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ORIGINAL ARTICLE

High rates of (treated) hypothyroidism among chronic migraine patients consulting a specialized headache clinic: are we missing something?

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Abstract

Background Roughly three percent of episodic migraine patients evolve into the most burdensome chronic form of this condition every year. While some of the determinants behind this transformation are well established, others are still ill defined. Hypothyroidism is a prevalent endocrinological disorder that can both produce a secondary headache or aggravate a pre-existing primary headache disorder such as migraine.

Objective We aimed to re-assess the association between hypothyroidism and chronic migraine controlling for factors such as hormone replacement treatment status and bodyweight.

Methods We retrospectively analyzed the medical records of episodic and chronic migraine patients who consecutively consulted our headache clinic in order to determine the prevalence of adequately treated hypothyroidism in each group. Only patients receiving a stable dose regimen were included. The body mass index and other possibly confounding covariates were also collected.

Results Data from 111 migraine patients was included for analysis. Most (88.6%) of chronic migraine sufferers were overusing acute medication. Treated hypothyroidism was significantly more prevalent in chronic migraine patients (29.55%) compared to episodic migraine patients (8.96%). This association was independent of the patients' body mass index or other variables.

Conclusion Alterations of neuronal metabolism, deficient calcitonin release, or focal inflammation causing local hormonal deactivation might explain why hypothyroidism, in spite of levothyroxine replacement therapy, is associated with migraine chronification. Further studies evaluating these factors are warranted.

Keywords Medication overuse headache · Obesity · Metabolism · Calcitonin · Inflammation

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Abbreviations

TSH	Thyroid stimulating hormone
T4	Thyroxine
BMI	Body mass index
TRH	Thyrotropin-releasing hormone
T3	Triiodothyronine

Introduction

Migraine is a disabling neurological condition that affects around 11% of the world population [1, 2]. According to the amount and features of headache days experienced by patients every month, migraine can be sub-categorized into an episodic (EM) and chronic forms (CM). Chronic migraine

is significantly more disabling than episodic migraine and entails a more substantial burden for both the individuals that suffer from it and for the populations that they comprise [3].

About three percent of migraine patients in general will evolve into the chronic form of this condition every year [4]. This rate raises up to ≈14% when considering headache patients who are being followed in specialized centers [5]. While several comorbidities and risk factors associated with migraine chronification are well defined (such as medication overuse [6] or childhood traumatic experiences [7, 8]), the determinants of this complication in many patients often remain puzzling [9]. Therefore, an in-depth scrutiny of modifiable and treatable risk factors is always necessary [10–12].

One of such factors is hypothyroidism. Hypothyroidism is an endocrinological disorder defined by a deficiency of thyroid hormone secretion. It is diagnosed on the basis of biochemical parameters including thyroid stimulating hormone (TSH) and thyroxine (T4) levels. Its prevalence ranges between 0.3 and 3.7% in the USA and 0.2 and 5.3 in Europe [13–17], with females being at higher risk for developing this condition [15]. The most common symptoms of hypothyroidism include fatigue, lethargy, cold intolerance, weight gain, constipation, voice changes, and dry skin, but the clinical presentation tends to differ with respect to age, sex, and time between onset and diagnosis [18]. Hypothyroidism treatment mostly relies on hormone replacement therapy using levothyroxine which compensates for the final steps of the hypothalamic-pituitary-thyroid axis.

Although hypothyroidism itself is a known cause of headache (classified as headache attributed to a disorder of homeostasis—code 10.4— in the 3rd edition of the International Classification of Headache Disorders 3 (ICHD-3) [19]), its interaction with the different forms of migraine becomes perhaps more important on clinical grounds. In the past, several studies have linked migraine with hypothyroidism [20–24], with one prior study specifically suggesting that thyroid hormone deficiency could be a risk factor for migraine chronification [25]. Nonetheless, the presence of comorbid obesity (which is common to both hypothyroidism and chronic migraine [26–30]) was not taken into account in that study and, furthermore, treatment status (i.e., treated, untreated, titration) was also not considered. Thus, the effects of hormone replacement therapy and the possible influence of bodyweight on this hypothyroidism-related chronic migraine risk augmentation merit to be better elucidated.

Because of that, and based on our clinical observations, we aimed to retrospectively analyze the prevalence of adequately treated hypothyroidism among episodic and chronic migraine patients visiting our specialized headache clinic taking into account possible interference of patients' bodyweight and other demographic variables. We hypothesized that hypothyroidism rates would remain high between chronic migraineurs in spite of successful hormonal treatment.

Materials and methods

The medical records of 137 migraine patients consecutively consulting our specialized headache clinic between April 2019 and April 2020 were retrospectively analyzed. Information regarding sex, age, height, weight, ICHD-3 diagnosis, analgesic consumption frequency, and personal history of hypothyroidism were retrieved. When hypothyroidism was present, only patients receiving a stable dose regimen of levothyroxine for at least 6 months and considered euthyroid (corrected) according to their endocrinologist were included. Patients under evaluation for possible hypothyroidism, or those in the dose-titration process, were excluded. The body mass index (BMI) was calculated by dividing the patient's weight in kilograms by the height in meters squared. Demographic, anthropometric, and clinical variables were then compared between episodic and chronic migraine patients. Continuous variables were contrasted using Student's t-tests or Mann–Whitney tests depending on the variables' distribution, and categorical variables were compared using the Chi-squared test. In addition, a multivariate regression analysis model including sex, age, BMI and hypothyroidism as predictors of migraine diagnosis (episodic vs chronic) was built. Given that in our primary analysis a non-significant difference in the mean age of episodic and chronic migraine patients was observed, we conducted a post hoc case–control supplementary analysis in order to further control for this cofactor. In this secondary analysis, an investigator blinded to hypothyroidism diagnosis (TCZ) selected age, gender, and BMI matching controls from the episodic migraine sample database to be compared with the "cases" (patients in the chronic migraine group). Statistical analyses and figures were carried out using Microsoft Excel, Prism GraphPad, and IBM SPSS. This study was approved by the National Clinical Hospital of Córdoba ethics committee.

Results

Complete data from 111 migraine patients (67 episodic and 44 chronic, 39 (88.6%) with current medication overuse (ICHD-III code 8.2)) fulfilling inclusion criteria were available for analysis. A retrospective power calculation [31] indicated that this sample size should result sufficient for statistical inference with an estimated α of 0.05 and 1-β of 20.8 based on our results. There were no significant differences regarding age, gender proportions, or BMI between the two groups (Table 1). Treated hypothyroidism (dose stable)

Table 1 Characteristics of patients included in the primary analysis

	Episodic migraine	Chronic migraine	p Value
N	67	44	
Age	36.22 ± 11.28	40.43 ± 11.28	0.06
% of females	92.5%	93.2	0.90
Migraine days	4,0 ± 3,371	12,63 ± 7,74	< 0.01
Headache days	9,64 ± 5,79	24,96 ± 5,59	< 0.01
BMI (Kg/m^2)	24,67 ± 4,672	24.94 ± 4.806	0.83
Hypothyroidism	8.96%	29.54%	< 0.01

Table 3 Characteristics of patients included in the supplementary post hoc case–control analysis. The numerical difference in age between groups observed in the primary analysis is reduced. The asterisk (*) denotes statistical significance

	Episodic migraine	Chronic migraine	p Value
N	44	44	
Age	39.45 ± 11.39	40.43 ± 11.28	0.68
% of females	90.90909%	93.18182%	0.69
BMI (Kg/M^2)	24.94 ± 4.806	25,29 ± 4,843	0.55
Hypothyroidism	4.54%	29.54%	< 0.01*

was significantly more prevalent among chronic migraine patients (29.55%) than in episodic migraine patients (8.96%; $\chi = 7{,}937$, $p < 0.01$), with an estimated odds ratio of 4.26 (95% confidence interval = 1.48 to 12.30). Results from the binary logistic regression model are displayed in Table 2. From all the variables included in the model, only the presence of hypothyroidism reached statistical significance ($p = 0.01$) as a predictor of migraine diagnosis (i.e., chronic or episodic). The post hoc complementary case–control analysis that we performed adequately corrected the numerical difference in age between the groups observed in the primary analysis of the whole sample (Table 3). Results of this supplementary test were in line with the original analysis, with a slightly more accentuated difference in hypothyroidism prevalence (Fig. 1).

Discussion

Our results corroborate the contribution of hypothyroidism to migraine chronification previously described [25] and, in addition, demonstrate that this risk factor persists in spite of adequate thyroid hormone replacement therapy. Furthermore, our findings show that this association is independent of the patients' body weight and, considering that most chronic migraine patients in our study also fulfilled the current criteria for medication overuse headache, suggest that this complication can also be related to hypothyroidism, which was not fully clear before [25]. The possible implications of these observations are discussed below.

Migraine has an important metabolic facet [32]. Previous experiments indicate that one of the major alterations in the brain of most migraine patients is the presence of a mismatch between energetic supply and demand at the cortical level [33, 34]. Migraine patients exhibit enhanced sensory processing [35], which might be difficult to cope with from a metabolic perspective, and have been reported as a crucial factor in determining unfavorable outcomes [36]. Considering that hormones of the thyroid axis are chiefly involved in cell metabolism, it could be hypothesized that hypothyroidism aggravates migraine by accentuating this relative metabolic deficit. Of note, treatment with levothyroxine would be expected to improve metabolic deficiencies in neural cells expressing thyroid hormone receptors, but, through a feedback-mediated suppression of the release of hormones secreted at the higher levels of the thyroid axis (i.e., thyroid stimulating hormone (TSH) and thyrotropin-releasing hormone (TRH)), levothyroxine supplementation could also impair metabolism in other cells of the central nervous system. Indeed, this upstream inhibitory mechanism entails a significant pathophysiological interest considering that human astrocytes (the main responsibles of neuronal metabolism) possess TSH receptors [37] and that a recent gene network analysis in migraine has pointed towards the thyrotropin-releasing hormone receptor suggesting its implication in the pathogenesis of this disease [11]. In fact, higher levels of TSH have been found to be associated with fewer episodes of both migraine and non-migraine headache [38] and attacks of shorter duration together with better response to medication [39] in previous clinic-epidemiologic studies.

On the other hand, prior evidence suggests that in most cases, primary hypothyroidism is associated to calcitonin deficiency, an alteration that does not revert after T4 supplementation [40]. The calcitonin gene superfamily includes calcitonin, amylin, katacalcin, adrenomedullin, and calcitonin gene–related peptide (CGRP). This last peptide neurotransmitter is largely involved in migraine pain [41]. The interaction between circulating levels of calcitonin and CGRP or its receptor in migraine patients is still unclear

Table 2 Summary of binary logistic regression model results. The asterisk (*) denotes statistical significance

	B	S.E	p Value
Age	-0.031	0.019	0.095
BMI	0.004	0.045	0.923
Sex	0.275	0.785	0.726
Hypothyroidism	-1.418	0.553	0.010*
Constant	1.505	1.476	0.308

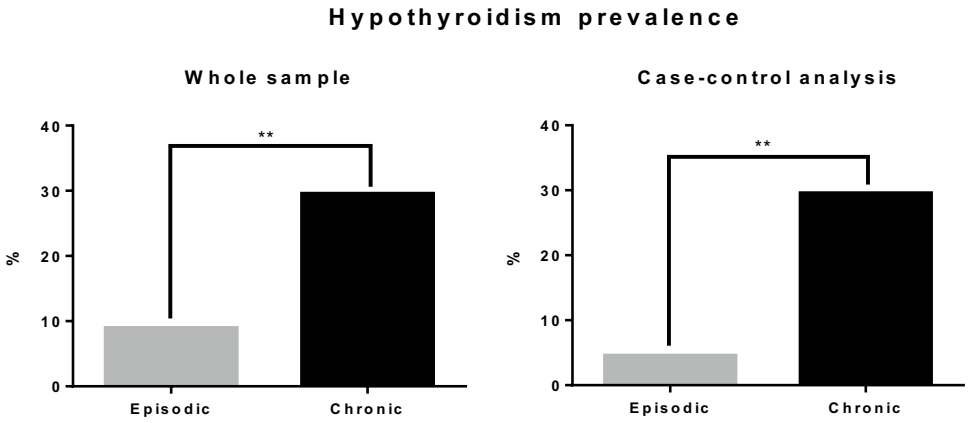

Fig. 1 Bar charts showing the prevalence of treated hypothyroidism among episodic (grey bars) and chronic (black bars) migraine patients in the whole sample (left) and the supplementary post hoc case–control analysis (right). The asterisks (**) denote a p value < 0.01

[42], but, considering the structural similarity between peptides of this family, and the cross-reactivity observed between their receptors, our results might suggest that calcitonin deficiency could exert an effect on migraine chronification. Interestingly, the role played by calcitonin at the central and peripheral nervous system in other chronic pain conditions, including forms of neuropathic pain, has been already recognized before [43, 44].

From another perspective, treated hypothyroids have a higher ratio of free T4:T3 when compared to euthyroids because approximately 20% of T3 comes from thyroid secretion [45–47]. T3 is considered to be the predominantly active form of thyroid hormones [48]. Deiodinases type 1 and 2 (D1 and D2) convert T4 into T3, and deiodinase type 3 (D3) converts it into an inactive subproduct [49, 50]. D3 has a high affinity for T3 and is important in its regulation [51]. D3's activity is induced by inflammation [52], and D1's activity is reduced by it [53, 54]. Given that migraine is associated with increased C-reactive protein [55] and cytokine [56, 57] levels, which are inflammatory markers, it may be hypothesized that focal inflammation (as observed in migraine) [58] could produce a local hormonal deficit and thus worsen the symptoms facilitating chronification.

Furthermore, it is worth to notice that because of the methodological nature of our study, no temporal direction can be traced regarding the association between chronic migraine and hypothyroidism. Thus, another possibility that merits to be discussed is whether hypothyroidism is a consequence rather than a cause of chronic migraine. Interestingly, a study including 8788 patients followed during 20 years found that individuals with possible migraine had a 41% increased risk for developing hypothyroidism [59]. The authors of the study proposed that immunological, genetic, environmental (pollutants), and other factors may be the reason behind this alteration [59]. We would also consider that on hypothetical grounds, repetitive analgesic and/or antimigraine drugs consumption could contribute as another risk factor in this list. Further studies addressing this possibility are warranted.

Finally, a possibility that merits discussion is whether treatment itself may have been the cause of migraine aggravation. Levothyroxine use has been associated with intracranial hypertension [60–62], a common mimic of chronic migraine. Therefore, direct (CSF opening pressure measurement) or indirect (ophthalmological) evaluation of this differential diagnosis should be recommended in some of these patients.

Our study has several limitations worth to mention. One is the lack information regarding the serum thyroid hormone levels of our patients which would have provided us additional pathophysiological clues. Second, the sample size that we included was merely sufficient, and the retrospective design of our study entails inherent limitations that warrant a cautious interpretation of our results. Therefore, larger replication studies, or prospective studies, in other locations would be desirable before our results can be generalized, in particular considering that most patients in our setting consume large amounts of ergotamine and dipyrone (metamizol) [63] which are restricted in other countries. Third, given that this is a clinic-based study in which medical records were retrospectively analyzed, the number of variables that we were able to gather is rather limited, and it is possible that some confounding factors might have been overseen. Nonetheless, in spite of these limitations, our study provides valuable information that helps to clarify the role of hypothyroidism as a risk factor for migraine chronification which, although previously associated with burdensome migraine forms in the past, receives perhaps too little attention nowadays [64, 65].

Data availability All data is available upon request.

Declarations

Ethics approval This study was approved by the National Clinical Hospital of Córdoba ethics committee.

Conflict of interest The authors declare no competing interests.

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