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The Results of the Study on Prenatal Estrogen-Testosterone Imbalance as a Risk Factor in the Development of Headache from Medication Overuse Headache

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Abstract: This article highlights the significance of prenatal estrogen-testosterone balance as a risk factor in the genesis and early diagnosis of medication overuse headache (often referred to as abuse headache) in primary headaches such as migraine and tension headache. To date, while there is information regarding the origin and development of medication overuse headache, the role and significance of prenatal sex steroid hormones as risk factors have not been fully clarified. In these instances, it is crucial to investigate not only the sexual hormonal imbalance during puberty but also alterations during the prenatal period.

Keywords: migraine, tension headache, medication overuse headache, risk factors, prenatal period, estrogen-testosterone balance, 2D:4D digit ratio

1. Introduction

In the first edition of the International Classification of Headache Disorders in 1988, the term "medication overuse headache" (MOH), initially referred to as "drug abuse headache" or "abuse headache," was introduced to describe headaches caused by the overuse of substances such as ergotamine, analgesics, and others. The current classification system defines MOH as a secondary headache occurring in a person with a predisposition to a primary headache disorder due to substance overuse.

The prevalence of MOH varies between 0.5% and 7.2% in the general population, a range that may fluctuate over time due to changes in diagnostic criteria. The condition is more frequently observed in middle-aged women (female to male ratio of 3:1 to 4:1) but is also reported in 21% to 52% of children with chronic headaches and in 35% of individuals over 64 years of age with headaches. Moreover, MOH has been noted in individuals suffering from rickets.

Among people with primary headache disorders, particularly those with chronic migraines, MOH is quite common, with an estimated prevalence of 11% to 70%. Although MOH is more often a consequence of migraines and tension-type headaches, it can also develop in individuals with cluster headache disorders, especially if they have a personal or family history of migraines and persistent daily headaches.

The aforementioned data indicate gender differences in the occurrence of medication overuse headaches. The influence of sex hormones is also evident in the pathophysiology of migraines and MOH, which are considered primary headaches that can lead to medication overuse. Scientific studies have shown that migraines and MOH are observed more frequently in women than in men by a factor of 1.5 times, highlighting a significant link between these conditions and sex hormones. More than 25% of women with medication overuse headaches (MOH) reported experiencing various headaches during their menstrual cycle, while 3% of the general population suffers from menstrual migraines [[9]]. Research by Rasmussen et al. has shown that 40% of women with migraines and 50% of women with MOH reported a cessation of headaches during pregnancy, and the other 50% noted a reduction in migraine frequency [[10]]. These findings suggest that sex hormones play a role in the development of headaches, but questions regarding the importance of sex hormones in the prenatal period and their ratios remain largely unanswered.

It is technically possible to measure fetal sex hormones in amniotic fluid, umbilical cord blood, and the blood of the pregnant mother; however, these methods are not employed in studies involving adult research participants. Sex steroids can directly influence the relative length of bones by affecting the prenatal development of phalanges or the growth of metaphyses. The influence of sex steroid receptors on the fetus primarily occurs in the first trimester of pregnancy, during the development of testicles and the surge in androgen production in the male fetus.

Sex steroids primarily affect metaphyseal tissues through estrogen receptors alpha and beta. The impact on long bones in adolescent boys is mediated by the local aromatization of testosterone [15]. Although it is known that androgen receptors play a role in growth [16], the specific effect of androgen receptors on bone length remains unclear. These observations highlight the intricate relationship between sex hormones and physical development, particularly their potential impact on conditions such as medication overuse headaches. A basic interpretation of the effects mediated by estrogen receptors on metaphyseal growth is that they enhance growth plate synthesis through the accelerated degeneration of hypertrophied chondrocytes [13]. Furthermore, sex steroids are known to trigger growth spurts associated with the early stages of puberty via the estrogenic pathway [14].

The growth-inhibitory effects of estrogens are thought to be contingent upon their growth-promoting actions, as high levels of estrogens stimulate hypertrophied chondrocytes, leading to their shrinkage and eventual degeneration [13]. Males typically achieve greater height and often longer fingers than females through a process known as hypermorphosis. The differential effects of sex steroids on primordial or metaphyseal growth could explain the observed variances in relative finger bone length, which may be due to differences in bone sensitivity to sex steroids or differences between bones themselves.

Sex differences in finger proportions might emerge if the bones of different fingers are affected differently by sex steroids, due to variations in receptor activity, aromatase activity, or the interaction between steroid complexes and growth factors, creating diverse conditions. Moreover, sex differences could also stem from differences in the timing of bone growth, even if the bones of different fingers respond similarly to sex steroids. Variations in the period of peak bone growth, or the onset of chondrification or ossification, coupled with sex differences in steroid production, might lead to distinct effects of sex steroids despite similar patterns of sensitivity and action on bones. Additionally, prenatal steroids have the potential to influence the development of various tissues, indicating the broad scope of their effects beyond bone growth and development. This underscores the complexity of sex hormone interactions and their significant role in physiological development and potential pathological conditions.

The 2D:4D digit ratio serves as an indicator of the prenatal balance between androgens and estrogens, with noticeable sexual dimorphism (where males typically have a longer fourth digit in comparison to the second digit) identified as early as the 19th century. However, the hypothesis that the 2D:4D ratio is influenced by genes involved in the development of limbs and the genitourinary system, negatively associated with prenatal testosterone (PT) and positively with prenatal estrogen (PE), was not proposed until 1998.

Research shows that the 2D:4D ratio, or the length ratio of the second (index) to fourth (ring) finger, is generally lower in males than in females, indicating sexual dimorphism. This ratio exhibits considerable variation within populations, and for both sexes, the second digit may be either longer or shorter than the fourth. It is established that sexual dimorphism is set during early fetal development under the influence of sex hormones, making the 2D:4D ratio relatively stable after the early fetal stages or beyond two years of age.

Studies, like those conducted by Garn et al. (1975), have found that the mean phalangeal and metacarpal dimensions in human fetuses from seven weeks of age onward closely resemble those of adults. While Phelps (1952) did not specifically examine the 2D:4D ratio in fetuses but rather in adults, it has been concluded from various studies that the fetal 2D:4D ratio can be less than one, greater than one, or equal to one.

Malas et al. (2006) discovered a significantly higher 2D:4D ratio in female fetuses compared to male fetuses in a study of 161 fetuses without external anomalies. The 2D:4D ratios and their correlation with sex-related traits have been extensively researched, revealing that although the 2D:4D ratio varies by ethnicity during sexual development, males consistently have a lower 2D:4D ratio across all ethnic groups. This difference is observable by hand and manifests early in fetal development. The 2D:4D ratio has been proposed as a biomarker for certain gender-specific conditions, such as autism, athletic ability, and osteoarthritis.

Despite the considerable body of research on the 2D:4D ratio and its implications, the significance of prenatal factors, especially sex steroid exposure (2D:4D ratio), as a potential risk factor for medication overuse headaches (MOH) in the realm of primary headaches, has not been fully explored. The goal of this article is to examine the influence of prenatal sex steroid exposure (2D:4D ratio) as a potential risk factor for MOH, underscoring the necessity for further research into these prenatal determinants.

Purpose: The main purpose of this study is to assess whether the ratio of exposure to sex steroids during pregnancy is a risk factor for abuse headache in the population of Uzbekistan.

2. Methods

The study you've described appears to focus on understanding the prevalence and characteristics of medication overuse headache (formerly termed as "abuse headache") among different groups in Tashkent, Uzbekistan, between 2022 and 2023. This study categorizes participants into specific groups based on their headache types

and includes a control group of healthy individuals. Here is a summary of the methodology and criteria used for this study:

Study Methodology:
Location: Tashkent, Republic of Uzbekistan
Period: 2022 to 2023
Setting: Outpatient treatment facilities
Consent: All participants voluntarily agreed to partake in the study.
Inclusion Criteria for Study Participants:
Age between 18-45 years.
Individuals experiencing medication overuse headache secondary to migraine.
Individuals experiencing medication overuse headache secondary to tension headache.
Patients diagnosed with migraine.
Patients diagnosed with tension headaches.
Healthy participants without headache complaints.
Exclusion Criteria:
Pregnant or lactating women.
Individuals with severe concurrent somatic diseases.
Patients with epilepsy.
Individuals with mental illness, alcoholism, or drug addiction.
Patients with organic brain diseases.
Subject Recruitment:
Migraine Group: 50 individuals with migraine headaches.
Tension Headache Group: 50 individuals with tension headaches.
Additional groups including individuals specifically with medication overuse headaches secondary to migraine and tension headache, and a control group of healthy individuals, each consisting of 30 participants.
Diagnostic Criteria:
The diagnosis of medication overuse headache was established following the 2013 diagnostic criteria of the International Headache Society (ICHD-3). The study aimed to investigate the factors contributing to medication overuse headache in both migraine and tension headache groups.

Medication Overuse Headache (MOH) Diagnostic Criteria (Based on ICHD-3):
Although not explicitly listed in your query, the ICHD-3 typically defines MOH as headache occurring on 15 or more days/month in a patient with a pre-existing headache disorder and who has been overusing one or more acute or symptomatic headache medications for more than three months. The headache in MOH develops or significantly worsens during the period of medication overuse.

This structured approach to studying MOH in Tashkent will likely provide valuable insights into the prevalence, characteristics, and risk factors associated with medication overuse headaches among patients with migraine and tension headaches, as well as compare these findings to a healthy control group.

International Headache Classification criteria for abuse headache:	
Patients with a history of headache with chronic headache ≥15 days/month	
Regular abuse of 1 or more medications that may be taken for more than 3 months to treat acute or symptomatic headaches	
When - ICHD-3	
Subclasses of MOHs	
MOHMOH caused by ergotamine abuse	Taking ergotamine regularly for more than 10 days per month for 3 months
MOH caused by triptan abuse	Regular use of one or more triptans, in any formulation, more than 10 days per month for 3 months
MOH caused by non-opioid analgesic abuse	Taking non-opioid analgesics (NSAID / ASK / Other) regularly for more than 15 days per month for 3 months
MOH caused by opioid analgesic abuse	Regular use of one or more opioids more than 10 days per month for 3 months

MOH caused by abuse of combined analgesics	Regular intake of one or more combined analgesics for more than 10 days per month for 3 months
MOH caused by the abuse of several classes of drugs that are not used individually	Taking any combination of the MOHve drugs regularly for more than 10 days per month for 3 months without overusing any drug or drug class.
MOH caused by the abuse of several unspecified or unproven drugs	.Regular intake of any combination of the MOHve medications for a total of ≥10 days/month for 3 months without overuse of any drug or drug class.
MOH caused by abuse of other drugs	Regular overuse of one or more drugs other than 1 drug used to treat acute or symptomatic headache for more than 10 days per month.
Abbreviations: ASA - acetyl salicylic acid; , International classification of headache diseases; - ICHD, nosteroid anti-inflammatory drugs.-NAD	

The length of digits 2 and 4 was measured with a digital sliding vernier caliper accurate to 0.01 mm according to the standard anthropometric procedure of Martin measurements [22].
The length of the digits on both hands was measured between the pseudophalangion and dactylion points [23].
Based on these measurements, 2D:4D digital ratios and 2D:4D ratio difference between arms were calculated (D2D:4D = 2D:4D R - 2D:4D L). The free software Auto-metric [24] was used to measure the ratio between the second and fourth digit lengths (2D:4D).

Statistical Analysis

Statistical analysis was performed using GraphPad Prism 7 software. The collected data were analyzed using Microsoft Excel. The obtained data were presented in average values, standard deviation and percentages. Statistical threshold
* is considered significant at $r < 0.05$, ** $r < 0.01$, *** $r < 0.001$, and *** $r < 0.0001$.

3. Results

All research participants belonged to the Uzbek nationality, totaling 190 people (134 women, 56 men). Age ranged from 18 to 45, the average age was 30.58±6.72

Table 1 shows the age and gender distribution of the patients included in the study.
Table 1
Demographics of the study sample:

		% of patients with MOH due to migraine (n=50)	% of patients with MOH due to tension headache (n=50)	Patients with migraine % (n=30)	Patients with % tension headache (n=30)	Control group % (n=30)
Sex	Women %	91,5% (46)	55 % (28)	70 % (21)	67 % (20)	62% (19)
	men %	8,5% (4)	45 % (22)	30%(9)	33 % (10)	38% (11)
Age at time of examination	men %	25,25±3,2	29,41±8,33	33,11±7,47	28,2±2,86	26,18±4,09
	Women %	36,28±7,25	33,89±5,08	31,48±9,32	29,65±8,5	31,32±8,21

2D:4D aspect ratio data of the study sample:

	% of patients with MOH due to	P	% of patients with MOH due to	p	Patients with migrain e	p	Patients with % tension	P	Control group % (n=30)

		migraine (n=50)		tension headache (n=50)		% (n=30)		headache (n=30)		
men %	Right hand	1±0,06	p=0,0035	1,01±0,03	p‹0,0001	0,97±0,04	p=1	0,97±0,02	p=1	0,97±0,02
	Left hand	1,01±0,06	p‹0,0001	0,98±0,04	p‹0,0001	0,96±0,03	p‹0,0001	0,96±0,01	p‹0,0001	0,94±0,02
Women %	Right hand	0,96±0,03	p‹0,0001	0,94±0,02	p‹0,0001	0,98±0,03	p‹0,001	0,97±0,03	p‹0,0001	1,01±0,03
	Left hand	0,97±0,02	p‹0,0001	0,96±0,02	p‹0,0001	0,98±0,03	p‹0,0001	0,98±0,03	p‹0,0001	1±0,02

The results of the study showed that the 2D:4D ratio was lower in the group of MOH women with migraine than in the control group (right arm: 0.96±0.03 vs 1.01±0.03 p‹ 0.0001; left hand: 0.97±0.02 and 1±0.02 p‹0.0001)
. In the male group, on the contrary, the 2D:4D ratio was higher compared to the control group (right hand: 1±0.06 and 0.97±0.02 p=0.0035; left hand: 1, 01±0.06 and 0.94±0.02 p‹0.0001). The 2D:4D ratio was lower in the group of women with MOH from tension headache compared to the control group (right arm: 0.94±0.02 vs 1.01±0.03 p‹0.0001; left hand: 0.96±0.02 and 1±0.02 p‹0.0001).
.The male group had a higher 2D:4D ratio compared to the control group (right hand: 1.01±0.03 vs 0.97±0.02 p‹0.0001; left hand: 0.98 ±0.04 and 0.94±0.02 p‹0.0001).
The 2D:4D ratio was lower in the group of women with migraine compared to the control group (right arm: 0.98±0.03 vs 1.01±0.03 p‹0.001; left arm: 0.98 ±0.03 and 1±0.02 p‹0.0001).
In men, compared to the control group, the 2D:4D ratio was equal in the right hand (0.97±0.04 and 0.97±0.02 p=1) and higher in the left hand (0.96± 0.03 and 0.94±0.02 p‹0.0001).
The 2D:4D ratio was lower in the group of women with tension headache compared to the control group (right hand: 0.97±0.03 vs 1.01±0.03 p‹0.0001; left hand: 0 .98±0.03 and 1±0.02 p‹0.0001. In the male group, compared to the control group, the 2D:4D ratio was equal in the right hand (0.97±0.02 and 0.97±0.02 p=1) and higher in the left hand (0.96 ±0.01 and 0.94±0.02 p‹0.0001).
The 2D:4D ratio was lower in the group of women with MOH from migraine than in the group of women with migraine (right arm: 0.96±0.03 vs 0.98±0.03 p‹0.0001; left arm λ: 0.97±0.02 and 0.98±0.03 p‹0.0001).

This ratio was higher in men (right hand: 1±0.06 and 0.97±0.04 p=0.0173; left hand: 1.01±0.06 and 0.96±0 .03 p=0.0007).
The same result occurred in patients with MOH and patients with tension headache due to tension-type headache. in women: right hand: 0.94±0.02 and 0.97±0.03 p‹0.0001; left hand: 0.96±0.02 and 0.98±0.03 p‹0.0001; men: right hand: 1.01±0.03 and 0.97±0.02 p‹0.0001; left hand: 0.98±0.04 and 0.96±0.01 p‹0.0001)

4. Discussion

The digit ratio (2D:4D) is sexually dimorphic. It is determined as early as the 14th week of fetal life and remains unchanged in adulthood [25].
Hormonal environment in the fetus may be associated with several disorders during puberty, one of which is abusus headache.
. Manning and Bundred (2000) focused on the role of the prenatal hormonal environment in the development of several diseases and proposed the 2D:4D digital ratio as a potential predictor [26].
. The 2D:4D ratio has been studied in several diseases, including breast cancer [27], lung cancer [28] and carpal tunnel syndrome [29] in women, and prostate cancer [30] and heart disease in men [31].
Migraines and tension headaches, which are considered primary headaches, are multifactorial, including sex hormones, but prenatal sex hormone imbalances are not fully understood until now. has not been studied, and the imbalance of prenatal sex hormones in the development of abusus headache has not been clarified to date.

Therefore, we can only analyze primary headaches from previous studies in our study
.Prenatal testosterone levels have been suggested to be relevant to migraine etiology by Geschwind and Galaburda, but they did not analyze the cause [32].
A study by Xie et al found that women with a lower bilateral digit ratio (2D:4D) were more likely to suffer from migraines and tension headache.
There was no significant difference in the 2D:4D ratio between male migraineurs and tension headache sufferers and controls.
the results suggest that numerosity is a risk factor for migraine and tension headache, and suggest that prenatal estrogen and testosterone balance in utero may influence primary headache disorders in adults with physiological and psychological factors (Xie et al. The Journal of Headache and Pain (2015) 16:11 DOI 10.1186/s10194-015-0494-8)
.In their study of migraine patients, Kobus et al., according to sex, different ratios of prenatal sex steroids may be a risk factor for migraine in adults.concluded that women with migraine were exposed to higher levels of testosterone relative to estrogen in prenatal life, and men with migraine were exposed to higher levels of estrogen relative to testosterone in prenatal life.(Kobus et al. The Journal of Headache and Pain (2021) 22:119 https://doi.org/10.1186/s10194-021-01326-3). In our study, we could not determine the prenatal ratio of all types of sex hormones, and determining whether only the prenatal sex hormone ratio is sufficient for the origin of headaches remains the main issue for our further research.

5. Conclusion

Although many studies have been conducted on the relationship between headaches and sex hormones, the pathophysiology is not fully understood.
Our conclusion from our study is that women with a low 2D:4D ratio, i.e., prenatal testosterone elevation (migraine-induced MOH: right arm: 0.96±0.03 and 1.01± 0.03 p‹0.0001;left hand: 0.97±0.02 and 1±0.02 p‹0.0001; MOH from tension headache: right arm: 0.94±0.02 and 1.01±0.03 p‹0.0001;left arm: 0.96±0.02 and 1±0.02 p‹0.0001) and vice versa men with low prenatal testosterone and numerical ratio 1≤ (migraine-induced MOH: die ng arm: 1±0.06 vs 0.97±0.02 p=0.0035;left hand: 1.01±0.06 and 0.94±0.02 p‹0.0001; MOH from tension headache: right arm: 1.01±0.03 and 0.97±0.02 p‹0.0001;left hand: 0.98±0.04 and 0.94±0.02 p‹0.0001) are prone to abuse headaches.This suggests that prenatal estrogen-testosterone balance is a risk factor in the development of abuse headaches in adults. In addition, our study showed that these changes in number ratio were reliably different in patients with abuse headache compared to primary headache.(migraine-induced MOH and women with migraine: right arm: 0.96±0.03 and 0.98±0.03 p‹0.0001; left arm: 0.97±0.02 and 0.98±0.03 p‹0.0001;in men: right hand: 1±0.06 and 0.97±0.04 p=0.0173; left hand: 1.01±0.06 and 0.96±0.03 p=0.0007; MOH and tension headache caused by tension headache:in women: right hand: 0.94±0.02 and 0.97±0.03 p‹0.0001; left hand: 0.96±0.02 and 0.98±0.03 p‹0.0001;men: right hand: 1.01±0.03 and 0.97±0.02 p‹0.0001; left hand: 0.98±0.04 and 0.96±0.01 p‹0.0001).Our research complements the research on the role of sex hormones in the origin of headaches.

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