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ORIGINAL ARTICLE

Migraine and Subclinical Hypothyroidism: A Possible Co-morbidity

Engy M. Emad[1*], Mayada M. Mousa[2] , Nahed Shehta [1]
Engy Mohamed Emad
Department of Neurology, Faculty of Medicine, Zagazig University, El Sharkia, Egypt.
Mayada Mohamed Mousa
Department of Internal Medicine, Faculty of Medicine, Zagazig University, El Sharkia, Egypt.
Nahed Shehta
Department of Neurology, Faculty of Medicine, Zagazig University, El Sharkia, Egypt.

Corresponding Author
Engy Mohamed Emad
Address: Department of Neurology, Faculty of Medicine, Zagazig University, El Sharkia, Egypt.
Tel: 01205202639
E-mail: engyesol79@gmail.com
http://Orcid.org/0000-0002-8304-7490

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ABSTRACT

Introduction: Migraine and subclinical hypothyroidism (SCH) are common medical diseases, both share similar pathophysiological changes. **Aims**: To estimate the frequency of SCH among migraine patients and to evaluate the impact of SCH on migraine as regard severity and disability. **Methods**: Using a case control strategy, 130 patients with migraine and 130 healthy control subjects were recruited. Measurement of thyroid hormones levels was done for all the participants. Numerical Pain Rating Scale (NPRS) was used to detect the intensity of pain. Migraine severity and disability in different activity domains were assessed by Migraine Severity Scale (MIGSEV) and Headache Disability Index (HDI), respectively and patients' response to migraine treatment was evaluated by Headache Under-Response to Treatment Questionnaire (HURT). **Results:** The frequency of SCH was significantly higher among migraine patients than control subjects (p=0.002; OR=2.89; at 95% CI). Intensity of pain and migraine disability were significantly high in migraine patients with SCH when compared to migraine patients without SCH (p=.0001, p= 0.01, respectively). Most of migraine patients with SCH had grades II and III of MIGSEV scale (p=0.01, p= 0.04). The control of migraine was not good in 44.8% of the group with SCH versus 19.4% of the group without SCH (p=0.005). **Conclusions:** Subclinical hypothyroidism is more frequent among patients with migraine in respect to control subjects. Moreover, SCH has negative impacts on migraine regarding severity and disability.

Key words: Migraine; Subclinical hypothyroidism; Migraine disability.

INTRODUCTION

Migraine is one of the most prevalent neurological disorders that cause considerable physical and psychological functional impairment **[1]**. Based on the Global Burden of Disease Survey, approximately 1.04 billion patients suffer from migraine [2], with global prevalence of 14.7% in female and 6.9% in males **[3].** Migraine is ranked as the second leading cause of disability in both gender and the first cause of global lost of healthy life in females, worldwide **[4]**. Migraine has negative impact on quality of life, social activities, occupational and academic life. Migraine is imposing marked health and economic burdens as the annual costs of migraine accounts for 17 billion dollars **[5].**

Migraine is a neurovascular disorder characterized by persistent headache of moderate or severe intensity, unilateral location, and pulsating pain, lasting from hours to days, frequently associated with nausea, vomiting, photophobia, phonophopia and aggravated by physical activities **[6]**.

Migraine is usually coexisting with various morbidities such as epilepsy, myocardial infarction, stroke, fibromyalgia, bronchial

asthma, and depression **[7]**. Recently, novel study revealed that migraine could be a potent risk factor for development of both overt and subclinical hypothyroidism (SCH) **[8]**.

Subclinical hypothyroidism or compensated hypothyroidism is a mild grade of primary hypothyroidism. It is defined biochemically as a mild elevation of thyroid stimulating hormone (TSH) level with normal free thyroxine level (fT4) **[9]**. Subclinical hypothyroidism is a frequent medical disease with a prevalence ranging from 5 to 16% of the general population. Women and elderly individuals are linked with a higher frequency of SCH **[10]**. Despite the fact that SCH is purely a biochemical diagnosis but it has been shown to be associated with fatigue, mild deterioration of working memory and mild depressive disorders. In addition, SCH linked to different comorbidities such as cardiovascular, cerebrovascular and renal diseases, probably related to mild grade inflammation and endothelial dysfunction **[11]**

Recently, great attention has been devoted to bidirectional relation between migraine and SCH including underlying pathophysiological changes that affect immune and autonomic nervous system **[7]**.

The aim of this study was to estimate the frequency of SCH among migraine patients and to evaluate the impact of SCH on migraine as regard severity and disability.

Methods

In this case- control study, we examined one hundred and thirty patients with migraine and one hundred and thirty healthy control subjects in Neurology Department and Neurology outpatient clinic of Zagazig University Hospitals. The diagnosis of migraine based on the International Classification of headache Disorders (ICHD)-III beta criteria- third edition **[12]**.

The control group was recruited among relatives of the patients or other patients referred to outpatient clinic for complains other than migraine or headache. The control subjects were matched to the patients regarding age and gender.

The inclusion criteria of this study included subjects of both gender with age ranging from 18 to 55 years. Exclusion criteria were; pregnancy , abnormal neurological examination, secondary headache, co-morbid illness known to affect thyroid hormones level such as renal diseases, overt hypothyroidism or hyperthyroidism, using of medication that could affect thyroid hormones levels such as Propranolol ,lithium and Amiodarone, 2 months prior to the study.

Clinical assessment

All the patients underwent general and neurological examination, full history taking focusing on duration of migraine, headache characteristics, frequency, Prophylactic and therapeutic migraine medication used. Infrequent migraine attacks were defined as one attack occurred per month on average less than 12 days per year. Frequent attacks were defined by more than 10 attacks per month with at least 10 attacks occurred within 1 -14 days per month for more than 3 months on average (12 to less than 180 days / year). Chronic migraine was defined as attacks of migraine that re-occurred > 15 days per month for more than 3 months **[8]**.

To detect the intensity of pain during migraine attacks, Numerical Pain Rating Scale (NPRS) was used **[13]**. Patient rated their pain on an eleven-point numerical scale. Zero indicates no pain and 10 represents the worst imaginable pain. Migraine severity was assessed by Migraine Severity Scale (MIGSEV) **[14]**. It is a scale measuring the intensity of migraine attacks and the resistance or tolerability to treatment. Assessment of migraine related disability in different activity domains was performed by using Headache Disability Index (HDI) **[15]**. It is a 25-item questionnaire, measuring burdens of headache during and in between attacks. It evaluated the functional and emotional impairment in the patients' life. The Headache Under-Response to Treatment (HURT) Questionnaire is self-administered questionnaire that was used to evaluate current headache outcomes and measure response to migraine treatment **[16].** According to the patients' answer the

migraine control was labeled as good headache control, better management is needed, not good headache control and disabling headache.

Laboratory assays

Five ml of venous blood were collected from all the participants included in this study, in the morning under complete aseptic condition. Electrochemiluminescence assay was performed to measure Thyroid stimulating hormone (TSH), free triiodothyronine(fT3) and free thyroxine (fT4) levels by Cobas 8000 module e (602). The normal reference values for TSH, fT4 and fT3 were; 0.5-5Mu/L, 0.8- 1.9 ng/dl, and 2.3-4.2 pg/ml, respectively. Subclinical hypothyroidism was defined as high TSH level (TSH > 4.5mU/L) with normal fT4 level **[17].**

All the participants were informed about the study and written consent were provided. Institutional Review Board, Faculty of medicine Zagazig University approved this study (ZU-IRB#9032). The study was done according to the code of Ethics of World Medical Association (Declaration of Helsinki) for the studies involving humans.

Statistical analysis

The statistical analysis of that study based on IBM SPSS (Statistical Package for the social sciences) statistics for windows, version 23.0 IBM Corp, Armonk, NY: USA. Quantitative data were expressed as the mean ± SD and for qualitative data we used number and percentage. Shapiro Walk test was used to check the normality of Continuous data. The frequency of SCH among migraine patients was assessed by using Odds ratio (OR) with 95% confidence intervals (CIs). The statistical significance of differences between the groups was detected by using Chi-square test or Fisher Exact test to compare proportions, Student's t test to compare continuous data and Mann Whitney U test to compare non-normally distributed variables. The significance level assumed when p value is less than 0.05.

RESULTS

Demographic data of all participants was summarized in **Table 1.** No significant differences in age (p=0.532**),** gender (p= 0.67), BMI (p= 0.61) were found between migraine patients and control subjects.

Patients with migraine showed a significantly high TSH level in comparison with control group (3.3±2.7 Mu/L vs. 1.98±1.48 Mu/L respectively, p=0.0001). However fT4 and f T3 levels did not show any significant differences when compared patients to control subjects (1.33±0.34 ng/dl vs. 1.34±0.34 ng/dl and 3.35±0.43 pg/ml vs. 3.32±0.36 pg/ml, p=0.651, 0.572, respectively) **(Table 2)**.

Among migraine patients, there were 98 (75.4%) patients had normal thyroid function, 29 (22.3%) had SCH and 3(2.3%) patients had overt hypothyroidism. Control subjects were distributed as 117(90%) subjects with normal thyroid function, 12(9.2%) with SCH, and 1(0.8%) with overt hypothyroidism. The statistical analysis evaluating SCH frequency by using Odds ratio revealed that patients with migraine showed a higher frequency of SCH (2.98 times) than control subjects (P= 0.002). However there was no significant difference between two groups regarding overt hypothyroidism frequency **(Table 3)**.

By comparing migraineurs with and without SCH, we found no significant differences as regard age (p= 0.94), BMI (p= 0.493), gender (p= 0.44), marital status (p=0.56), using of Contraceptive pills (p=0.94), smoking status (p= 0.99) and prophylactic migraine medication (p= 0.99). Migraine patients with SCH had higher TSH level than migraineur without SCH (6.7 Mu/L vs.1.8 Mu/L, p= 0.0001), with no significant differences between the two groups regarding fT4 and fT3 level (p=0.138, p= 0.676, respectively) **(Table 4).**

The analysis of headache features assessment did not show significant differences between migraine patients with and without SCH in migraine duration (p= 0.77) or clinical subtypes of migraine (p= 0.62). Among migraine patients with SCH there were twelve (41.4%) patients had frequent migraine and 3(10.3%) had chronic migraine versus 30(30.6%) patients had frequent migraine and 5(5.1%) had chronic migraine in migraine patients without SCH. However the statistical

analysis did not demonstrate any significant differences between two subgroups regarding migraine frequency (p=0.26). The mean NPRS score was significantly higher in migraine patients with SCH than migraineur without SCH (7 vs. 4, p = 0.0001). According to MIGSEV scale, grade I was significantly higher among migraine patients without SCH compared to patients with SCH (63.3 % vs. 20.75%, p = 0.001). While grade II and grade III were significantly higher among migraine patients with SCH on comparison to migraineurs without SCH (48.3% vs.24.5%, and 31% vs.12.2%, p = 0.01, 0.04 respectively), indicating significant increase of the migraine severity in the migraine patients with SCH. The migraine patients with SCH had a higher HDI score than migraine patients without SCH (40 vs. 29, p=0.012). Based on HDI grades , migraine patients without SCH showed a higher frequency of mild grade as compared to migraine patients with SCH (p= 0.002). While migraine patients with SCH showed a higher frequency of moderate grade than patients without SCH (p= 0.01). According to HURT questionnaire, migraine control was good in 17.3% of migraine patients with SCH versus 45.9% of migraine patients without SCH with significant differences between them (p=0.005). The control of migraine was not good in 44.8% of the group with SCH versus 19.4% of the group without SCH with significant differences between them (p=0.005). However there was no significant difference between the two groups as regard the number of migraine patients who needed better migraine management (p= 0.75) **(Table 5)**.

Tables

Table1. Demographic data of patients and healthy control subjects.

	Studied groups		**χ^2**	**p-value**
	Migraine group n.130	Healthy control group n.130		
Age per years Mean±SD	41.55±7.5	40.73±8.52	0.81 ^	0.41
Gender				
males	39(30%)	42(32.3%)	0.161	0.67
females	91(70.0%)	88(67.7%)		
BMI (kg/m2) Mean±SD	27.76±2.21	27.19±2.14	0.69^	0.61

SD: Standard deviation, χ 2:Chi square test, ^ t: t test of significant, significant p<0.05

Table2. Thyroid hormones profile among migraine patients and control subjects.

	Studied groups		**u**	**p-value**
	Migraine group n.130	Healthy control group n.130		
TSH (Mu/L) Mean±SD	3.3±2.7	1.98±1.48	4.523	0.0001
fT4 (ng/dl) Mean±SD	1.33±0.34	1.34±0.34	0.452	0.651
fT3 (pg/ml) Mean±SD	3.35±0.43	3.32±0.36	0.449	0.572

SD: Standard deviation, U:Mann-Whitney U, significant p<0.05

Table 3. Frequency of SCH among migraine patients and control subjects.

		Studied groups		χ^2	Odds ratio (95% C.I.for EXP(B))
		Migraine group n.130	Healthy control group n.130		
Normal	n	98	117	9. 2 P=0.002	1
	%	75.4%	90.0%		
Subclinical Hypothyroidism	n	29	12		2.89(1.4-5.9)*
	%	22.3%	9.2%		
Overt hypothyroidism	n	3	1		3.58(0.37-35)
	%	2.3%	0.8%		

χ 2: Chi square, SCH: Subclinical hypothyroidism,*significant p<0.05, 3.58(0.37-35): not significant

Table 4. Clinical and laboratory data of migraine patients with and without SCH.

variables	Migraine patients with SCH (n= 29)	Migraine patients without SCH (n= 98)	t/χ^2	p-value
Age per years Mean±SD	41.24±6.42	41.36±7.78	0.073	0.94
BMI (kg/m2) Mean±SD	27.96±2.25	27.64±2.2	.688	.493
Gender				
Males	7 (24.1%)	31 (31.6%)	0.59	0.44
Females	22 (75.9)	67 (68.4)		
Marital status				
Married	26 (89.7%)	82 (83.7%)	f	0.56
Single	3 (10.3%)	16 (16.3%)		
Contraceptive pills				
no	22 (75.9%)	75 (76.5%)	0.006	0.94
yes	7 (24.1%)	23 (23.5%)		
Smoking				
No	27 (93.1%)	92 (93.9%)	f	0.99
Yes	2 (6.9%)	6 (6.1%)		
Prophylactic migraine medication			f	0.99
yes	3 (10.3%)	10 (10.2%)		
no	26 (89.7%)	88 (89.8%)		
Thyroid hormones profile				
TSH (Mu/L) Mean±SD	6.7	1.8	U= 8.165	.0001
fT4 (ng/dl) Mean±SD	1.27±0.29	1.37±0.32	1.491	.138
fT3 (pg/ml) Mean±SD	3.41±0.48	3.37±0.35	0.422	.676

SD: Standard Deviation, χ 2: Chi square test, f: Fisher Exact test, t: t test of Significant, U: Mann Whitnney u test, SCH: subclinical hypothyroidism, significant p<0.05 .

Table 5. Comparison between migraine patients with and without SCH regarding migraine features and clinical scales.

	Migraine patients with SCH (n = 29)	Migraine without SCH (n= 98)	χ^2	p-value
Migraine features				
Duration migraine (years)	9	9	0.29	0.77
Migraine subtypes				
With aura	10 (34.5%)	29 (29.6%)	0.25	0.62
Without aura	19 (65.5%)	69 (70.4%)		
Migraine frequency				
Infrequent	14 (48.3%)	63 (64.3%)		
Frequent	12 (41.4%)	30 (30.6%)	2.7	0.26
Chronic	3 (10.3%)	5 (5.1%)		
NPRS score Mean±SD	7	4	4.063	.0001
MIGSEV				
Grade 1	6 (20.7%)	62 (63.3%)	16.58	(0.001)+
Grade II	14 (48.3%)	24 (24.5%)	P=0.0001	(0.01)++
Grade III	9 (31%)	12 (12.2%)		(0.04)+++
HDI grade				
Mild	6 (20.7%)	58 (59.2%)	13.67	(0.002)+
Moderate	17 (58.6%)	32 (32.7%)	P=0.001	(0.01)++
Severe	6 (20.7%)	8 (8.1%)		(0.13)+++
HDI score Mean±SD	40	29	2.504	0.01
Hurt				
Good control	5 (17.3%)	45 (45.9%)		(0.005)+
Better management needed	11 (37.9%)	34 (34.7%)	10.48	(0.75)++
Not good control Disabling headache	13 (44.8%) -------	19 (19.4%) -------	P=0.005	(0.005)+++

SD: Standard Deviation , χ 2: Chi square test, f: Fisher Exact test , t :test of significant, U:Mann Whitnney u test, (grade1/mild)+ , (grade1I/ moderate)++ , (grade III/ severe)+++, NPRS:Numerical Pain Rating Scale, MIGSEV:Migraine Severity Scale, HDI: Headache Disability Index , Hurt: Headache Under-Response to Treatment, significant $p<0.05$,

DISCUSSION

In this study we detected a high frequency of SCH among migraine patients when compared to healthy control subjects. Our data showed that there were 22.3% of migraine patients had SCH versus 9.2% of healthy control subjects. Our results are in accordance with findings of **Abou Elmaaty et al**. **[8]** who found in their study of 212 patients of migraine and tension headache that the prevalence of SCH was 23.3% in the patients of headache versus 9% in healthy controls. **Khan et al**. **[18]** reported that 22% of patients with primary headache had SCH and 7.2% had overt hypothyroidism versus 11.2% had SCH and 1.2% had overt hypothyroidism in the healthy control group. Among few studies that evaluated the association between migraine and SCH, the study of **Fallah et al**. **[19]** conducted on 104

children with migraine is of great interest. The study showed that the prevalence of SCH was 24% among migraine patients and recommended to perform thyroid function tests to the children presenting with migraine as the SCH is considered as an exacerbating factor of migraine. In addition, **Mirouliaie et al**. in a cross sectional study **[20]** reported a high frequency of SCH in young patients with migraine.

Furthermore, our findings are in agreement with studies showing that in patients with SCH there was a high risk for developing migraine. **Rubino et al**. **[7]** investigated the prevalence of migraine in patients with SCH and the results of their study clearly suggested that those patients have a significantly higher lifetime risk of developing migraine in comparison with healthy subjects. **Rainero et al**. **[21]** found that the prevalence of migraine in 75 patients with SCH was 62%. **Lima Carvalho et al**. **[22]** pointed out that 35% of SCH patients developed migraine

There are different probable mechanisms that could explain the association between migraine and subclinical hypothyroidism including unidirectional or bidirectional relationships and the common genetic and environmental factors **[23]**.

The inflammation that occurs during migraine could predispose to autoimmune thyroiditis. Several clinical evidences indicated elevation of C-reactive protein and changes of T lymphocytes proportions in migraineur in between attacks as well as marked elevation of cytokines and leukocytes adhesion molecules levels during migraine attacks **[24]**. Likewise, similar alteration of cytokines and leukocytes cell surface receptors exists in autoimmune thyroiditis **[23]**. According to **Taylor et al**. **[25],** autoimmune thyroiditis is considered one of the primary causes of SCH. A pervious human study detected a significant alteration of immunoregulation and regulatory CD4+ and CD25+ T cells levels in migraine pathogenesis [26]. Intriguingly, the same CD4+ and CD25+ T cells have a potential role in the development of autoimmune thyroiditis in experimental studies [7].

Migraine and SCH could be related through genetics links. Elevated serum homocysteine level was detected in migraine and SCH **[27, 28].** Genetic analysis linked mutation of methyltetrahydrofolate reductase (MTHFER) to migraine and hyperhomocystemia**.** Therefore, hyperhomocystemia as result of MTHFER gene mutation might contribute to development of both migraine and SCH **[23]**. Thyroid autoimmune diseases are mediated by polymorphisms in different genes regulating immune system, such as human leukocyte antigen (HLA) gene, cytokines genes, and thyroid specific genes **[29]**. Interestingly, polymorphisms of HLA genes have also been detected in the migraine **[30]**.

A previous experimental study reported that air pollutants such as bisphenol A (BPA) could affect function of thyroid peroxidase enzyme, the key enzyme that is involved in thyroid hormone formation **[31]**. Based on the study of **Vermeer et al**. **[32]** BPA is one of the trigger factors for migraine development.

On the other hand, there are controversial data regarding the frequency of SCH among migraine patients. **Ekici and Cebeci**. **[33]** reported that SCH was not a common comorbidity of migraine in both children and adolescents. According to Turkish study, only 1.3% and 0.4% of migraineurs had SCH and overt hypothyroidism, respectively **[34]**. Another Norwegian study demonstrated that the frequency of headache decreased with elevation of TSH level **[35]**.

To best of our knowledge, few studies that evaluated SCH effect on the migraine. The present study showed that the intensity of pain during migraine attacks was more sever in migraine patients with SCH than migraine patients without SCH. In addition, our findings indicated that the severity of migraine was more significant in migraineurs with SCH on comparison to migraineurs without SCH. The pain threshold is regulated by mutual modulation of noradrenergic and serotonergic brain stem nuclei. Therefore low adrenergic tone in hypothyroid status could up regulate serotonergic tone with subsequent pain development **[36].** Additionally, thyroid hormones have a neuromodulatory role in the

central nervous system and TSH receptors are distributed in the cortical neurons and cerebral vasculature. Hence, Hpothalamic – pituitary – thyroid axis is considered to play an important role in pain control systems **[7]**.

Assessment of quality of life and disability has become a necessary complementary step for the evaluation of migraine burden. Our study showed a significant migraine disability in migraine patients with SCH when compared to patients without SCH, indicating significant SCH related disability in migraine patients. Previous studies demonstrated that SCH has negative impact on health related quality of life **[37, 10].** Based on the study of **Gulseren et al**. **[38]** the obvious risk factors for disability in daily activities in SCH were fatigue, muscle ache, memory impairment and depressive symptoms. **Pradeep et al**. **[2]** pointed out that migraine disability due to severe headache could be related to associating physical fatigue that could deteriorate the daily activities of the patients. The disability of migraine could also be attributed to migraine related symptoms such as, emotional distress, anxiety and depression **[39].** Consecutively, concurrent presence of migraine and its associated symptoms could increase the magnitude of subclinical hypothyroidism related disability.

Based on HURT questionnaire, we found that migraine patients with SCH did not achieve good response to migraine treatment when comparing to migraineurs without SCH. In this context, **Mirouliaie et al**. **[20]** drew attention to the fact that subclinical hypothyroidism treatment was effective in reducing the frequency, duration, and severity of migraine attacks. The improvement of migraine after SCH treatment could be due to serotonin reducing effect of thyroid hormone, thyroxine antinociceptive effect, and decreasing of cerebral excitability associating with hypothyroidism **[18]**.

CONCLUSIONS

The results of this study clearly suggested that SCH is a common comorbidity of migraine as we detected a higher frequency of SCH among migraine patient compared to control subjects. In addition, the obvious migraine's severity and disability encountered in migraine patients with SCH indicated that SCH has negative impact on migraine. Therefore, checking thyroid hormones levels is necessary step in migraine management.

Conflict of interest

The authors declared that they have no conflicts of interest with respect to the authorship and/ or publication of this article.

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Author contributions

All the authors carried out this work. Engy M. Emad and Nahed Shehta designed the study and collected patients. Engy M. Emad and Mayda A Mousa conduct analysis and interpretation of the data and write the manuscript. All authors were involved in drafting the article and revising it for important intellectual content and all authors read and approved the final version to be published.

Availability of data

Data supporting the results of this article are included within article.

Ethics approval and constant to participate

The study was approved from the Institutional Ethics of the faculty of medicine. Zagazig University (ZU-IRB#9032). Written informed consent was obtained from all the participants after explaining the details and benefits as well as risks to them. The study was done according to the code of Ethics of World Medical Association (Declaration of Helsinki) for the studies involving humans.

REFERENCES

1) Woldeamanuel Y and Cowan R. Migraine affect 1 in 10 people worldwide featuring recent rise: a systematic review and meta-analysis of community-based studies involving 6 million participants. J.Neurol. Sci. 2017 ; 372:307–315.
2) Pradeep R, Nemichandra S, Harsha S, and Radhika K. Migraine disability, Quality of life, and its predictors. Ann. Neurosci J. 2020; 27(1): 18-23.
3) Burch R, Rizzoli P, and Loder E. The prevalence and impact of migraine and severe headache in the United States: figures and trends from government health studies. Headache. 2018; 58(4):496-505.
4) Steiner T , Stovner J, Jensen R, Uluduz D and Katsarava Z. Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. J Headache Pain. 2020; 21:137.
5) EL-Metwally A , Toivola P, AlAhmary K, Bahkali S, AlKhathaami A, Al Ammar S, et al,. The Epidemiology of Migraine Headache in Arab Countries: A Systematic Review. Sci. World J. 2020. Vol.2020.

6) Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2013; 33(9):629-808.
7) Rubino E, Rainero I, Garino F, Vicentini C, Govone F, Vacca A, et al. Subclinical hypothyroidism is associated with migraine: a case-control study. Cephalalgia. 2019; 39:15–20.
8) Abou Elmaaty A, Flifel M, Belal T and Zarad C. Migraine and tension headache comorbidity with hypothyroidism in Egypt. Egypt J Neurol Psychiatr Neurosurg . 2020; 56:78-85.
9) Cooper D and Biondi B. Subclinical thyroid disease. Lancet. 2012; 379: 1142–1154.
10) Danicic J , Inder W, and Kotowicz M. Impact of subclinical hypothyroidism on health-related quality of life: a narrative review. Intern. Med. J. 2021;51: 1380–1387.
11) Biondi B, Cappola A, and Cooper D. Subclinical hypothyroidism. JAMA. 2019; 322(2):153-160.
12) Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211.
13) Jensen MP and McFarland C. Increasing the reliability and validity of pain intensity measurement in chronic pain patients. Pain. 1993; 55:195-203.
14) El Hasnaoui A, Vray M, Richard A, and MIGSEV Group. Assessing the severity of migraine: development of the MIGSEV scale. Headache. 2003;43:628–35.
15) Jacobson G, Ramadan N, Aggarwal S, and Newman C. The Henry Ford Hospital headache disability inventory (HDI). Neurology. 1994;44:837-842.
16) Buse D, Mark Sollars C, Steiner T, Jensen R, Al Jumah M, and Lipton R. Why HURT? A Review of Clinical Instruments for Headache Management. Curr Pain Headache Rep. 2012; 16:237–254.
17) Salvatore D, Davies TF, Schlumberger MJ, Hay ID, and Larsen PR. Thyroid physiology and diagnostic evaluation of patients with thyroid disorders. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. Williams Textbook of Endocrinology. 12th ed. Philadelphia, PA: Elsevier Saunders; 2016: chap 11.
18) Khan H, Shah P, Bhat H , and Imran A. Association of hypothyroidism in patients with migraine and tension- type headache disorders in Kashmir, North India. Neurol. Asia. 2015; 20(3):257-261.
19) Fallah R , Mirouliaei M, Bashardoost N and Partovee M. Frequency of subclinical hypothyroidism in 5- to 15-year-old children with migraine headache. J Pediatr Endocr Met 2012; 25(9-10): 859–862**.**
20) Mirouliaie M, Fallah R, Partovee M, Ordooei M. Efficacy of Levothyroxine in Migraine Headaches in Children with Subclinical Hypothyroidism. Iran J Child Neurol Autumn. 2012; 6(4):23-26 .
21) Rainero I, Rubino E, Vicentini C, Garino F, Ragazzoni F, Lorenz P, et al. Prevalence of migraine in subclinical hypothyroidism: a case-control study. J.Headache Pain. 2015; 16(Suppl 1):A81.
22) Lima Carvalho M, de Medeiros J, Valenca M. Headache in recent onset hypothyroidism: prevalence, characteristics and outcome after treatment with levothyroxine. Cephalalgia. 2017; 37:938–46.
23) Martin A T, Susan M. Pinney, Xie C, Herrick R, Bai Y, et al. Headache disorders may be a risk Factor for the development of new
onset hypothyroidism. Headache. 2017; 57:21-30.
24) Sarchielli P, Alberti A, Baldi A, Coppola F, Rossi C, Pierguidi L, et al. Proinflammatory cytokines, adhesion molecules, and lymphocyte integrin expression in the internal jugular blood of migraine patients without aura assessed ictally. Headache. 2006; 46:200-207.
25) Taylor P, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus J, Dayan C, et al. Global epidemiology of hyperthyroidism and hypothyroidism. Nat Rev Endocrinol 2018; 14: 301–16.
26) Arumugam M and Parthasarathy V. Reduction of CD4+ CD25+ regulatory T-cells in migraine: Is migraine an autoimmune disorder? J Neuroimmunol 2016; 290: 54–59..
27) Lippi G, Mattiuzzi C, Meschi T, Cervellin G,and Borghi L. Homocysteine and migraine. A narrative review. Clin Chim Acta. 2014;433:5-11.
28) Zhou Y, Chen Y, Cao X, Liu C, and Xie Y. Association between plasma homocysteine status and hypothyroidism: A meta-analysis. J Neurol Sci 2014;7:4544-4553.
29) Lee H, Li C, Hammerstad S, Stefan M, and Tomer Y. Immunogenetics of autoimmune thyroid diseases: A comprehensive review. J Autoimmun 2015; 64: 82–90.
30) Rainero I, Fasano E, Rubino E, Rivoiro C, Valfre W, Gallone S, et al. Association between migraine and HLA-DRB1 gene polymorphisms. *J Headache Pain*. 2005; 6: 185–187.
31) Song M, Kim Y, Park K, and Ryu C. Changes in thyroid peroxidase activity in response to various chemicals. J Environ Monit. 2012; 14:2121-2126.
32) Vermeer L, Gregory E, Winter M, Mc Carson K, and Berman N. Exposure to bisphenol A exacerbates migraine-like behaviors in a multibehavior model of rat migraine. Toxicol Sci. 2014; 137:416-427.
33) Ekici B, and Cebeci A. The debate on the link between subclinical hypothyroidism and childhood migraine: is initial endocrinological evaluation necessary for children with migraine? Acta Neurol Belg. 2015; 115: 123–7.

34) Toprak D, Demirkukan K, and Ellidokuz H . Is it important to test thyroid function tests in migraineurs? TJFMPC.2007; 4:47–51.
35) Hagen K, Bjoro T, Zwart J, Vatten L, Stovner J,and Bowim G. Low headache prevalence amongst women with high TSH values. Eur J Neurol.2001; 8:693–699.
36) Singh SK. Prevalence of migraine in hypothyroidism. J Assoc of Phys of India. 2002; 50:1455–6.
37) Kelderman-Bolk N, Visser T, Tijssen J, and Berghhout A. Quality of life in patients with primary Hypothyroidism related to BMI. Eur J Endocrinol. 2015; 173:507-515.
38) Gulseren S, Gulseren L, Hekimsoy Z, Cetinay P, Ozen C, and Tokatlioglu B. Depression, anxiety, health-related quality of life, and disability in patients with overt and subclinical thyroid dysfunction. Arch Med Res 2006; 37: 133–9.
39) Minen M, Begasse De Dhaem O, Kroon Van Diest A, Powers S, Schwedt J, Lipton R, et al. Migraine and its psychiatric comorbidities. J Neurol Neurosurg Psychiatry 2016; 87: 741–749.

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