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Assessment of the Relationship Between Genetic Determinants of Migraine and Thyroid Dysfunction - Review

1. Justyna Kwiecień [JK]: Department of Internal Medicine, District Medical Center in Grójec, Piotra Skargi 10 street, 05-600 Grójec https://orcid.org/0000-0002-1969-209X
kwiecien.jstn@gmail.com

2. Beata Getka [BG]: Military Medical Institute, Szaserów 123 street, 04-349 Warszawa https://orcid.org/0009-0004-1951-7680
beata.getka@gmail.com

3. Michał Łata [MŁ]: District Medical Center in Grójec, Piotra Skargi 10 street, 05-600 Grójec https://orcid.org/0009-0001-0462-1141
michal.lataa@gmail.com

4. Kinga Przyborowska [KP]: The National Institute of Medicine of the Ministry of Interior and Administration, Wołoska 137 street, 02-507 Warszawa https://orcid.org/0009-0009-8320-1580
kmprzyborowska@gmail.com

5. Katarzyna Wiejak [KW]: Medical University of Warsaw, UCK WUM, Stefana Banacha 1a street, 02-097 Warszawa https://orcid.org/0009-0006-2128-7612
kasia.wiejak@gmail.com

6. Mateusz Rukat [MR]: Mazovian Provincial Hospital in Siedlce, Poniatowskiego 26 street, 08-110 Siedlce https://orcid.org/0009-0003-7742-6499
mateuszrukat97@gmail.com

Abstract

Introduction and objective: The purpose of this paper is a systematic review of articles and research in the context of the relationship between genetic determinants of migraine and thyroid dysfunction.

Materials and methods: A non-systematic review of the scientific literature was carried out according to the following keywords: PubMed was searched and 76 articles published up to 2023 were analyzed.

Description of the state of knowledge: Epidemiological studies confirm the co-occurrence of migraine and thyroid dysfunction, especially hypothyroidism, which are considered to be diseases with a strong genetic background. Thyroid function parameters such as TSH and fT4 are susceptible to genetic influences. However, there is a lack of consistent interpretation of the observational results, which highlights the need for further research. Analysis of gene overlaps and links between headache and thyroid function, based on GWAS data, could shed light on the complex genetic interactions underlying this association.

Summary: The genetic associations revealed in the study enhance our comprehension of the intricate relationship between migraine and thyroid dysfunction. These findings not only offer the prospect of developing biomarkers for identifying migraine patients who might benefit from thyroid hormone therapy but also underscore the promising potential of future genetic studies in providing biological insights to advance clinical decision-making in understanding and addressing these interconnected phenomena.

Keywords: Migraine; Thyroid dysfunction; Hypothyroidism; Genetics; candidate gene studies; epidemiological studies.

1. Introduction

1.1 Migraine

Globally, the burden of neurological diseases, as measured by the absolute number of DALYs (sum of years lost [YLL] and years lived with disability [YLD]), continues to grow. The most important neurobiological factors of DALY include stroke (42.2%) and migraine (16.3%) [24, 25]. Headaches account for 4.4% of all medical consultations worldwide, 20% of consultations in neurology clinics, and 5% of hospital admissions [28,29,30]. The prevalence of migraine in the general population is estimated to be 12-18%. Migraine is more common in women, with a male-to-female ratio of 0 ·7 [23,24, 27]. It is one of the most common neurological diseases, the main characteristic symptom of which is the appearance of attacks of unilateral, throbbing headache of great intensity. The pain can last from a few to 72 hours. Accompanying neurological symptoms such as photophobia, phonophobia, and vegetative disorders, especially those affecting the functioning of the digestive system, such as nausea and vomiting, are common. Pain may be preceded by focal neurological symptoms, such as flashes in the field of vision, visual disturbances, speech disorders, or features of hemiparesis. In the case of their occurrence, it is a migraine with aura [31,32,33,34].

The diagnosis of migraine is based on clinical criteria. Due to the heterogeneous nature of the disease, the diagnosis of migraine headache, which is the main symptom of the disease, does not have to be the most bothersome of the symptoms during the duration of a migraine attack in all patients [6, 7]. Migraine consists of a succession of key phases: the warning (prodromal) phase, the aura, the pain, and the postdromal phase [8,9], which often overlap. Migraine is a neurological disease that is associated with significant disability and loss of productivity, ranking eighth in the world and fourth in women in terms of strain. It is therefore a huge economic burden worldwide [26].

1.2 Thyroid dysfunction

The thyroid gland is an odd endocrine organ responsible for the secretion of triiodothyronine (T3) and thyroxine (T4). The function of the thyroid gland is controlled by thyrotropin (TSH) secreted by the glandular part of the pituitary gland. T3 and T4 increase the metabolic rate of the cell. Thyroid hormone (TH), produced by the thyroid gland, plays a key role in various physiological processes, such as metabolism and brain development, that occur in all vital

organs and systems. Optimal TH levels are extremely important for the proper functioning of these processes, especially during the development of the nervous system [40,41,42]. Thyroid diseases are among the most common endocrine disorders. Their incidence has increased over the last two decades [11]. Drugs acting on the endocrine system are among the top prescribed drugs [14]. The most common thyroid gland dysfunctions include hypothyroidism and hyperthyroidism [2].

Hyperthyroidism recurs in 1.3% of the population in the USA, 0.78% in China, and 0.8% in Europe [15,16,17,18]. This condition is characterized by an increase in basal metabolic rate and increased oxidative stress through the induction of mitochondrial enzymes overpowered by excess thyroid hormones. This results in increased activity in the nervous, circulatory, and digestive systems.

Hypothyroidism affects as much as 5% of the general population (0.3-3.7% in the USA and 0.2-5.3% in Europe) and accounts for about 30% to 40% of cases in endocrinology practice [19]. It is estimated that 5% of cases in the general population remain undiagnosed. Subclinical hypothyroidism occurs in approximately 12% of the adult population. In the group of patients with hypothyroidism, more than 99% suffer from its primary form [12,20,21,22]. Common symptoms in adults include fatigue, lethargy, cold intolerance, weight gain, constipation, voice changes, dry skin, and muscle aches. The clinical picture may vary depending on gender, and age, among others. The subjective nature of the symptoms of this disease varies depending on the level of thyroid hormones. Clinical symptoms in thyroid diseases may present themselves as a life-threatening condition, but they may also be imperceptible to the affected person. The clinical picture may vary depending on gender, age, and many other factors. Studies have shown a duality of correlation between migraine and disorders of the secretory function of the thyroid gland [13].

1.3 Genetic background in migraine

Migraine is a complex disruption of brain function that can be explained by the interaction of hereditary and environmental factors [10]. In the case of monogenic migraines, such as familial migraine or migraine with aura associated with hereditary small vessel disorders, identified genes encoding proteins present in neurons, glial cells, or vessels play a key role in increasing susceptibility to spreading cortical depression [23,38, 39]. The results of studies on monogenic depression indicate an important role of the neurovascular unit in this disease. Genome-wide association studies, on the other hand, identify numerous susceptibility variants,

each of which only slightly increases the overall risk of migraine. There are more than 180 known variants that fit into several complex molecular networks associated with migraine, primarily neuronal or vascular [35,36,37].

2. Materials and method

An unsystematic review of the scientific literature was carried out according to the following keywords: Migraine; Thyroid dysfunction; Hypothyroidism; Genetics; candidate gene studies; epidemiological studies. Key information from the review of articles and studies is presented.

PubMed was searched and 76 articles published up to 2023 were analyzed. Review, quantitative, and qualitative studies were included in the analysis. The criteria for qualifying records for the review were: the title, the content of the abstract, and the topic related to the relationship between genetic determinants of migraine and thyroid dysfunction.

In the last decade, studies have been conducted on the relationship between migraine and thyroid features, using observational and cross-sectional methods. Recent genome-wide association studies (GWAS) aimed to identify genetic factors associated with these traits, revealing increased co-occurrence of migraine and thyroid traits, as well as identifying SNPs (single nucleotide polymorphism) and genes associated with this phenomenon [1].

Analysis of GWAS statistics revealed a significant genetic correlation between migraine and hypothyroidism, hyperthyroidism, secondary hypothyroidism, and fT4. In addition, a meta-analysis of various traits and gene analysis revealed a common genetic basis for migraine and thyroid traits [3,4,5].

Causal studies have shown a significant association between migraine and hyperthyroidism and migraine and secondary hypothyroidism. Linkage Disequilibrium Score Regression (LDSC) tests confirmed a positive genetic correlation between migraine and hypothyroidism, which is consistent with previous case-control studies [62,63,64].

Pleiotropic loci common to migraine and thyroid traits were identified. Two pleiotropic areas were found for migraine and TSH, and as many as eleven for migraine and fT4. Three key pleiotropic regions were located on chromosome 9 (135.3–137 Mb), chromosome 6 (31.0–31.6 Mb), and chromosome 17 (15.0–16.4 Mb) [65].

New loci from the GWAS meta-analysis, including cross-traits, were translated to genes such as RERE, BTBD16, HTT, TGFB2, PFDN1, ATXN2, BRD3, and SLC14A2. For example, the RERE (arginine-glutamic acid dipeptide repeats) gene on chromosome 1p36, encoding a nuclear receptor coregulator, is associated with hyperthyroidism and migraine with aura [66,67]. The BTBD16 gene, associated with bipolar disorder, has been linked to both migraine and hypothyroidism. PFDN1 on chromosome 5 is associated with migraine and TSH as well as migraine and fT4. The exact role of these genes in migraine and thyroid traits is not fully understood, but their expression in brain and thyroid tissues suggests a potential impact on these conditions [68]. Genetic analyses showed an overlap of genetic factors between migraine and thyroid traits (pgen < 0.05). Of the genes with new loci, six (RERE, TGFB2, APLF, SLC9B1, SGTB, and BTBD16; migraine and hypothyroidism), three (GADD45A, PFDN1, and RSPH6A; migraine and TSH), and three (SSBP3, BRD3, and TEF; migraine and fT4) were considered statistically significant (pFCP < 2.04 × 10-6) [2] [69].

The TGFB2 gene is involved in the regulation of gene expression and GADD45A activates p38/JNK pathways associated with pain and inflammation [70].

Pathway analysis using overlapping genes for migraine and thyroid traits demonstrated links with the immune system and the ability to regulate them through immune mechanisms. Research confirms a two-way link between TH and immune regulation. Changes in C3 and C4 levels and total complement activity in migraine patients confirm complement system involvement [75].

A strong negative causal relationship between migraine and hyperthyroidism has been revealed, as well as a positive causal relationship between migraine and secondary hypothyroidism. This suggests possible shared geneti c mechanisms and causality. Although the mechanism(s) of this phenomenon are unknown, the role of the hypothalamus in the coexistence of migraine and thyroid dysfunction is being considered [74].

Activity of the limbic system and hypothalamus during a migraine attack has been observed, which is associated with hormonal changes and the menstrual cycle. Migraine correlates with neuroendocrine changes affecting TSH, testosterone, and growth hormone levels. Migraine pain transmitted to the hypothalamus can affect TSH and fT4 levels, which contributes to thyroid dysfunction in people with migraine [71,72,73].

Genetic analysis indicates that even small changes in fT4 levels in the reference range correlate with migraine. In the case of primary or secondary hypothyroidism, fT4 levels below the reference range or very high in hyperthyroidism correlate with migraine through other mechanisms. It is recommended to evaluate TSH and fT4 levels in patients with migraine, especially when symptoms of thyroid dysfunction are observed [76].

In a comparative analysis of genetic variants in CGAS vs. GWAS for migraine and thyroid traits, the TGFB1 gene (rs1800469) was found to be relevant at the genomically relevant level (GWS) for migraine only. The other three SNPs showed nominal significance for TSH and fT4 but did not reach the significance threshold [44,45,46]. The lack of replication of CGAS results in GWAS is likely due to the small number of samples (low statistical power) in CGAS, which can lead to false positive results [1,43]. It may also be due to the specificity of the studies for a particular population.

Among the variants observed in MTHFR candidate gene studies, rs1801133 (C677T) and the APOE E2/E4 polymorphism provided the most consistent evidence for association with migraine and thyroid features [47,48,49,50]. Similarly, observations of SNPs in THADA and ITPK1 associated with GWAS migraine and thyroid traits provided the most consistent evidence, especially the association of rs12712881 in THADA and rs11624776 in ITPK1 with migraine and TSH, and rs10186921 in THADA and rs6575306 in ITPK1 with TSH and migraine. These variants in THADA and ITPK1, while mutually confirming, were not conclusively associated with both migraine and thyroid dysfunction at the GWS level, with a low splicing balance between the two ($r2 = 0.9676$ and $r2 = 0.4754$, respectively) [51,52].

The interaction of the ovarian sex hormone, estrogen, with CGRP is also intriguing [53,54,55]. Healthy women showed a significant increase in CGRP compared to men and was further increased in women using hormonal contraceptives [56,57]. In contrast, lower estrogen levels have been reported in patients with menstrual migraine (MM), associated with a decrease in estrogen during the menstrual cycle. The role of estrogen in thyroid dysfunction is unknown; however, a study correlating thyroid dysfunction with MM showed a reduction in MM-related fT4 levels. Therefore, further research into the role of estrogen in thyroid dysfunction may provide a clearer picture of this issue [58,59,60,61].

In addition to future studies evaluating the interplay of MTHFR, APOE, THADA, and ITPK1 variants in large deep phenotyped cohorts, genetic analyses of thyroid-related gene overlap

studies for migraine and GWAS at the SNP, gene, and genome-wide levels have great potential to identify specific genetic risk factors and biological mechanisms underlying the association between migraine and thyroid dysfunction.

3. Conclusion

These genetic associations expand our understanding of the genetic relationship between migraine and thyroid dysfunction. In addition, they provide an opportunity to develop biomarkers that will allow the identification of patients with migraine who could potentially benefit from thyroid hormone therapy. Furthermore, they indicate that future genetic studies, based on different traits, have promising potential to provide biological information, which could advance our understanding of the relationship between these phenomena and support decision-making for clinical interventions. Additional research and advancements are required and anticipated in the upcoming years. It is hoped that this ongoing effort will further increase awareness regarding a multifaced phenomenon impacting millions of individuals globally.

Disclosures

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Conceptualization: Justyna Kwiecień, Michał Łata; methodology: Kinga Przyborowska, Katarzyna Wiejak, Mateusz Rukat; formal analysis: Beata Getka, Kinga Przyborowska, Justyna Kwiecień; investigation: Justyna Kwiecień; writing-rough preparation: Justyna Kwiecień, Michał Łata, Kinga Przyborowska, Katarzyna Wiejak; writing-review and editing: Beata Getka, Justyna Kwiecień, Mateusz Rukat; visualization: Justyna Kwiecień

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Board statement:

Not applicable - this review included an analysis of the available literature.

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