and the other as chronic myofascial pain patients.

An 18 FDG PET study[49] compared 68 healthy controls to 16 chronic migraineurs with MOH and found marked hypometabolism in several brain regions: orbitofrontal cortex, bilateral thalamus, anterior cingulate gyrus, ventral striatum, insula and right inferior parietal lobule. Notably, after detoxification, hypometabolism reverted in all areas except the orbitofrontal cortex, suggesting a possible causative relationship to MOH.[45,50-51]

A single magnetic resonance spectroscopy study[52] did not demonstrate any significant biochemical (N-acetylaspartate/creatine ratio) neuroimaging difference in chronic migraineurs between those with MOH and those without.

Treatment

"Prevention is always better than cure."

Many of the drugs defined by specific cut-off points for MO are readily accessible due to their availability over-the-counter (OTC). Consequently, the likelihood of a primary care physician offering advice on avoiding MO, and thereby preventing MOH in the future, is minimal. A feasible preventive measure would be to include a warning on the packaging of OTC analgesics, stating that overuse of the drug may worsen headaches or increase resistance to prophylactic treatment if used excessively. Such warnings should be mandated by authorities such as the EMA and FDA.

Similarly, nationwide campaigns could raise awareness about MOH resulting from MO. A study conducted in Denmark[53] targeted the general population and specific groups such as pharmacists and general practitioners (GPs). The two main stakeholders in this campaign were the National Headache Center and the Association of Danish Pharmacists, with the Migraine and Headache Patient Organization joining in later stages. This campaign succeeded in raising awareness from 31% to 38%, although the implementation percentage remains unknown.

Nevertheless, prevention is the best way to ensure the avoidance of future development of MOH.

Treatment strategies after the diagnosis of MOH

The main options of management of established MOH are[54]:

- Educational counselling, meaning brief advice alone.
- Withdrawal of overused medications, either abrupt or gradual, with or without supportive medications during the withdrawal phase.
- Preventive treatment initiation, either pharmacological or not.
- Combinations of two or all three of the above.

-Advice alone

The first treatment strategy was investigated by an Italian open-label trial,[55] which studied 120 MOH patients (according to ICHD-2 criteria) without psychiatric comorbidities, previous detoxification failures, or overuse of barbiturates, benzodiazepines, or opioids (non-complicated MOH). The patients were randomized into three detoxification treatment groups:

A) advice alone

B) advice + preventive treatment + steroids

C) advice + preventive treatment + steroids + fluid replacement and antiemetics

After 2 months, 75.4% of patients succeeded in detoxification, defined as a reversion to an episodic headache type from the chronic one (MOH represents a chronic type of headache) or use of symptomatic medications for fewer than 10 days/month. There was no significant difference between the three groups.

A few years later, the same researchers conducted a similar study with 137 MOH patients who had psychiatric comorbidities, previous detoxification failures, various environmental and socioeconomic problems, and nearly daily medication overuse, including barbiturates, benzodiazepines, or opioids (complicated MOH).[56] In this study, group C (pharmacological intervention) reverted chronic headaches to episodic ones or reduced medication overuse to simple use in 89% of patients, compared to 60% in groups A and B.

A Norwegian cluster-randomized trial, the BIMOH trial,[57-60] recruited GPs in primary care and randomized them into two groups:

-The brief intervention group (BI), where GPs provided educated advice to MOH patients (according to ICHD-2R criteria).

-The business-as-usual (BAU) group, where GPs continued their usual practice

Subsets of the study were blinded (during the first 6 months), open-label (after the first 6 months), or used a cross-over design (for those initially randomized to the BAU group). The open-label part of the trial started after the first 6 months and continued up to the end of the 16-month follow-up period. Despite the large sample of the general population screened, only 259 MOH patients were diagnosed (1.02%),[60] and 60 patients completed the study. At the end of the 16-month follow-up, both the BI and BAU groups demonstrated significant decreases in monthly headache days and monthly medication days. The BI group (both early and late) experienced a decrease in headache days

per month by 8.7 (6.4–10.9) and medication days per month by 13.9 (11.2–16.7), representing nearly a 70% improvement compared to 26% in the BAU group. Additionally, 50% of the BI group reverted from chronic to episodic headaches, compared to only 6% in the BAU group.

The Akershus study, another Norwegian study on the effect of brief information in treating MOH, was uncontrolled. The results showed a 76% decrease in medication overuse, and the number of headache days per month decreased from 22 to 6.[61]

The conclusion, supported by the EAN committee recommendation, is to first try advice for MO avoidance in all MOH patients, except for those with complicated MOH as defined above.[54]

-Preventive treatment

All the approved drugs for migraine conducted pivotal clinical trials for the episodic and chronic types only. Clinical trial especially designed for MOH are very rare. For the vast majority of the approved drugs, the evidence supporting the efficacy of the drug on MOH is based on the post hoc analyses of their pivotal clinical trials for chronic migraine. Thus, there is no robust evidence for any of the new or old drugs regarding MOH.

Nevertheless, a recent randomized pragmatic trial, the MOTS trial, warrants that the use of preventive treatment in MOH is efficacious, using whatever drug is approved and marketed in the USA at the present time.[62] This trial enrolled 720 MOH participants randomized into 2 groups and every group initiated the preventative treatment. The difference between them was that the one group continued the overused drug, while the other reverted the overused drug into simple use, that is ≤2 days per week. The baseline headache d/m were 22.5 and 21.4 d/m the medications overuse. The two groups demonstrated very similar reduction of headache d/m: 9.3±7.2 the group with reversal of medications overuse and 9.1±6.8 the other group. The conclusion from this study is that even the switching of the overused drug to simple use is not necessary if the preventive treatment is initiated. However, a third arm with complete withdrawal might be necessary for more definite conclusions. The publication of the MOTS trial was not available at the time of preparation of the EAN guidelines and thus is not included in the review.[54]

Sodium Valproate is one the preventive treatments with a randomized trial designed especially for the study of MOH, the SAMOHA trial.[63] In this 3-month study randomized 88 MOH patients to 800mg of Sodium Valproate or placebo, along with outpatient detoxification and 3 months follow-up. The 50% responder rate for Sodium Valproate was 45.0% versus 23.8% for placebo.

Topiramate conducted 2 clinical trials for chronic migraine, a European trial[64] and a second trial conducted in the USA.[65] Both performed post hoc analysis to extract the subset of MOH patients and analyze their data. The European study was too small (recruited only 59 chronic migraineurs and the MOH subset included 46). The mean migraine d/m reduced by 3.5 d/m in the topiramate group versus 0.8 d/m increase in placebo. The USA study, with 306 patients, did not find any significant difference in comparison to placebo.

All four monoclonal antibodies (mAbs) published post hoc analyses of their chronic migraine pivotal clinical trials, and all of the comparisons favored the mAb versus placebo, except from Eptinezumab. Also, in all cases of mAbs the overused drugs did not withdraw. More specifically, the post hoc analysis of Fremanezumab decreased the migraine d/m in the MOH patients by 4.7 with the monthly injection and 5.2 with quarterly versus 2.5 d/m in the placebo group.[66] The Erenumab trial for chronic migraine demonstrated a decrease of 6.6 d/m for both 70mg and 140mg dose in MOH patients versus 3.5 d/m in placebo.[67] The 50% responder rate was 36% for 70mg, 35% for 140mg and 18% for placebo. The REGAIN trial for chronic migraine of Galcanezumab[68] showed a decrease of migraine d/m, in the MOH subset of patients, by 4.8 d/m in 120mg dose, by 4.5 d/m in 240mg and by 2.3 d/m in the placebo group. Finally, the SUNLIGHT trial of Eptinezumab for chronic migraine was analyzed post hoc and extracted the patients fulfilling the diagnostic criteria of MOH.[69] The difference of MOH group from placebo in mean migraine d/m was 1.2 d/m (p=0.1484) and the mean difference of migraine d/m with acute headache medication was 1.3 (p=0.1363).

OnabotulinumtoxinA also performed a post hoc analysis of the two PREEMPT (1 & 2) phase 3 studies for chronic migraine.[70] The headache and migraine days of MOH patients decreased by 8.2 days per month and 8.1 days per month for OnabotulinumtoxinA, and by 6.2 days per month and 6.0 days per month for placebo. However, the acute headache medication intake did not show any significant difference from placebo, except from triptans. Recently, published a new randomized, double-blind, placebo-controlled clinical trial conducted in the Netherlands.[71] This trial compared OnabotulinumtoxinA to placebo after the abrupt withdrawal of overused medications. The design of this trial differed from the PREEMPT protocol in the placebo arm by injecting normal saline in every extracranial site, as defined by the protocol, except for the 7 frontal injection sites, where they injected 2.5 units of OnabotulinumtoxinA in each site, totaling 17.5 units. The authors justified this approach to maximize double-blinding. The

PREEMPT trials had been criticized for not adequately masking the disappearance of wrinkles, which occurred only in the OnabotulinumtoxinA arm, making both doctors and patients aware of the substance injected in the forehead and thus unblinding the trial. The surprising result of this meticulously designed randomized controlled trial (RCT) was the absence of any significant difference between OnabotulinumtoxinA and placebo in all outcome measures. This trial challenges the findings from the PREEMPT trials, where OnabotulinumtoxinA showed a significant reduction in headache and migraine days. An expert in OnabotulinumtoxinA criticized the study's methodology for injecting 17.5 units in the frontal area of the patients in the placebo arm, which is 50% of the officially recommended dose.[72] The authors replied that 17.5 units is the lowest ever dose given in humans, not only for headaches but for other diseases as well, citing multiple references.[73] Despite these contradictory results between this RCT and the post hoc analyses of the PREEMPT trials, as well as real-world evidence studies showing significant decreases in headache days after OnabotulinumtoxinA treatment,[74] the robustness of the quality of evidence always favors RCTs. Nevertheless, the EAN guidelines recommend the use of OnabotulinumtoxinA for MOH at present, though the debate regarding the 17.5 units of placebo in the forehead continues.

The EAN guidelines also caution against methods like acupuncture, occipital nerve stimulation, or drugs with small trial sizes, like sodium valproate,[63] pregabalin, beta-blockers, or amitriptyline, that lack well-documented evidence for MOH. However, for some drugs like amitriptyline, it is affordable due to the high prevalence of depression in MOH patients.[54] Additionally, the cost of new and well-documented drugs is high, leading many social security organizations in developed countries to establish prescribing rules that place new drugs as a last resort. Thus, older drugs with poor or absent documentation become an inevitable part of the therapeutic algorithm.

-Withdrawal of Overused Treatment and Predicting Relapse

There is a longstanding belief among headache experts that withdrawing the overused medication can relieve headache pain and improve responsiveness to prophylactic treatment. However, this is not well-documented with high-quality evidence in the literature.[75] For patients, the most affordable approach during the withdrawal stage is the limited use of acute headache medications, with the addition of treatments like antiemetics, antidepressants, or steroids. This approach was applied in the COMOESTAS protocol,[76] achieving a 46% cessation of overuse, conversion to simple use, and reversal of chronic headache to an episodic one. Contrastingly, some researchers, particularly in Northern Europe, advocate for abrupt and complete withdrawal, citing better results.[77] In a small RCT involving 72 MOH patients, 59 completed detoxification. One group was not allowed any acute headache medications, while the other could use them up to two days per week. After detoxification, preventives were initiated if indicated. At six months, the first group saw a 46% reduction in mean migraine days per month, versus 22% in the second group. Additionally, the chronic headache reverted to an episodic one in 70% of the first group versus 42% in the second. However, the number of days of acute medication intake did not show a significant difference between the groups. A slow tapering procedure is recommended for MOH patients overusing drugs such as barbiturates, opioids, or tranquilizers, and inpatient treatment is advised in these cases.[54] Two RCTs investigating the role of steroids as an adjunct treatment during withdrawal found no difference from placebo.[78-79]

Relapse rates vary significantly after detoxification. At six months, relapse rates range from 0% to 41%,[54,58] and at 12 months, they range from 13% to 41%.[54] The longest observational study[80] followed 56 patients for nine years, reporting that 32% met the criteria for MOH at the ninth year. Most of these relapses were in patients who responded poorly to the initial detoxification and had persistent chronic headaches after nine years. The majority of relapses occur within the first year after detoxification.[81] Predictors of relapse include the type of headache and the class of overused drug. The greatest risk of relapse was for patients with a combination of migraine and tension-type headache (TTH), followed by TTH alone, with migraine presenting the lowest risk. Common analgesics posed the greatest relapse risk, while triptans posed the lowest.[81] Other predictors include an increased number of previous preventative treatments, a higher number of headache days per month either before or after withdrawal,[82] a higher score on depression inventories like Beck's, a previous withdrawal attempt within the last three years, and a referral to an emergency department.[83] Combining pharmacotherapy with a short-term psychodynamic psychotherapy program can decrease the relapse rate at six and twelve months,[84] although mindfulness training does not have the same effect.[85]

Conflict of Interest

The author declares no conflict of interest.

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PATENT FORAMEN OVALE AND MIGRAINE: A REVIEW

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Abstract
Introduction: Evidence exists in literature connecting a patent foramen ovale (PFO), a common cardiac septal defect, with migraine. Understanding the potential relationship between PFO and migraine could be crucial for developing effective management strategies. This narrative review aims to synthesize current evidence on the connection between PFO and migraine, exploring epidemiological data, pathophysiological mechanisms, and clinical and therapeutic implications.
Methods: A comprehensive literature search was conducted across multiple databases, including PubMed and Cochrane Library, for studies published up to May 2024, using specific keywords and inclusion/exclusion criteria.
Results: The prevalence of PFO is significantly higher in migraine patients, particularly those with migraine with aura (MA), compared to the general population. The pathophysiology behind this interaction is not yet clear; potential mechanisms linking PFO to migraine include right-to-left shunting, allowing microemboli or vasoactive substances to enter cerebral circulation, altered cerebral hemodynamics, and common genetic pathways. Clinical studies on the efficacy of PFO closure for migraine prevention have yielded mixed results, with MA patients often seeing a significant improvement of their symptoms.
Discussion: While a higher prevalence of PFO in migraine patients and plausible pathophysiological mechanisms support a potential link, the clinical benefits of PFO closure for migraine prevention remain inconclusive in non-aura migraine. Further research is needed to identify patient subgroups that may benefit from targeted interventions and to clarify the pathogenesis.

Keywords: headache, migraine, migraine with aura, patent foramen ovale, right-to-left shunt

ΑΝΟΙΚΤΟ ΩΟΕΙΔΕΣ ΤΡΗΜΑ ΚΑΙ ΗΜΙΚΡΑΝΙΑ: ΑΝΑΣΚΟΠΗΣΗ

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Περίληψη
Εισαγωγή: Αρκετά δημοσιευμένα στοιχεία συνδέουν το ανοικτό ωοειδές τρήμα (PFO), μία συχνή ανωμαλία του μεσοκολπικού διαφράγματος, με την ημικρανία. Η κατανόηση μιας πιθανής σχέσης μεταξύ PFO και ημικρανίας θα μπορούσε να είναι σημαντική για την ανάπτυξη αποτελεσματικών θεραπευτικών στρατηγικών. Η παρούσα ανασκόπηση στοχεύει στη σύνθεση των τρεχόντων στοιχείων, διερευνώντας επιδημιολογικά δεδομένα, παθοφυσιολογικούς μηχανισμούς, και κλινικές και θεραπευτικές επιπτώσεις.
Μέθοδοι: Πραγματοποιήθηκε ολοκληρωμένη βιβλιογραφική αναζήτηση σε πολλαπλές βάσεις δεδομένων, συμπεριλαμβανομένων των PubMed και Cochrane Library, για μελέτες δημοσιευμένες έως τον Μάιο του 2024, χρησιμοποιώντας συγκεκριμένες λέξεις-κλειδιά και κριτήρια συμπερίληψης/αποκλεισμού.
Αποτελέσματα: Ο επιπολασμός του PFO είναι σημαντικά υψηλότερος σε ασθενείς με ημικρανία, ιδιαίτερα σε εκείνους με ημικρανία με αύρα (MA), σε σύγκριση με τον γενικό πληθυσμό. Όμως, η παθοφυσιολογία αυτής της αλληλεπίδρασης δεν είναι ακόμη σαφής. Πιθανοί μηχανισμοί περιλαμβάνουν την επικοινωνία από δεξιά προς τα αριστερά, επιτρέποντας σε μικροέμβολα ή αγγειοδραστικές ουσίες να εισέλθουν στην εγκεφαλική κυκλοφορία, την αλλοιωμένη αιμοδυναμική του εγκεφάλου, καθώς και κοινές γενετικές οδούς. Κλινικές μελέτες σχετικά με την αποτελεσματικότητα της σύγκλισης του PFO για πρόληψη της ημικρανίας είχαν μικτά αποτελέσματα, με τους ασθενείς με αύρα να βλέπουν συχνά σημαντική βελτίωση της νόσου τους.
Συζήτηση: Ενώ ο υψηλότερος επιπολασμός του PFO σε ασθενείς με ημικρανία και οι προτεινόμενοι παθοφυσιολογικοί μηχανισμοί υποστηρίζουν μια πιθανή σύνδεση, τα κλινικά οφέλη της επιδιόρθωσης του PFO για την πρόληψη της ημικρανίας παραμένουν ασαφή. Απαιτείται περαιτέρω έρευνα για τον εντοπισμό υποομάδων ασθενών που μπορούν να επωφεληθούν από στοχευμένες παρεμβάσεις και για την αποσαφήνιση του ρόλου του PFO στην οντότητα της ημικρανίας.

Λέξεις-κλειδιά: κεφαλαλγία, ημικρανία, ημικρανία με αύρα, ανοικτό ωοειδές τρήμα, δεξιά-προς-αριστερά διαφυγή

Introduction

Patent foramen ovale (PFO) is a congenital cardiac defect resulting from the incomplete closure of the foramen ovale, an opening in the septum between the right and left atria of the heart. This defect is present in approximately 25% of the general population, remaining asymptomatic in most individuals.[1] However, PFO has been implicated in various medical conditions, including cryptogenic stroke, decompression sickness, and, more controversially, migraine, particularly migraine with aura (MA).[2–4]

The potential link between PFO and migraine has garnered considerable interest in the medical community over the past few decades, which has led to the hypothesis that PFO may play a role in the pathophysiology of migraine through various mechanisms. With inconclusive or contradicting results in published literature, the clinical implications and even the nature of the link itself remain a topic of ongoing debate.[3,5-6]

This review aims to provide a comprehensive narrative of the current evidence on the relationship between PFO and migraine. By synthesizing findings from epidemiological studies, exploring proposed pathophysiological mechanisms, and evaluating clinical outcomes and therapeutic interventions, it seeks to clarify the potential role of PFO in migraine pathogenesis and inform clinical practice.

Methods

A comprehensive literature search was conducted to identify studies examining the relationship between PFO and migraine. The search was carried out in the PubMed, SCOPUS, and Cochrane Library databases, covering articles published up to May 2024. The following keywords and their combinations were used: "patent foramen ovale", "PFO", "headache", "migraine", "migraine with aura", "migraine without aura". Boolean operators (AND, OR) were utilized to refine the search results. Additional articles were identified through manual searches of reference lists from relevant studies and reviews.

Studies were included if they met the following criteria: (a) original research articles, review articles, or meta-analyses; (b) full-text publication in English; (c) investigated the prevalence, pathophysiology, or clinical implications of PFO in patients with migraine; and (d) involved human subjects. The exclusion criteria were as follows: (a) studies not available in full text; (b) non-peer-reviewed articles, conference abstracts, responses or letters; and (c) animal studies.

After data extraction, the narrative synthesis was organized thematically, focusing on several key areas, including the prevalence of PFO in migraine, the pathophysiology linking PFO and migraine, the clinical outcomes and potential benefits of PFO closure for migraine, and any current recommendations for managing patients with the two coexisting conditions.

As this review utilized previously published data, ethical approval was not required.

Results

Epidemiological data

The evidence of correlation between PFO and migraine has been at times inconclusive, with results both supporting and disproving any link.[6–9] However, systematic analysis of the literature has shifted the narrative in the last few years and the correlation has become more apparent.[4,10] According to these results, the prevalence of PFO in migraine without aura ranges from 11-34.1% and in MA from 14.6-77.9%.(3,5,11,12) In case-control studies this prevalence could be as high as 96% for MA, compared to a range of 16-25.7% in controls.[10] A systematic review by Schwedt et al. showed a higher prevalence of PFO in patients with migraine compared to the general population, and especially higher for MA (OR=2.54 and 3.21, respectively).[13] Observational data suggests that the prevalence of PFO does not differ significantly between episodic migraine and chronic migraine patients.[14]

As this link has been more highlighted, other factors have been identified as well, potentially leading us to better understand the pathophysiology behind it. A 2015 study has associated the degree of severity of PFO with the frequency of visual aura symptoms, although without a complete quantitative relation.[15] The impact of right-to-left shunt (RLS) in PFO is of particular interest. A higher prevalence of MA compared to a healthy control group was also identified in individuals with a high degree of RLS or with PFOs over 2.0mm (large PFO)[16] and RLS has also been connected to an earlier onset of MA.[17] RLS is thus possibly crucial in decrypting the mechanism (or mechanisms) connecting PFO and migraine, as we will examine below.

Despite the amounts of evidence in favor, larger population studies might be crucial to conclusively make a case for the degree of involvement of PFO in migraine, as the small patient groups examined in present case-control or observational studies lead many researchers to concerns of bias or low clinical significance.[6,13]

Pathophysiology

The pathophysiological processes that could be involved in this correlation are several and variable. One prevalent theory involves Cortical Spreading Depression, or CSD. CSD is a wave of transient neuronal and glial depolarization that spreads across the cortex and activates the trigeminal neurovascular

system. It is considered a major factor in the creation of migraine pain and has been particularly linked to the aura phase of migraine.[18] It is proposed that microemboli can pass through the PFO, bypassing the pulmonary circulation, and through their impact on the blood vessels of the brain, could trigger CSD through hypoperfusion or microinjuries, which is supported by the documented ability of focal ischemias to cause CSD.[19,20]

CSD can also be triggered through a low oxygen saturation in cerebral blood supply, which too can be caused by RLS, potentially giving us another clue about the aforementioned increase in prevalence and severity.[21] Another hypothesis involving the atrial shunt considers its impact on serotonin metabolism. Serotonin, which plays a significant role in migraines, is primarily produced by platelets peripherally, and PFO has been associated with increased serotonin production.[22,23] Peripheral serotonin normally gets inactivated in the lungs, but by not undergoing pulmonary filtration, the increased production and decreased inactivation could lead to changes in serotonin levels that can be linked to migraine attacks.[24] Sufficient evidence to support or disprove these theories does not exist at this moment.

Genetic factors could also be at play. One such factor could be found in the NOTCH receptor family, specifically the Notch3 gene. Notch3, a gene whose polymorphisms have been involved in CADASIL and MA, was shown to be associated with PFO closure in animal models.[25,26] However, neither this nor other genetic susceptibility theories have been confirmed and these hypotheses are not yet mature.[4]

Management

Although the therapeutic intervention most widely studied for migraineurs with PFO is closure of the septal defect, some evidence exists regarding pharmacological treatments. Potential medication regimens include antiplatelet agents like clopidogrel, as well as P2Y12 inhibitors such as ticagrelor.[27,28] In particular, research has identified that P2Y12 antagonists effectively inhibit the oxidative stress-induced platelet-associated tissue factor and reactive oxygen species expression, which are all implicated in the inflammatory and oxidative processes that trigger migraines.[29]

In general, the interpretation of clinical studies that have considered the efficacy of PFO closure for alleviation of migraine has yielded mixed results and has been the source of much of the controversy surrounding the subject. Three main RCTs have thus far evaluated the potential benefit for patients.[30-32] In all three RCTs, a large reduction in the frequency of migraine symptoms or a cessation of episodes was considered the primary endpoint of each trial. None of the trials reached their primary endpoint, although all noted a reduction in frequency.[30-32]

The MIST trial, conducted in 2008, identified no differences in migraine cessation after 6 months in patients who had received transcatheter PFO closure versus the control group, which was submitted to a sham procedure. The implant group did display a greater reduction overall headache days (P=0.027) and the importance of RLS in MA was again identified in the patient group.[30] A 2016 trial was prematurely ended due to enrollment issues, but analysis of the data post-hoc showed both a reduction in migraine with aura days and a higher percentage of total cessation of MA in the PFO closure group.[31] Finally, in the PREMIUM trial, the PFO closure group experienced a significantly greater reduction in migraine days compared to the control (P=0.025).[32]

Subsequent review of the data both from RCTs and other studies provides a comprehensive examination of the overall effects of repair, and the conclusions derived can provide a clearer picture. Four metanalyses have been conducted, combining a range of different studies. Their results generally show that PFO closure has resulted in significantly higher rates of migraine cessation, and significantly higher reduction in migraine days and migraine frequency in patients that underwent PFO closure.[33-36] Furthermore, with regards to changes on the impact of headache on daily life, closure has been associated with a significant decrease in patients' HIT-6 scores (SMD 1.23, 95% CI 0.52–1.95), although a similar finding was not discovered for MIDAS scores.[36] Despite the subjective nature of the HIT-6 score, data tend to support this observation, especially for patients with a larger pre-treatment RLS.[37,38]

Even though all metanalyses observed this benefit of treatment on headache duration and frequency, their interpretation of the overall indications in the data can vary, due in some part to the statistical differences between the MA patients and the greater migraine group or migraine without aura subgroup.[34] One study observed the reduction in migraine frequency was much more pronounced for MA compared to migraine without aura (P=0.03), which could again point to a separate causative pathway.[35] This concurred with results both from RCTs and from individual observational studies.[39] Extending those results, two more research teams concluded that PFO closure should be considered for treatment of MA, while refraining from supporting this for patients without aura.[34,35] The difference in response in MA patients is so great that it should possibly be considered a separate research entity.

While none of the previously published or analyzed studies dealt with pediatric patients, which should perhaps be considered a subgroup of their own, a recently-published retrospective analysis of 86

adolescents who underwent PFO closure as a treatment for migraine showed significant improvement in headache burden (83% with >50% reduction) or total cessation (54%).(40) In this patient population, too, patients with aura symptoms displayed greater improvement compared to patients without aura,[40] suggesting an age-agnostic mechanism.

Discussion

Even though the correlation of PFO and migraine has been controversial in literature, over the past years it has become more widely accepted that a link does exist.[6,8,33,36] Gradually, more supportive data are produced on the potential pathophysiological connections between migraine and an extant PFO. While the bypass of pulmonary circulation and filtration, with the subsequent action of microemboli and other vasoactive substances causing CSD, is the leading theory, other genetic or biochemical factors could be at play.[4]

Despite multiple studies synthesizing available data, the evidence on clinical benefits of closure for these patients is not yet concrete enough, at least not as an umbrella solution. Our limitations include the lack of large groups of patients, which preclude our ability to conduct better stratification analysis of the MA patient subgroup, which appears to be the one most benefiting from intervention.[6,34,36]

The results of this narrative review have their own limitations, which include the heterogeneity of the included studies in terms of design and outcome measures. Additionally, publication bias and language bias were considered as the search was limited to articles published in English. These factors were taken into account when interpreting the findings and drawing conclusions and should be kept in mind.

The current consensus does not propose that PFO closure should be performed explicitly for migraine prevention and treatment. It is unclear whether the most recently available results will create a demand for the reexamination of this statement; nevertheless, more data is needed for a comprehensive understanding of the complex situation, and especially research into clarifying the role of PFO in migraine pathogenesis as well as identifying patient subgroups that could benefit from targeted interventions may prove fruitful.

Conflict of Interest

The authors declare no conflict of interest.

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PERSONALITY TRAITS AND MEDICATION ADHERENCE IN PATIENTS WITH MIGRAINE: A NON-SYSTEMATIC REVIEW

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Abstract
Introduction: Treatment non-adherence is a highly recognized reason of efficacy failure of medical treatments. Causes of non-adherence in chronic migraine treatment may include personality traits. Studies of personality traits may help in individualizing our treatment plans. **Methods:** An electronic search in the National Center for Biotechnological Information's National Library of Medicine. All relevant results were to be selected for presentation and critical discussion. **Results:** The search for studies of any type using all three keywords < (personality traits) AND headache AND (adherence OR compliance)> that was performed on May 23, 2024 retrieved 5 hits, of which 3 were considered relevant to our question. **Discussion**: The retrieval rate of studies specifically relevant to our clinical question was very low, however some raw assumptions can be made and possible future approaches can be suggested. Investigating personality traits that correlate with adherence to prophylactic treatment for migraines is a complex endeavor as revealed in the low volume of related research. It certainly can be approached from several angles; psychological, demographic, or neurophysiological. **Conclusion**: Much more relevant and interdisciplinary research regarding understanding and management of the highly burdensome problem of non-adherence to migraine prophylactic treatments is urgently needed.

Keywords: personality, adherence, compliance, migraine, headache

ΧΑΡΑΚΤΗΡΙΣΤΙΚΑ ΠΡΟΣΩΠΙΚΟΤΗΤΑΣ ΚΑΙ ΣΥΜΜΟΡΦΩΣΗ ΜΕ ΤΗ ΦΑΡΜΑΚΕΥΤΙΚΗ ΑΓΩΓΗ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΗΜΙΚΡΑΝΙΑ: ΜΙΑ ΜΗ ΣΥΣΤΗΜΑΤΙΚΗ ΑΝΑΣΚΟΠΗΣΗ

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Εισαγωγή: Η μη συμμόρφωση στη θεραπεία είναι ένας ευρέως αναγνωρισμένος λόγος αποτυχίας της αποτελεσματικότητας των φαρμακευτικών θεραπειών. Οι αιτίες της μη συμμόρφωσης στη χρόνια θεραπεία της ημικρανίας μπορεί να περιλαμβάνουν τα χαρακτηριστικά της προσωπικότητας. Μελέτες των χαρακτηριστικών της προσωπικότητας μπορούν να βοηθήσουν στην εξατομίκευση των θεραπευτικών μας σχεδίων. **Μέθοδοι:** Ηλεκτρονική αναζήτηση στο National Center for Biotechnological Information's National Library of Medicine. Όλα τα σχετικά αποτελέσματα επρόκειτο να επιλεγούν για παρουσίαση και κριτική συζήτηση. **Αποτελέσματα:** Η αναζήτηση μελετών οποιουδήποτε τύπου χρησιμοποιώντας και τις τρεις λέξεις-κλειδιά < (personality traits) AND headache AND (adherence OR compliance) > που πραγματοποιήθηκε στις 23 Μαΐου 2024, ανέσυρε 5 αποτελέσματα, από τα οποία 3 θεωρήθηκαν σχετικά με το θέμα μας. **Συζήτηση:** Ο ρυθμός ανάσυρσης μελετών που σχετίζονται ειδικά με την κλινική μας ερώτηση ήταν πολύ χαμηλός, ωστόσο μπορούν να γίνουν κάποιες αδρές υποθέσεις και να προταθούν πιθανές μελλοντικές προσεγγίσεις της έρευνας. Η διερεύνηση των χαρακτηριστικών της προσωπικότητας που συσχετίζονται με τη συμμόρφωση στην προφυλακτική θεραπεία για ημικρανίες είναι μια σύνθετη προσπάθεια, όπως αποκαλύπτεται από τον χαμηλό όγκο των σχετικών ερευνών. Μπορεί να προσεγγιστεί από τρεις κύριες οπτικές: ψυχολογική, δημογραφική και νευροφυσιολογική. **Συμπέρασμα:** Είναι επειγόντως απαραίτητη πολύ περισσότερη σχετική και διεπιστημονική έρευνα σχετικά με την κατανόηση και τη διαχείριση του ιδιαίτερα επιβαρυντικού προβλήματος της μη συμμόρφωσης στις προφυλακτικές θεραπείες για την ημικρανία.

Λέξεις κλειδιά: χαρακτηριστικά προσωπικότητας, συμμόρφωση, κεφαλαλγία, ημικρανία

Introduction

Treatment non-adherence (a term interchangeably used with the term non-compliance) is usually defined as taking medication at a dose different to more than 20% of the prescribed dose, and it usually refers to taking less. Types of non-adherence include, among others, premature discontinuation of treatment, prescription filling but not execution, taking the wrong dosage, taking medication at incorrect times, increasing or decreasing the frequency of doses, and voluntary intermittent intake.[1]

The non-adherence rate in general is reported to range between 50-60% for long-term medication treatments and lower, between 20-30% for short-term treatments. Non-adherence to lifestyle changes is reported to be the highest, at 70-80%.[2] In patients with chronic headache, non-adherence to prescribed medication treatments may be one of the highest reported, at a rate of 50–60%.[3]

The World Health Organization (WHO) distinguishes non-adherence factors into patient-related (e.g., self-efficacy), healthcare system-related (e.g., trust in the doctor and treatment), treatment-related (e.g., strong burden of side effects), condition-related (e.g., comorbidities), and socioeconomic (e.g., low socioeconomic status).[1]

Non-adherence can vary with time. According to a study regarding acetylsalicylic acid,[4] four typical types of non-adherence patients are distinguished: those who do not adhere from the beginning (40.2%), those who stop adhering along the way (13.6%), those who start adhering along the way (9.6%), and those who adhere throughout the treatment (36.6%).

Medical non-adherence has been recognized as a major public health problem that imposes significant economic burden on modern healthcare systems. The estimated total cost ranges from $100 billion to $290 billion in the United States, €125 billion across Europe, and AU $7 billion in Australia, as of 2010. In a cross-sectional analysis to explore the effects of headache frequency and preventive medication failures on the quality of life and economic burden in European migraine sufferers,[5] data from 1106 individuals indicated that those with two or more medication failures had worse physical and mental health outcomes, greater functional impairment, and higher net healthcare costs compared to those with fewer or no failures.

But how may migraine differ or not from other chronic medical conditions regarding non-adherence? Commonly, subjectively reported causes of non-adherence in chronic migraine treatment may be related to side effects, unsatisfactory treatment efficacy, forgetting to take medication including due to complexity of instructions, difficulty in scheduling appointments at headache clinics, premature discontinuation due to improvement, and other reasons.[3]

Calling patients to remind them of appointments and recalling those who miss a scheduled appointment, simplified and tailored medication regimens (e.g., minimized number of medications and dosing, fixed-dose combinations, cue-dose training, stimulus control), and screening and management of psychiatric comorbidities, especially depression and anxiety are considered as proactive measures to prevent non-adherence.[3]

Anxiety and depression are especially relevant as migraines are often comorbid with anxiety and depression.[6] However, on top of that, personality traits like impulsivity, neuroticism, or negativism may obviously be an important factor for self-care, including adherence to the treatment of chronic debilitating-but-not-life-threatening medical conditions such as migraine.

It is important to consider that personality traits are enduring patterns of thoughts, feelings, and behaviors that differentiate individuals from one another, which are relatively stable over time and across situations, while, on the other hand, personality disorders are enduring patterns of behavior, cognition, and inner experience that deviate significantly from the expectations of an individual's culture, that are inflexible, pervasive, and lead to significant distress or impairment in social, occupational, or other areas of functioning.[7]

Methods

An electronic search in the National Center for Biotechnological Information's National Library of Medicine using the keywords 'personality traits' AND headache AND (adherence OR compliance) was performed. This search may be used as a sample to lead a systematic review in the future. We preferred the broader term 'headache' instead of 'migraine' in order to include studies all over the medical specialties and disciplines. All relevant results were to be selected for presentation and critical discussion.

Results

The search for studies of any type using all three keywords < (personality traits) AND headache AND (adherence OR compliance)> that was performed on May 23, 2024 retrieved 5 hits, of which 3 were considered relevant to our question.

The first one (Pain Medication Beliefs in Individuals with Headache), to evaluate beliefs about pain medication among individuals suffering from headaches, was a cross-sectional study that analyzed data from 215 adults with headaches using the Pain Medication Attitudes Questionnaire (PMAQ) and other psychological assessments. Participants were categorized

into three groups based on their medication beliefs: "trusting and unconcerned," "skeptical and somewhat worried," and "skeptical and concerned." Higher levels of mistrust and concerns correlated with increased depressive symptoms. Beliefs about pain medications varied widely among headache sufferers, influencing their adherence to medication. Negative beliefs were associated with higher levels of depression, highlighting the need for tailored approaches to address it.

The second study (Evaluation of Attachment Style and Social Support in Patients With Severe Migraine), aiming to describe social support and attachment styles among migraine patients and their impact on doctor-patient relationships and treatment adherence, assessed migraine impact, disability, and various psychological factors on 101 patients using validated questionnaires. Migraine patients had an overrepresentation of insecure attachment styles and lower levels of social support compared to the general population. Attachment style and social support influenced the therapeutic alliance and treatment adherence. The conclusion was that personalized treatment plans considering attachment styles and social support can improve patient care. Support groups are recommended to enhance social support systems for migraine patients.

The third study (Barriers to Behavioral Treatment Adherence for Headache: An Examination of Attitudes, Beliefs, and Psychiatric Factors) aimed to identify psychological factors contributing to low adherence to non-pharmacological treatments for headaches. It was conducted as a narrative review by an interdisciplinary team who examined various psychological factors affecting treatment adherence. Factors such as attitudes, beliefs, motivation, locus of control, self-efficacy, and psychiatric comorbidities were identified as barriers to adherence. The study concludes that addressing these psychological barriers through assessment and intervention can enhance adherence to behavioral treatments, ultimately improving outcomes for headache patients.

Discussion

The retrieval rate of studies specifically relevant to our highly relevant clinical question was very low, however some raw assumptions can be made and possible future approaches can be suggested.

Studies demonstrate a number of methodological shortcomings in general headache adherence research so far.[8] Investigating personality traits that correlate with adherence to prophylactic treatment for migraines is a complex endeavor as revealed in the low volume of related research. It certainly can be approached from several angles—psychological, demographic, or neurophysiological—each offering unique insights.

Psychological aspect

Specific psychological approach may be significantly facilitated by the largely established statistical model of "Big Five OCEAN Personality Type".[9] The five traits (Openness, Conscientiousness, Extroversion, Agreeableness, Neuroticism) can be associated with the adherence to migraine treatment and they can tailor adjustments to the doctor-patient communication and treatment plan.

Lower extraversion level has been found among patients with headaches, including both migraines and medication-overuse headache.[10] Extroversion may positively influence adherence to migraine treatment through strong social support networks, effective communication with healthcare providers, an active lifestyle, and a positive outlook. However, potential challenges such as balancing social activities and the need for immediate results must be addressed. Strategies like leveraging social support, enhancing communication, providing flexible treatment options, and setting realistic expectations can help optimize adherence for extroverted patients.

The severity of migraine disability, general health dimensions, and personality types in patients with and without aura was not different regarding high or low conscientiousness.[11] Conscientiousness may significantly enhance adherence to migraine treatment through organized planning, a strong sense of responsibility, goal-oriented behavior, and self-discipline. However, potential drawbacks like perfectionism and rigidity must be taken into consideration. By supporting their organizational skills, encouraging self-compassion, promoting flexibility, and setting realistic goals, healthcare providers can help conscientious individuals effectively manage their migraine treatment and improve their health outcomes.

Agreeableness may positively influence adherence through cooperative behavior, strong relationships with healthcare providers, sensitivity to others' expectations, and a tendency to seek support. Potential negative consequences are avoidance of confrontation and over-reliance on external validation to ensure sustained adherence. Encouraging open communication, building a support network, and educating patients can help leverage the strengths of agreeable individuals while mitigating potential barriers.

Neuroticism, with its emotional instability and anxiety, is expected to negatively affect adherence as those individuals may be more prone to worries about medication side effects or may have difficulty maintaining a routine and openness to experience, expected to have mixed effects. Given that stress and anxiety can trigger migraines, individuals high

in neuroticism may experience more frequent attacks, which could impact their ability to adhere to treatment plans. Their heightened sensitivity to symptoms and potential side effects might also influence adherence. [12]

Openness is an interesting personality trait; on one hand, individuals high in openness might be more willing to try and adhere to new treatments. On the other hand, their tendency to seek novelty might lead them to switch treatments frequently, reducing overall adherence. Openness may decrease the risk of co-occurrence of depression and migraine.[13]

Demographic aspect

Migraine sufferers who perceive the treatment as beneficial are more likely to stick with it. Surveys about patients' beliefs about the efficacy and necessity of the prophylactic treatment should thus be incorporated.[14]

Additionally, surveys of social support are valuable, including family and friends is an expected relevant factor, as strong social support networks can encourage adherence by providing reminders, emotional support, and practical help with managing medication schedules.[15]

Cultural beliefs about illness and treatment can also affect adherence. In some cultures, there might be a preference for alternative treatments, which can impact adherence to conventional medical regimens.[16]

On another demographic approach, the relationship between patients and their healthcare providers can be studied as it significantly influences adherence and effective communication, trust, and regular follow-ups can improve it.[17]

Income and education may also be evaluated, as higher income and education levels are often associated with better adherence, while these individuals may have better access to healthcare resources, greater health literacy, and fewer financial barriers to treatment. Individuals with lower socioeconomic status do not receive equal prescription medicine opportunities to manage their chronic pain conditions.[18] Moreover, stable living conditions with access to healthcare facilities and pharmacies make it easier for patients to adhere to treatment.[19] Besides those, the high cost of newer prophylactic medication against migraine (e.g. CGRP-related monoclonal antibodies, gepants, and ditans) can directly affect adherence, as the newer medications lead to better convenience, efficacy, and side effect profiles than the conventional pharmaceutical approaches, awaiting only regulations on compensation policies and cost and the final answers on long-term safety. [20] Surveys related to patients income may help to make a case for broader availability of expensive treatments as well as their price adjustments related to an enlarging market share.

Neurophysiological aspect

Studies might investigate imbalances in neurotransmitters like serotonin and dopamine, both of which may influence both migraine susceptibility and adherence to treatment. In general, dopamine seems to signal expectations and serotonin seems to signal the end results, which is highly relevant to medical treatments.[21]

Chronic stress is a known trigger for migraines, as well, making stress management crucial.[22] Adherence to prophylactic treatments may be influenced by the level of stress as determined by objective measurements of the slow response hypothalamus-pituitary-adrenal system and the fast response sympathetic-adreno-medulla system. [23]

Perhaps the psychological approach is the most directly relevant and impactful one for understanding and proactively improving adherence to migraine prophylactic treatments. Personality traits are crucial in determining how well patients stick to their treatment plans and intrinsically linked to the daily experiences and challenges of managing migraine.

In conclusion, as it had already been concluded one decade ago, future research should use objective measures of adherence, examine demographic, psychological, and behavioral correlates of adherence and examine the efficacy of adherence interventions in individuals with headache.[8] We highlight that much more relevant and interdisciplinary research regarding understanding and management of the highly burdensome problem of non-adherence to the migraine prophylactic treatments is urgently needed.

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SUBJECTIVE EXPERIENCE OF MIGRAINE SUFFERERS: PSYCHOEMOTIONAL EXPERIENCE AND QUALITY OF LIFE OF SUFFERERS

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Abstract
Migraine is a severe headache that usually occurs together with other symptoms, creating significant dysfunction in the sufferer's daily life. Taking into account its diverse impact on the patient's life, the present qualitative research aimed both at investigating the subjective experience of migraine, as well as at the perceived consequences that occur on the quality of life of the sufferers, women and men. At the same time, it was sought to enable sufferers to express their personal experience of migraine, which is often treated as an "invisible" disease. 14 people participated in the research, of which three were men and eleven were women. From the thematic analysis of the research material, three main themes emerged; the subjective experience of the sufferers, the strategies developed by sufferers to remain functional, and the impact of migraine on the various aspects of the social domain, the attitude, and way of dealing with significant others towards the patients. Based on the findings, the necessity for further investigation of the experience of migraine patients over time, as well as the need for psychological support and systematic counseling of themselves and their relatives, can reasonably be seen.

Key-words: migraine, subjective experience, psycho-emotional experience, quality of life

ΥΠΟΚΕΙΜΕΝΙΚΗ ΕΜΠΕΙΡΙΑ ΠΑΣΧΟΝΤΩΝ ΑΠΟ ΗΜΙΚΡΑΝΙΑ: ΨΥΧΟΣΥΝΑΙΣΘΗΜΑΤΙΚΟ ΒΙΩΜΑ ΚΑΙ ΠΟΙΟΤΗΤΑ ΖΩΗΣ ΤΩΝ ΠΑΣΧΟΝΤΩΝ.

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Περίληψη
Η ημικρανία είναι μία σοβαρή κεφαλαλγία που συνήθως εμφανίζεται μαζί με άλλα συμπτώματα, δημιουργώντας σημαντική δυσλειτουργία στην καθημερινότητα του πάσχοντα. Λαμβάνοντας υπόψη την ποικιλότροπη επίδραση αυτής στη ζωή του ασθενή, η παρούσα ποιοτική έρευνα στόχευσε τόσο στη διερεύνηση του υποκειμενικού βιώματος της ημικρανίας, όσο και στις αντιλαμβανόμενες συνέπειες που επέρχονται στην ποιότητα ζωής των πασχόντων, γυναικών και ανδρών. Ταυτόχρονα, επιδιώχθηκε να δοθεί η δυνατότητα στους πάσχοντες να εκφράσουν το προσωπικό τους βίωμα για την ημικρανία, η οποία συχνά αντιμετωπίζεται ως μια «αόρατη» ασθένεια. Στην έρευνα συμμετείχαν 14 άτομα, εκ των οποίων οι τρεις ήταν άνδρες και έντεκα γυναίκες. Από τη θεματική ανάλυση του ερευνητικού υλικού προέκυψαν τρία κύρια θέματα· το υποκειμενικό βίωμα των νοσούντων, οι στρατηγικές που αναπτύσσουν οι πάσχοντες ώστε να παραμένουν λειτουργικοί και η επίδραση της ημικρανίας στις διάφορες πτυχές του κοινωνικού τομέα, η στάση και ο τρόπος αντιμετώπισης των σημαντικών άλλων προς τους ασθενείς. Βάσει των ευρημάτων προκύπτει εύλογα η αναγκαιότητα για περαιτέρω διερεύνηση του βιώματος των ημικρανιακών ασθενών διαχρονικά, καθώς και η ανάγκη για ψυχολογική υποστήριξη και συστηματική συμβουλευτική των ίδιων και των οικείων προσώπων.

Λέξεις κλειδιά: ημικρανία, υποκειμενική εμπειρία, ψυχοσυναισθηματικό βίωμα, ποιότητα ζωής

Introduction

Migraine is described as a rhythmic pain, usually located on one or both sides of the head.[1]. Often the localization changes, i.e. sometimes one side hurts, sometimes the other, or even the whole head.[1] Migraine is divided into two main types; with aura (classic migraine) and without aura (common migraine).

The diagnostic criteria taken into account are the duration (4 - 72 hours), its form, i.e., if it is a holocranium or migraine, if it is contralateral, throbbing, moderate to severe or aggravated by movement, combined with nausea, vomiting, photophobia or phonophobia, and finally the combination with aura (visual or sensory warning symptoms).[2]

Some of the key points to pay attention to when taking a migraine history, in addition to those mentioned above, are onset, frequency, warning signs and triggers, exacerbation or exacerbation (e.g., activity, bending), relief from treatment or other measures, systemic sequelae (weight loss, scalp tenderness), and family history.[2]

Based on the World Health Organization,[3] it is estimated worldwide that the percentage of adults who present, even symptomatically, some headache episodes amounts to 50%. It occurs in a ratio of 3:1 in women over men, with 90% of cases without aura and manifests mainly between the ages of 25–50 years.[4]

In addition, migraine is now considered the third most common disorder and the third most common cause of disability in women and men over 50 years of age.[3] Migraine is the sixth leading cause of lost work hours due to disability, while overall headache disorders are the third most common cause.

Regarding the Greek data, there are more than one million people who suffer from migraine, while the percentages are higher for women.[1] In a study by Kouremenos et al.,[5] 610,000 patients reported migraine episodes. Patients reported a decrease in functional ability about three times a month. A point that causes concern is the fact that only 1/5 of Greeks seek medical help and the greater percentage do not take preventive measures to deal with migraine.

Quality of life is a term that is closely related to any disease. It is often defined as the individual's subjective perception of his position in life, in the context of the values and cultural characteristics of the society in which he lives, in relation to his personal goals, interests, expectations and criteria he has set.[3] Regarding the connection of migraine with the quality of life, the first burdens the sufferers significantly, causing a reduction in both their daily activities in view of migraine episodes, and more general limitations in the way of life before the onset of such episodes. The impact of migraine appears to negatively affect all social aspects of patients.

Taking the above into account, the present qualitative research focuses both on the investigation of the subjective experience of migraine, as well as on the perceived consequences that occur on the quality of life of the sufferers, both women and men. It also attempts to show the aspects of daily life that are affected by the occurrence of migraine episodes, to identify ways of supporting and dealing with migraines, as well as the psycho-emotional changes observed in individuals. At the same time, it seeks to give sufferers the opportunity to express their personal experience of migraine, which is often treated as an "invisible" disease.

The aim of the research is to answer the following research questions:

1) How do patients define the subjective experience of migraine at a psycho-emotional, cognitive, physical and social level?
2) In what ways do sufferers manage the symptoms during migraine and also preventively?
3) What is the attitude of significant others towards sufferers during a migraine attack?

Method

Research design – Sampling

The method followed to investigate the above questions is the qualitative one, through which it is sought to conduct a more extensive study as well as an in-depth understanding of the personal migraine experience of each of the sufferers. The individual semi-structured interview was used to collect the data, so that a global and in-depth understanding of the personal experience of migraine was possible. In the semi-structured type of qualitative interview, a set of questions is planned that will act as a guide for the topics that are sought to be covered.[6]

Participants

The survey, which lasted from November 17, 2020 to December 4, 2020, involved 14 people, three of whom were men and eleven women. Their ages ranged from 20 to 73 years (with an average age M= 42.36 years) and they came from different regions of Greece. The selection of the sample was random, provided that they were adult patients with a medical diagnosis of migraine.

Data Collection Process

The interview process was carried out remotely using audio-visual media, due to the restrictive measures put in place in view of the Covid-19 virus, and its duration was approximately one hour. Complete anonymity and coding of names was observed when writing the research results for the protection of personal data, while all information provided is confidential and the confidentiality of the conversation was strictly observed.

Before starting the interviews, the participants were informed about the ethical principles governing the research process. Specifically, they were informed about the objectives of the research and the ways of utilizing the research material. Furthermore, they were informed and there was a mutual agreement regarding the right they had not to report information or not to answer questions they do not want, as well as the right to withdraw their participation from the research, if they considered this to be desirable. After it was clarified that anonymity, confidentiality and protection of personal data are guaranteed as a result of an ethical commitment, the consent of the participants for their voluntary participation in the research process was also ensured.

Data analysis method

As a research and data analysis method, thematic analysis was used, which is a particularly widespread method of qualitative research in psychology, as due to its nature it forms the basis for many of the other qualitative data analysis methods.[7]

Results

Through the data analysis, some main themes emerged regarding the subjective experience of migraine and sufferers' quality of life, which were broken down into sub-themes. The first refers to the subjective experience of patients, i.e. the way each individual experiences each migraine episode, the thoughts he has as soon as he feels the first symptoms, the feelings he has during and after the end of the migraine, the way he acts, the observed emotional changes as a result of accepting the illness and living with it. The second concerns the strategies that sufferers develop to remain functional, the ways in which they support themselves and manage migraines, either during an attack or preventively. The third theme is related to the effect of migraine on the various aspects of the social domain, the attitude and way of dealing with patients in the family, professional and friendly social circles, as well as the emotional changes observed between these two.

Subjective experience during the occurrence of a migraine episode

The definition of personal experience is difficult to define. In this research, the experience is defined by the psycho-emotional state during a migraine episode, the psycho-emotional state after the migraine attack, physical well-being, perceived triggering factors, and cognitive processing of the illness.

According to the narratives of the participants, the experience of migraine causes various and mixed emotions such as: irritation, feeling of helplessness, helplessness, disability, impasse, exhaustion, fatigue, suffering, frustration, fear, and sense of senseless loss of days of life, or even guilt about their situation.

The emotional change of sufferers after a migraine attack seems equally important, as positive feelings usually return: relief, euphoria, feeling of rebirth, spiritual upliftment, liberation, happiness, insatiable energy and strength, calmness, and relaxation are some of the predominant responses of patients.

Another aspect in which migraine seems to have a catalytic effect is the physical well-being of sufferers. All participants emphasize the experience of pain, with some considering that the effect of migraine is more pronounced on physical than on mental well-being.

Patients have often linked migraine to various triggers they have observed. Many sufferers associate migraine with stress as a trigger, while some argue that they are not affected by stress, or at least not consciously. Menstruation and various hormonal issues are also a common cause for almost the entire female sample.

Regarding the cognitive processing of the disease, the difficulty of moving sufferers from denial to acceptance is observed. Some sufferers refer to the mental work they have accomplished with themselves to understand, accept, and ultimately come to terms with the idea of migraine as a chronic illness. In some cases, however, there was a period of time where the patients were in complete denial, as it was impossible for them to perceive and accept the chronic nature of the disease.

After the attacks of pain, it is observed that review and evaluation of the important things in life and the appreciation of life, of the day that passes without pain, often follows. In the context of getting used to, reconciling with, and accepting the chronicity of the disease, the development of mental resilience emerges from the words of the participants.

Self-care and ways to treat migraines

Through the narratives of the participants, it is also seen how they try to both accept the chronic nature of the disease and to handle the symptoms and the multiple changes it brings about in their lives.

The primary concern for most sufferers in their daily lives is self-care. They engage in continuous self-care to minimize the effects of chronic disease on their health. In addition, all sufferers seek and pursue, often and in combination, a form of self-medication, that is, ways to relieve themselves at least temporarily from the pain. The combination of self-care with mental work seems to partially help sufferers, giving them strength to cope and not lose hope in finding possible, more effective

healing methods.

Preventive management of migraine attacks is mainly achieved through immediate medication, which also appears to help balance physical and mental well-being. Using a diary also appears to help sufferers identify and prevent possible aggravating factors of a migraine attack.

Regarding strategies to control and cope with migraine attacks, various forms of meditation and mental imagery seem to contribute to a first contact with the pain and temporary relief from it.

Impact of migraine in the social domain

Based on patients' narratives, social life and daily relationships are an important aspect of their struggle with migraine to find and maintain balance. When patients were prompted to talk about the coexistence of their social life with migraine, several mentioned the family and professional domains respectively as the main ones affected, while many claimed that both aspects were equally or almost equally affected. Sufferers also spoke of an effect on friendships and personal domains.

The family, which is one of the basic aspects of everyday life, is significantly affected by migraine attacks. The occurrence of migraine episodes implies the absence of the patients from various activities and events, family and non-family. Based on the narratives, the conflict of the multiple roles that sufferers play every day is perceived, with migraine making them dysfunctional, even for achieving simple things. Nevertheless, they continue to make maximum efforts to cope.

At the same time, migraine seems to affect the attitude and reactions of the patients' family. From their answers, a perceived support from the family is observed. The main reason for the positive attitude seems to be the personal experience of the family circle of patients with a migraine episode, as almost everyone reports a family history of migraine, usually on the mother's or father's side. Nevertheless, some patients, particularly women, talk about less supportive family contexts, referring mainly to the difficulty of understanding on the part of the husband.

Similarly, a significant effect is also observed in the wider personal and friendly sphere of the patients, themselves making daily restrictions, such as social isolation or stopping favorite activities due to the fear of triggering a migraine attack. Regarding the attitude of the friendly environment towards the sufferers, their opinions differ. Some speak of support while others report a lack of understanding of both the seriousness of the disease and the impact it has on sufferers' lives.

As far as the professional field is concerned, sufferers try to find balance, as the low functionality caused as a consequence of migraine attacks, makes work obligations difficult.

When participants were asked to talk about the desired attitude of significant others toward them during migraine episodes, they referred to a need for more understanding and a willingness to help. References were made to all the social contexts to which they belong: family, friends, work. The desire for empathy and support also becomes apparent, with sufferers expressing a sense of grievance.

Discussion

Considering the aims and objectives of the present research, a brief commentary on the findings follows.

Important findings of the work that emerged from the narratives of the patients are the change in the psycho-emotional state after a migraine episode, the desire to make use of the time lost due to a migraine attack, the feeling of fear for the next attack, the physical fixation, and the intense pain experience.[8-9] The last finding is considered important as, through the interview, the expression of each individual patient was achieved in terms of the way they personally experience pain. Regarding the cognitive processing of the disease, sufferers talked about the stages they have gone through, from denial to understanding, reconciliation, and finally, acceptance of migraine.[10]

Prevention is cited as another means of improved seizure management, particularly with prompt medication.[11] Notable aspects of the work are also the testimonies of the patients, who speak of a review and reassessment of life, and the day that passes without physical pain.[12]

On the other hand, as the effect of migraine on the social sphere as a whole seems enormous, the negative feelings possessed by the sufferers, as well as their personal need for a better understanding from the closer relatives.[8-11]

Limitations, challenges and directions for future research

As any research effort, this study is subject to some limitations. One of them could be considered the sample which consists of a relatively small number of participants due to the qualitative nature of the research. In addition, there was relatively low heterogeneity in the sample in terms of gender, as the participants were mostly female. This is of course partly justified by the fact that migraine occurs mainly in the female sex with a ratio of 3:1.

It also has to been considered that due to the conditions of the COVID-19 pandemic, it was impossible for the interviews to be conducted in person.

Considering the above conditions, it would be

interesting to investigate the experience of migraine patients longitudinally in order to see the effect of the COVID-19 pandemic and confinement over time. In addition, further research is suggested in a larger population sample to enrich our knowledge of the migraine experience and the resulting needs of patients.

Conclusion

Summarizing the conclusions of this paper, the conclusions drawn reveal the complexity of the subjective experience and experience of migraine patients. At the same time, the investigation of this experience offers the possibility for a deeper understanding of the difficulties faced by the sufferer, as well as an effort to inform and raise awareness of the general population as to the nature and severity of the disease.

Conflict of Interest

The authors declare no conflict of interest.

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Ενημερωτικές Σελίδες...

Συνέδρια - Ημερίδες - Συμπόσια - Επιστημονικές εκδηλώσεις

2024

- **29 Ιουνίου – 2 Ιουλίου 2024: 10th EAN Congress 2024,** *Helsinki*
- **16 Ιουλίου 2024: 4th Webinar of the Hellenic Society of Intensive Care Medicine**
- **26-28 Σεπτεμβρίου 2024: University of Ioannina, Summer School: The limbic structures of the brain: From bench to bedside,** *Ioannina*
- **26-29 Σεπτεμβρίου 2024: 18ο Πανελλήνιο Συνέδριο Επιληψίας,** *Θεσσαλονίκη*
- **2-4 Οκτωβρίου 2024: 27th Conference of the European Society of Neurosonology and Cerebral Hemodynamics, Andalucia,** *Spain*
- **21-24 Νοεμβρίου 2024: 12ο Πανελλήνιο Συνέδριο Αγγειακών Εγκεφαλικών Νόσων,** *Αθήνα*
- **12-15 Δεκεμβρίου 2024: 11ο Πανελλήνιο Συνέδριο Ελληνικής Ακαδημίας Νευροανοσολογίας,** *Θεσσαλονίκη*
- **29 Μαΐου-1 Ιουνίου 2025: 36ο Πανελλήνιο Συνέδριο Νευρολογίας,** *Θεσσαλονίκη*

Αρχεία Κλινικής Νευρολογίας

Για λόγους ενημέρωσης αρχείου, παρακαλούμε συμπληρώστε τα στοιχεία αλληλογραφίας σας και στείλτε το απόκομμα με fax στο: **210 7247556** ή αποστείλετε τα στοιχεία στο e-mail: **info@jneurology.gr**

ΟΝΟΜΑΤΕΠΩΝΥΜΟ:

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ΤΟΠΟΣ ΑΠΟΣΤΟΛΗΣ:

❑ ΔΙΕΥΘΥΝΣΗ ΟΙΚΙΑΣ:

Τ.Κ. ..... ΠΕΡΙΟΧΗ .....

ΤΗΛ.: .....

❑ ΔΙΕΥΘΥΝΣΗ ΙΑΤΡΕΙΟΥ:

Τ.Κ. ..... ΠΕΡΙΟΧΗ .....

ΤΗΛ.: ..... FAX: .....

ΚΙΝΗΤΟ: .....

- *Εάν επιθυμείτε να λαμβάνετε το περιοδικό «Αρχεία Κλινικής Νευρολογίας» και σε ηλεκτρονική έκδοση συμπληρώστε την ηλεκτρονική σας διεύθυνση:*

e-mail: .....

Σημειώσεις

Σημειώσεις

Σημειώσεις

Οδηγίες προς τους συγγραφείς

Το περιοδικό *ΑΡΧΕΙΑ ΚΛΛΙΝΙΚΗΣ ΝΕΥΡΟΛΟΓΙΑΣ* κυκλοφορεί κάθε δύο μήνες και αποτελεί το επίσημο όργανο της Ελληνικής Νευρολογικής Εταιρείας. Με την Υπουργική Απόφαση ΔΥ2α/Γ.Π.οικ. 66198/1/6/2006, που δημοσιεύθηκε στο Φ.Ε.Κ. 1034/Β/1-08-2006, προστέθηκε στον κατάλογο των περιοδικών με Εθνική Αναγνώριση.

Ύλη του Περιοδικού

1. Ανασκοπικά Άρθρα: Η έκτασή τους δεν πρέπει να υπερβαίνει τις 6.000 λέξεις.
2. Εργασίες: Κλινικές ή εργαστηριακές μελέτες. Δεν πρέπει να υπερβαίνουν τις 4.000 λέξεις (συμπεριλαμβανομένων έως 6 πινάκων και εικόνων). Δεν πρέπει να έχει προηγηθεί δημοσίευσή τους σε άλλο έντυπο. Περιλαμβάνουν σελίδα τίτλου, δομημένη περίληψη, εισαγωγή, μέθοδο, αποτελέσματα, συζήτηση και βιβλιογραφία.
3. Σύντομες ανακοινώσεις και Γράμματα προς τη σύνταξη: Σχόλια για εργασίες που έχουν δημοσιευθεί ή σύντομες αναφορές σε ένα θέμα. Δεν πρέπει να υπερβαίνουν τις 1.500 λέξεις και περιλαμβάνουν έως 2 πίνακες ή εικόνες.
4. Ενδιαφέροντα περιστατικά: Όριο λέξεων 1.500, με τη σελίδα τίτλου, περίληψη και τις βιβλιογραφικές αναφορές. Επιτρέπονται μέχρι 2 εικόνες ή πίνακες.
5. Νευρολογικές Εικόνες με εκπαιδευτικό ενδιαφέρον: Όριο 4 εικόνες για το ίδιο θέμα και 200 λέξεις.
6. Επιλογές και σχολιασμός της βιβλιογραφίας.
7. Νευρολογικά Νέα - Ειδήσεις - Ενημερωτικές Σελίδες, όπως νέα της Ελληνικής Νευρολογικής Εταιρείας και συγγενών εταιρειών, ανακοινώσει συνεδρίων και άλλων εκπαιδευτικών δραστηριοτήτων.

Δομή της ύλης

Γίνονται δεκτές εργασίες στα ελληνικά ή αγγλικά.
Υποβάλλεται πάντοτε ο τίτλος, τα ονόματα των συγγραφέων και η περίληψη και στα αγγλικά.
Τα κείμενα θα πρέπει να αποστέλλονται σε μορφή Microsoft Word document.
Σελίδα τίτλου: Περιέχει τον τίτλο, τα πλήρη ονόματα των συγγραφέων, το ίδρυμα προέλευσης, τη διεύθυνση και το τηλέφωνο του υπευθύνου για την αλληλογραφία και τον καταμετρημένο αριθμό λέξεων.
Περίληψη: Παρουσιάζει τα κυριότερα σημεία της εργασίας. Δεν πρέπει να υπερβαίνει τις 250 λέξεις. Στο τέλος της παρατίθενται 3-10 λέξεις ευρετηρίου.
Αγγλική περίληψη: Παρουσιάζει σε συντομία την εργασία. Η έκτασή της είναι ως 400 λέξεις. Στην αρχή της γράφονται τα ονόματα των συγγραφέων και ο τίτλος της εργασίας στα αγγλικά.
Λέξεις-κλειδιά: έως 6 λέξεις κλειδιά.
Βιβλιογραφία: Οι βιβλιογραφικές παραπομπές αριθμούνται με αύξοντα αριθμό ανάλογα με τη σειρά εμφάνισής τους στο κείμενο (Vancouver). Όλες οι βιβλιογραφικές παραπομπές να αναφέρονται μέσα σε αγκύλες. Π.χ. Ο Smith [1] ανέφερε ότι ... και τα ευρήματα αυτά επιβεβαιώθηκαν από τον Adams και συν [2]. Αναγράφονται έως και οι 6 πρώτοι συγγραφείς. Στον πίνακα της βιβλιογραφίας περιλαμβάνονται μόνο εκείνες οι βιβλιογραφικές παραπομπές που αναφέρονται στο κείμενο και ο πίνακας συντάσσεται με αύξοντα αριθμό που αντιστοιχεί στη σειρά εμφάνισης των βιβλιογραφικών παραπομπών στο κείμενο π.χ.
Πίνακες: Γράφονται σε ξεχωριστή σελίδα, μετά το τέλος των βιβλιογραφικών αναφορών. Αριθμούνται με τη σειρά εμφάνισής τους στο κείμενο και συνοδεύονται από σύντομη επεξήγηση.
Εικόνες: Αποστέλλονται τα πρωτότυπα σχέδια ή φωτογραφίες καλής ποιότητας. Να υποβάλλονται σαν αρχεία εικόνας ξεχωριστά από το κείμενο του MS Word. Αριθμούνται με τη σειρά εμφάνισης στο κείμενο. Στο κείμενο θα πρέπει να υπάρχει σαφής παραπομπή στον τίτλο των ηλεκτρονικών αρχείων. Σε ξεχωριστή σελίδα αναγράφονται οι τίτλοι των εικόνων και οι τυχόν επεξηγήσεις.
Ιατρική Δεοντολογία: Σε περιπτώσεις ερευνών που αφορούν ανθρώπους, η έρευνα πρέπει να έχει γίνει με βάση τη διακήρυξη του Ελσίνκι (1975). Σε περιπτώσεις φωτογραφιών ασθενών, θα πρέπει να υπάρχει έγγραφη συγκατάθεση.

Συνοδευτικό έντυπο υποβαλλόμενης εργασίας

Θα πρέπει να συμπληρωθούν ΟΛΑ τα σημεία του εντύπου. Άλλη συνοδευτική επιστολή δεν είναι απαραίτητη.

Είδος άρθρου (σημειώστε μόνο ένα)

❑ Ερευνητική εργασία ❑ Βραχεία εργασία - ενδιαφέρον περιστατικό ❑ Ανασκόπηση

❑ Βραχεία ανασκόπηση ❑ Ειδικό άρθρο ❑ Γράμμα στη σύνταξη ❑ Νευρο-εικόνες

Τίτλος:

Υπεύθυνος για την αλληλογραφία συγγραφέας:

Διεύθυνση:

Τηλέφωνο: FAX: e-mail:

Επιβεβαιώστε την πληρότητα της υποβολής του χειρογράφου σας, σημειώνοντας ΟΛΑ τα παρακάτω σημεία

- ❑ Τίτλος του άρθρου στα Ελληνικά και στα Αγγλικά με μικρά γράμματα
- ❑ Ονόματα συγγραφέων στα Ελληνικά και στα Αγγλικά *(πλήρη ονόματα π.χ. Νικόλαος Παπαδόπουλος)*
- ❑ Κέντρο προέλευσης της εργασίας στα Ελληνικά και στα Αγγλικά
- ❑ Δομημένη περίληψη στα Ελληνικά και στα Αγγλικά
- ❑ Έως πέντε λέξεις ευρετηριασμού *(κατά προτίμηση από το MeSH Hellas-Βιοϊατρική Ορολογία)* στα Ελληνικά και στα Αγγλικά
- ❑ Όλα τα ονόματα των συγγραφέων στις βιβλιογραφικές παραπομπές (*μέχρι 3 και στη συνέχεια* «*και συν.*» *ή* «*et al*»)
- ❑ Η βιβλιογραφία στις τελευταίες σελίδες των άρθρων

Δήλωση

Δηλώνω υπεύθυνα ότι:

1. Όλοι οι συγγραφείς της εργασίας συμφωνούν με το περιεχόμενό της και με την υποβολή της στο περιοδικό: *Αρχεία Κλινικής Νευρολογίας.*
2. Το ίδιο κείμενο ή τα αποτελέσματα της εργασίας δεν έχουν υποβληθεί για δημοσίευση σε άλλο Ελληνικό ή ξένο περιοδικό.
3. Δηλώνω υπεύθυνα ότι δεν υπάρχει θέμα υποκλοπής πνευματικής ιδιοκτησίας (σε περίπτωση εικόνων, πινάκων ή υλικού από άλλες δημοσιεύσει έχει ζητηθεί και ληφθεί η νόμιμη άδεια η οποία και συνυποβάλλεται).
4. Δεν υπάρχουν θέματα σύγκρουσης συμφερόντων – σε περίπτωση εξωτερικής χρηματοδότησης αυτό θα πρέπει να αναφέρεται στο τέλος της εργασίας.

Ο υπεύθυνος για την αλληλογραφία συγγραφέας

(υπογραφή)