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Review Paper

A Preliminary Meta-analysis of Regulatory T-cell Reduction in Patients With Migraine

Subalakshmi Sugumar[1], Saman Shah[2], Philo Hazeena[3], Deepa Avadhani[3], Pavithra Murugan[1], Murugesan Arumugam[1*]

1. Department of Pharmacology, Sri Ramachandra Faculty of Pharmacy, Sri Ramachandra Institute of Higher Education and Research, Chennai, India.
2. Department of Pathology, Hind Institute of Medical Sciences, Barabanki, India.
3. Department of Neurology, Sri Ramachandra Institute of Higher Education and Research, Chennai, India.

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ABSTRACT

Introduction: The etiology of migraine is not fully understood, but there is ongoing debate about the potential role of immune dysfunction in migraine pathophysiology. Some clinical studies have shown a reduction in CD4$^+$CD25$^+$ regulatory T-cells (Treg) in migraine patients compared to healthy people. However, these studies have not been systematically analyzed. The primary objective of this study is to conduct a systematic review of Treg level changes in migraine patients.

Methods: A detailed literature search was conducted on PubMed, Scopus, Embase, ProQuest, Cochrane Review, Clinical trials, Academic thesis, American Academy of Neurology resources, and Google Scholar databases from 2010 to 2023. Studies that were appropriately designed to quantify Treg cell levels in migraine patients were included in this meta-analysis.

Results: Out of 17 studies initially reviewed, only 4 studies with 121 migraine patients were included for analysis. The meta-analysis revealed a statistically significant reduction in Treg cell levels in migraine patients compared to healthy volunteers (Z=1.21; P=0.23).

Conclusion: The observation of lower levels of Treg cells in migraine patients, compared to healthy volunteers, supports the theory that migraine may be an autoimmune disorder. However, additional clinical data is required to understand the role of immune dysregulation in migraine pathogenesis fully. This is the first meta-analysis of Treg cell levels in the context of migraine research, significantly contributing to the existing literature on the topic.

*** Corresponding Author:**
Murugesan Arumugam, Assistant Professor.
Address: *Department of Pharmacology, Sri Ramachandra Faculty of Pharmacy, Sri Ramachandra Institute of Higher Education and Research, Chennai, India.*
E-mail: *murugeshcology@gmail.com*

Highlights

- Based on the data available about the Treg cell levels in migraine patients, we performed a meta-analysis.
- Compared to healthy individuals, a significant reduction in Treg cell levels was observed in migraine patients.
- For the first time in literature, Treg cell levels have been taken for meta-analysis as they are related to migraine research.

Plain Language Summary

Migraine is a complex condition, and its exact etiology is unknown. Recent studies have suggested that the immune system plays an important role in migraine. In particular, some studies have shown that people with migraine have lower levels of Treg cells, which helps maintain the immune system's balance. However, these findings have not been systematically reviewed. In this study, we conducted a systematic review and meta-analysis to investigate whether lower Treg cell levels are consistently observed in patients with migraine. We carefully examined the studies from 2010 to 2023. From 17 yielded studies, only 4 met our criteria and reviewed, representing a total of 121 patients. The analysis revealed that Treg cell levels were significantly lower in patients with migraine than in healthy individuals. This finding supports the idea that migraine may be linked to immune dysfunction, possibly through an autoimmune mechanism. However, further research is needed to confirm this link and better understand how the immune system contributes to migraine.

1. Introduction

Migraine is believed to be a chronic neurological disorder characterized by enervating, recurrent occurrences of unilateral throbbing headaches, afflicting about 10%-15% of the general population, with a preponderance for females (Andreou & Edvinsson, 2019). According to the global burden of disease study (2015), migraine is the most progressive neurological illness and the third leading cause of disability worldwide (Steiner et al., 2016). Migraine attacks involve a variety of neurological symptoms such as nausea, photophobia, phonophobia, osmophobia, exhaustion, and disruptions of autonomic, mental, sensory, and motor functioning, in addition to pain (Burstein, 2001). the international classification of headache disorders, third edition beta version (ICHD-III), categorizes migraine into two subtypes: Migraine without aura (MO) and migraine with aura (MA) (IHS, 2018).

The two basic ideas have dominated migraine research over the past three centuries: The vascular theory and the central neuronal theory (Isler, 1986 ; Tfelt-Hansen & Koehler, 2010). The efficacy of vasoconstrictors like ergotamine and triptans in treating acute migraine supported the vascular theory. Still, novel research shows that vasodilation is neither essential nor sufficient to trigger a migraine episode (Mason & Russo, 2018). Some studies have also indicated that migraine episodes can begin in areas of nociceptive neuromodulatory dysfunction in the brain stem (Welch, 2003; Brennan & Pietrobon, 2018). In addition, Levy and colleagues suggested that degranulation of meningeal mast cells, an inflammatory cell found in the intracranial region, may cause migraine (Levy et al., 2007). While numerous theories have been proposed for the etiology of migraine, none of these theories adequately explain the exact cause of migraine (Tfelt-Hansen & Koehler, 2010). Furthermore, there is no specific biomarker or diagnostic test for migraine, and it has often been misdiagnosed with other types of headaches.

On the other hand, there is emerging evidence that migraine may be caused by immune dysfunction (Arumugam & Narayan, 2019; Biscetti et al., 2021; Biscetti et al., 2022). In an earlier clinical study, our research group showed that $CD4^{+}CD25^{+}$ regulatory T-cells (Treg) were lower in migraine patients in comparison to healthy volunteers (Arumugam & Parthasarathy, 2016), which was the first study to identify levels of Treg variability in migraine patients. In support of this research, other clinical studies have also demonstrated a significant decrease in Treg cell levels in migraine patients (Faraji, et al., 2021; Nurkhametova et al., 2018; Li et al., 2022). However, a systematic analysis of the available data does not exist yet. Therefore, the current study attempted to analyze existing clinical data on decreasing levels of lymphocyte subsets, particularly the Treg population in migraine patients.

2. Materials and Methods

Literature search

A detailed literature search was conducted on PubMed, Scopus, Embase, ProQuest, Cochrane Review, Clinical trials, Academic thesis, American Academy of Neurology (AAN) resources, and Google Scholar databases from 2010 to 2022. The search details include "migraine in "regulatory T-cell," "$CD4^+CD25^+$," "inflammatory activity," "autoimmune disorder," "cytokines," and "neuromodulators." Each term's singular and plural variations, as well as regional spelling variations, were recognized. The analysis was characterized based on the age, number of migraine patients and healthy volunteers, MO and MA, new interventions, and consequent parameters. Studies that met these criteria were used in the analysis. Meta-analysis was performed using appropriate software (Revman software, version 5.4).

Eligibility criteria

Only studies that met the following criteria were included in the analysis. Clinical studies were conducted with MO and MA patients, quantitative analyses of the T lymphocyte subset population, especially Treg cells, and studies conducted with patients without recent immune suppression therapies.

Data extraction

Data were extracted from eligible studies, and the average values and standard deviation for Treg cell levels were collected from the selected articles. The number of cases or controls, average age, gender ratio, intervention performed, and outcome parameters were taken for the analysis. Other clinically significant findings were also collected.

3. Results

Description of the included studies

Following the initial screening and eligibility criteria, 17 records were selected for qualitative analysis and 4 observational study records (Arumugam et al., 2016; Faraji et al., 2021; Nurkhametova et al., 2018; Li et al., 2022) were taken for the final analysis (Figure 1). The inclusion criteria of the study were - parameters such as migraine type, age, comorbidity, and immunosuppressive treatments.

Analysis of the clinical studies in the pathophysiology of migraine

Throughout this study, 121 migraine patients (including MO and MA) and 94 healthy volunteers between the ages of 18 and 55 were included in the analysis (Table 1). Changes in Treg cell levels were compared between migraine patients and healthy volunteers. The results show a significant reduction of Treg cell levels in migraine patients compared to healthy individuals, and the overall effect (Z=1.21; P=0.23) (Figure 2). The standardized mean difference (SMD) shows -3.63 (P=0.007) with a 95% confidence interval of -6.28 to -0.99 (Figure 3). The true effect size of overall SMD in 95% CI of all comparable populations fall between the interval of -16.30 to 9.04 (Figure 3).

4. Discussion

The current meta-analysis data from 4 clinical studies show a substantial reduction of Treg cell levels in migraine patients compared to healthy volunteers. None of the studies found significant differences between MO and MA patients (Table 1). The Tregs are a specific subgroup of T cells, defined by the expression of CD4, CD25 (the IL-2 receptor a-chain), and the transcription factor forkhead box P3 (FOXP3) (Valencia & Lipsky, 2007). Treg cells are produced during thymocyte development and regulate the immunological response, preserving homeostasis and self-tolerance (Chang et al., 2005; Zhang e al., 2020; Genre et al., 2009). It can also inhibit the activation, proliferation, and effector functions of T-cells, natural killer cells, B-cells, and antigen-presenting cells (Sakaguchi et al., 2009). Thus, the reduced or abnormal regulation of Treg cells or mutation of FOXP3 enhances the probability of immunological imbalance in migraine patients. In addition, an increase in $CD4^+$ and a decrease in $CD8^+$ levels in migraine patients have been reported (Deng et al., 2019; Raphael et al., 2020; Arumugam & Parthasarathy, 2016). Variations in purinergic cells, such as $CD4^+$, $CD8^+$, $CD39^+$, $CD73^+$, and FOXP3 subsets, were also observed in migraine patients compared to healthy volunteers, and these outcomes are consistent with past reports (Mosnaim et al., 1998; Empl et al., 1999; Pavelek et al., 2020), indicating immune cells possible role in the physiopathology of migraine (Cseh et al., 2013; Leone et al., 1994).

Table 1. Characteristics of the included studies

No.	Study Characteristics	Arumugam et al., 2016	Faraji et al., 2021	Nurkhametova et al., 2018	Li et al., 2022
1	Total number of participants (migraine/healthy volunteers)	50/25	40/33	16/21	15/15
2	Study objective	Quantification of autoimmune markers, specifically lymphocyte subsets ($CD4^+$, $CD8^+$, and $CD4^+CD25^+$) decreasing in migraine patients	Correlation of different categories of migraine with Treg cell percentage and $CD4^+$, $CD25^+$, and FoxP3 protein	Characterize purinergic profiles of T-cells in patients with episodic migraine without aura	Comparison of non-classical monocytes ($CD14^+CD16^{++}$), helper T cells ($CD3^+CD4^+$) and regulatory T cells ($CD4^+CD25^+$)
3	Study design	Observational	Observational	Observational	Observational
4	Study subject	Postictal period of migraine patients included	Postictal period of migraine patients included	Performed during ictal and postictal period	Performed over the ictal period of chronic migraine
5	Inclusion criteria	A total of 50 migraine patients were studied, and CD4:CD8 ratios and $CD4^+CD25^+$ cell population in all migraine patients were compared with controls	Newly diagnosed patients with migraine	A total of 38 patients were assessed, previously diagnosed without aura; 12 patients had oncology, pregnancy, breastfeeding, 3 had migraine with aura, 7 declined, and 16 female patients were included	A total of 30 participants were studied using demographic data. Patients with frequent headaches and comorbid pain, whether having chronic migraine or not, were included. Overuse of medications among migraine patients were also included.
6	Analytical methods	Flow cytometry, monoclonal antibodies like anti CD4-FITC, anti CD25-PE, anti CD3-PERCPCY5.5 and anti CD8-APC were used for the gating protocol	Gating of $CD25^+$ and $FoxP3^+$ lymphocytes were considered	Expression pattern of CD45R0 and CD62L as naïve (N, CD45R0– $CD62L^+$), central memory (CM, $CD45R0^+CD62L^+$), effector memory (EM, $CD45R0^+CD62L$–), and terminally differentiated CD45RA-positive effector T-cells (TEMRA, CD45R0–CD62L–) were established for gating process	Flow cytometry screening, Statistical analysis (fluorescence-activated cell sorting (FACS) data, cytokine multiplex data), and The nonparametric Wilcoxon signed-rank test were used to compare the significance of lymphocytes and monocytes.
7	Study outcome	Migraine patients showed a significant reduction in the Treg population as compared with healthy volunteers, with no significant difference between migraine with aura and migraine without aura.	The number of Treg cells was significantly lower in newly diagnosed migraine cases.	Imbalance in Treg subsets in migraine patients and suggests the inability of Tregs to suppress inflammation in migraine effectively.	Migraine patients showed a significant reduction of Treg and T cells.

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Abbreviations: APC: Antigen-presenting cells; CD: Cluster of differentiation; CM: Central memory; EM: Effector memory; FACS: Fluorescence-activated cell sorting; FOXP3: Forkhead box P3; PERCPCY5.5: Peridinin chlorophyll protein-cyanine5. 5; TEMRA: Terminally differentiated effector memory T cells; Treg: Regulatory T-cells.

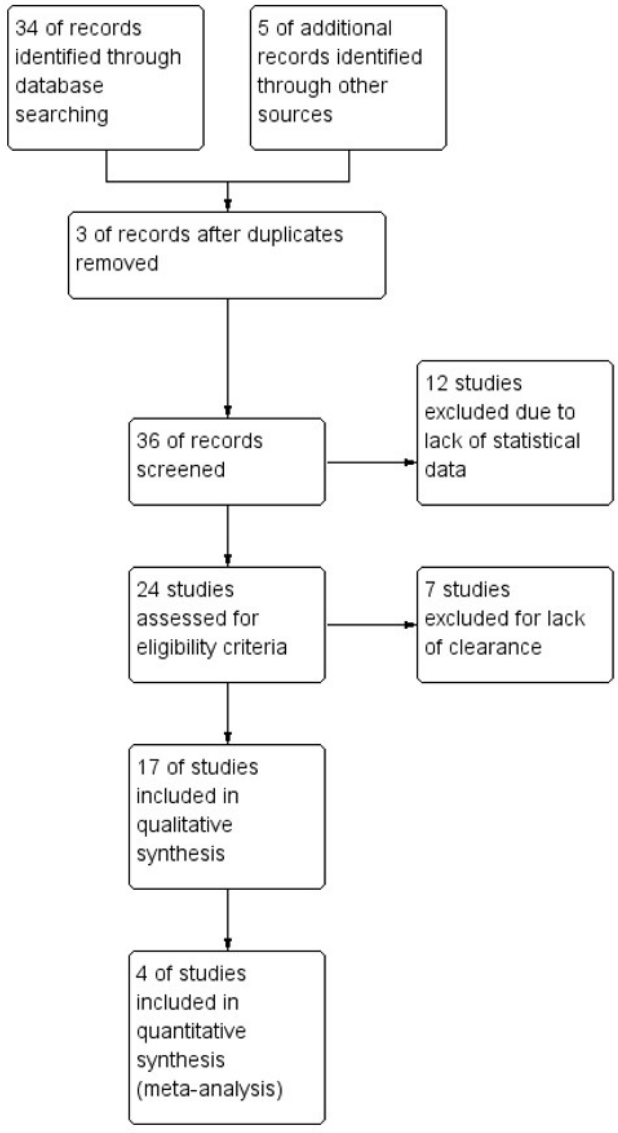

Figure 1. PRISMA flow diagram of the inclusion studies

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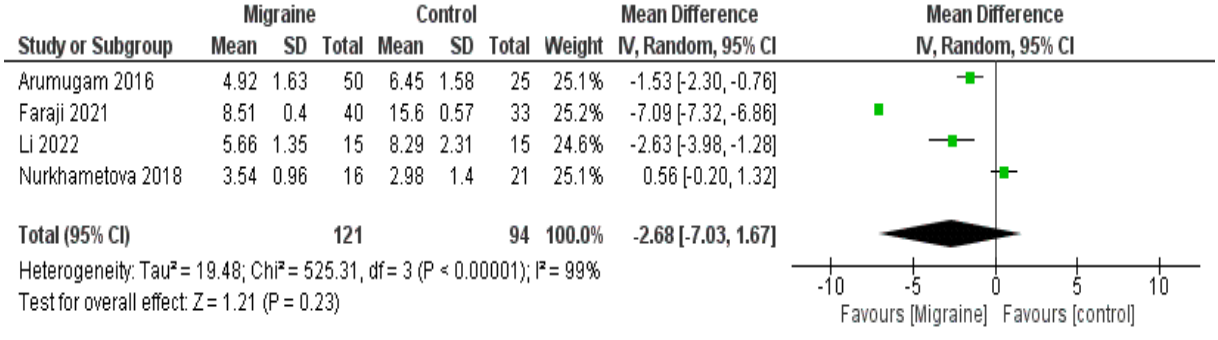

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Figure 2. Quantitative analysis of levels of $CD4^+CD25^+$ regulatory T-cell levels in migraine patients and healthy volunteers

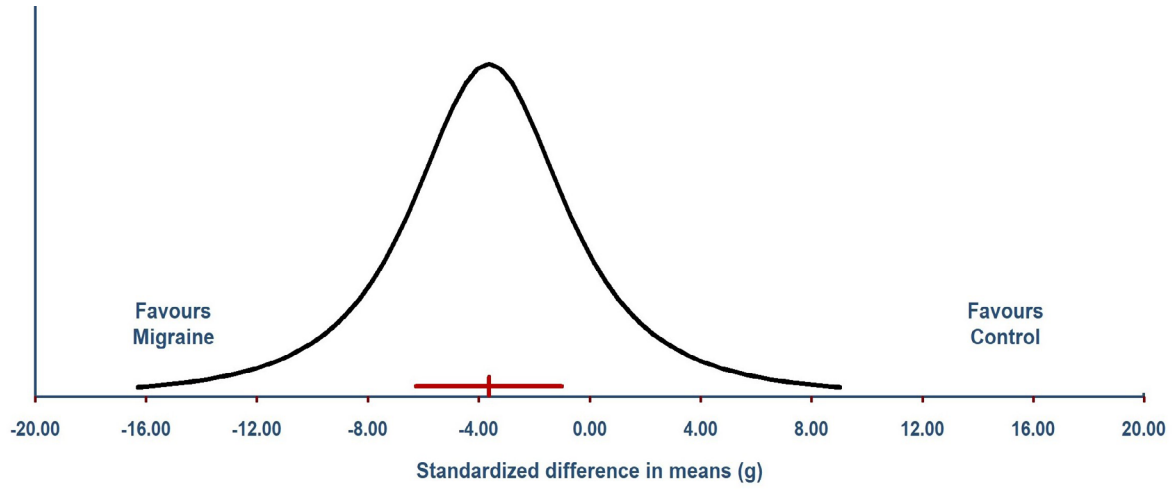

Figure 3. The standardized difference in mean between migraine and control groups

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However, numerous clinical studies show alteration in pro-inflammatory cytokines like IL-1, IL-6, and TNF, as well as anti-inflammatory cytokines like IL-1RA, IL-2, and IL-10, during migraine attacks (Boćkowski et al., 2010; Bruno et al., 2007; Yilmaz at al., 2010). In addition, a recent case report suggests that interferon-beta can induce or exacerbate migraine attacks during immunomodulation therapy in multiple sclerosis patients (Patti et al., 2012; Elmazny et al., 2020). These findings support the belief that immune cells, such as interferon beta, could also play a role in migraine attacks. Accordingly, contemporary approaches are opening the doors to recognizing the role of immune cells in migraine and raising the possibility of a link between immunological imbalance and migraine. Therefore, the current meta-analysis and existing evidence strongly suggest that immune cells can play a pivotal role in migraine pathogenesis.

For the first time in the literature, Treg cell levels were taken for meta-analysis about migraine research. The limitation of the study is that only four studies were analyzed. Nevertheless, exhaustive research is required to support the notion of a link between autoimmunity and migraine.

5. Conclusion

The meta-analysis of four clinical studies shows significant reduction of Treg cells in migraine patients compared to healthy volunteers. Decreased Treg levels support the theory that migraine could be due to immune dysfunction. More specific studies on the role of immune cells in the pathophysiology of migraine can contribute to a better understanding of migraine progression.

Ethical Considerations

Compliance with ethical guidelines

This study adhered to ethical standards in research and publication. Since this was a systematic review and meta-analysis of previously published data, no new human or animal subjects were included in this study. All data sources used in this study were obtained from publicly available, peer-reviewed articles. The original studies included in our analysis followed ethical guidelines, obtaining informed consent from participants and approval from relevant institutional review boards.

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Authors' contributions

Conceptualization: Subalakshmi Sugumar and Murugesan Arumugam; Study design: Philo Hazeena and Deepa Avadhani; Writing the original draft: Subalakshmi Sugumar; Review and editing: Subalakshmi Sugumar, Saman Shah, Pavithra Murugan and Murugesan Arumugam; Methodology, data curation, visualization and final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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