# Comparison of Headache Characteristics in Patients with and without Autoimmune Disease

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*https://doi.org/10.17925/USN.2025.21.1.9*

**Introduction**: The global prevalence of autoimmune diseases is about 5%. Patients with autoimmune conditions often report headaches. Headache has been reported to occur in patients with autoimmune disease, although its role as a direct symptom remains unclear. Differentiating whether the headache is related to autoimmune activity or represents a primary headache as a comorbidity is essential, as this distinction influences treatment strategies. The study aimed to describe the characteristics of patients with headache who have and do not have autoimmune disease. **Methods**: A cross-sectional study was conducted using secondary data from 1 January 2022 to 31 December 2022, with consecutive sampling. Bivariate analysis included the independent t-test, chi-square and Mann–Whitney tests. **Results**: Among 210 patients with headache, 22.4% had autoimmune diseases, mainly related to the connective tissue. The majority were females (77.6%) aged 18–45 years (50.5%). Over half of the patients with autoimmune diseases reported headaches after diagnosis, with a median onset of 4 years. The median headache frequency was 14 times per month, with a duration of 4 h and an intensity score of 5 on the numeric rating scale (NRS). Common triggers included fatigue (32.1%), while nausea and vomiting (66.7%) were more commonly reported as accompanying symptoms during headache attacks. Headache phenotypes varied between groups, with migraine more frequently reported in the autoimmune group (68.1%) and atypical presentations observed in 40.7% of patients with non-autoimmune disease. However, this may reflect referral patterns rather than true differences in underlying pathophysiology. Bivariate analysis showed significant relationships between age, gender, headache characteristics, onset and intensity with autoimmune status ($p<0.05$). **Conclusion**: The prevalence of patients with headache who have autoimmune disease was 22.4%. Significant associations were found between demographic and headache features and autoimmune status.

**Keywords**

Autoimmune disease, comparative study, disease characteristics, headache disorder, migraine disorder, nervous system in autoimmune disease

**Disclosures**: Tiara Aninditha, Elizabeth Albertin, Irma S. Madjid, Chelsea Kristiniawati, Raymond Aris N Alvonsius, Ahmad R Faiq and Henry R Sofyan have no financial or non-financial relationships or activities to declare in relation to this article.

**Review process**: Double-blind peer review.

**Compliance with ethics**: This retrospective study was conducted in accordance with the Declaration of Helsinki (1964) and its later amendments. Ethical approval was obtained from the Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia – Dr. Cipto Mangunkusumo National General Hospital (Approval No: KET-166/UN2.F1/ETIK/PPM.00.02/2023). Permission to access and use anonymized medical record data was granted by the institution. All data were de-identified prior to analysis, and no personal identifiers were included. As such, the requirement for individual informed consent was waived. Findings from this study will be disseminated through peer-reviewed journals, scientific meetings and institutional platforms. Permission to use patient medical record data was obtained with informed consent from all participants involved in the study. Patients were not directly involved in the design, recruitment or conduct of this research. However, their anonymized data contributed to the analysis and interpretation of findings. The results of this study may be shared with participants or the broader public upon request or through institutional dissemination channels.

**Data availability**: The datasets generated during and analysed during the current study are available from the corresponding author on reasonable request.

**Authorship**: All named authors meet the criteria of the International Committee of Medical Journal Editors for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval for the version to be published.

**Access**: This article is freely accessible at touchNEUROLOGY.com. © Touch Medical Media 2025.

**Received**: 24 June 2025

**Accepted**: 8 September 2025

**Published online**: 12 November 2025

**Citation**: *touchREVIEWS in Neurology.* 2025;21(1):86–92

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**Support**: No funding was received for the publication of this article.

In general, headaches can be classified into primary headaches (where no underlying disease is found) and secondary headaches (where a predefined condition is the cause of the headache). According to the International Classification of Headache Disorders, third edition (ICHD-3), primary headache types include migraine, tension-type headache, trigeminal autonomic cephalalgias (TAC) and other primary headache disorders defined by specific diagnostic criteria based on clinical features, frequency, duration of attacks and additional symptoms.[1,2]

The pathophysiology of headaches is related to inflammation and the complex regulation of the body's immune system. In primary migraine headaches, activation of the trigemino-vascular system induces an inflammatory response that increases the release of proinflammatory cytokines. Changes in inflammatory cytokine levels are associated with the pathophysiology of migraines both during interictal and ictal periods.[1] Additionally, in tension-type headaches, proinflammatory cytokines are thought to directly bind to afferent nerve receptors, including peripheral myofascial nociceptors, which increase pain hypersensitivity and are related to the pathophysiology of tension-type headaches.[1] Although primary headaches are defined as having no underlying cause, several autoimmune diseases are reported to be associated with a higher prevalence of primary headaches.

Autoimmune diseases are caused by dysfunction of the immune system, characterized by an abnormal immune response to self-antigens, resulting in damage or dysfunction of various body tissues. Based on the 2021 estimates from the Global Burden of Disease (GBD) study, the global prevalence of migraine is 15.2%, affecting 18.9% of women and 11.4% of men.[3] Migraine is the second leading cause of years lived with disability (YLDs) globally, accounting for 4.73% of all-cause YLDs.

The global prevalence of autoimmune diseases is approximately 5%, and patients with autoimmune diseases often present with complaints of headaches.[1,4] About 54.4% of patients with systemic lupus erythematosus (SLE) report headaches.[5]

In patients with autoimmune diseases, it is important to identify whether the headache is a clinical manifestation of the autoimmune disease or a primary headache occurring as a comorbidity, as this significantly affects the treatment provided. Patients with headaches associated with autoimmune diseases should receive treatment related to their autoimmune condition, including immunosuppressive drugs. Conversely, patients with autoimmune diseases presenting with primary headaches should be managed according to primary headache guidelines, such as administering abortive medications for acute conditions or prophylactic medications for chronic conditions, as indicated. These differences are often overlooked; thus, it is necessary to have baseline data on headaches and autoimmune diseases to raise clinical awareness in managing headaches in patients with autoimmune diseases. Therefore, the researcher is interested in studying the characteristics of headaches in patients with autoimmune diseases at the Neurology Clinic of Dr. Cipto Mangunkusumo National Central General Hospital.

## Materials and methods

This retrospective cross-sectional study was conducted using electronic medical records and the headache registry at the Department of Neurology, Faculty of Medicine, University of Indonesia – Cipto Mangunkusumo. The study included 210 patients with headache visiting the clinic from January to December 2022, grouped based on autoimmune disease status. Patients diagnosed with headache and autoimmune disease according to medical records and established criteria were included, while those with intracranial structural abnormalities were excluded. However, not all headache diagnoses adhered to the ICHD-3 criteria, as data were collected retrospectively from medical records,where clinicians may not have applied uniform diagnostic standards.

Data were collected from electronic medical records and the headache registry, with diagnoses of autoimmune diseases based on clinical and laboratory documentation recorded in the medical records, following standard criteria. Headache characteristics, including frequency, duration, intensity and type, were obtained via standardized interviews by trained professionals and supported by clinical notes. All assessments were carried out consistently across patients to ensure comparability between groups with and without autoimmune diseases. To minimize selection bias, all eligible patients during the study period were included using consecutive sampling. Data collection was performed by trained personnel using standardized forms, which helped reduce measurement bias. Diagnoses of autoimmune diseases were based on documented clinical and laboratory results following established criteria, ensuring diagnostic validity across groups. Normality was assessed using the Kolmogorov–Smirnov test. Comparisons between groups used chi-square tests for categorical variables, t-tests for normally distributed continuous variables and Mann–Whitney U-tests for skewed data. For non-normally distributed variables, data were summarized using median and interquartile range (IQR). Subgroup analyses stratified by age and gender, as well as interaction effects between autoimmune status and demographic variables, were evaluated using multivariable logistic regression with interaction terms. The total sample size was based on all eligible patients during the study period, and no formal sample size calculation was performed. Missing data were minimal and handled with complete case analysis, and sensitivity analyses were not performed due to the limited scope of data and sample size.

Ethical approval was obtained from the Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia – Dr. Cipto Mangunkusumo National General Hospital (Approval No: KET-166/UN2.F1/ETIK/PPM.00.02/2023). Permission to access and use anonymized medical record data was granted by the institution. All data were de-identified prior to analysis, and no personal identifiers were included.

## Results

Consecutive sampling gave approximately a 1:4 ratio in a case–control group. One-third of the control group was systematically randomly selected for bivariate analysis to avoid statistical bias. Our data revealed that 44.3% of patients had a migraine-type, headache-like phenotype.

This study included 210 patients with headache, comprising 47 patients with autoimmune disease and 163 without autoimmune conditions. The prevalence of patients with headache who have autoimmune disease was 22.4%. Patients were predominantly in the 18–45 age group (50.5%), female (77.6%), married (64.3) and unemployed (62.4%).

The baseline characteristics are described in *Table 1*. It showed that the population aged 18–45 years old (50.5%) was the primary age group in this retrospective study, with a mean age of 43.83 (±0.955) years. The patients with headache were predominantly females (77.6%) compared with males (22.4%). Most of the patients have married status (64.3%), and their occupational status was unemployed (62.4%).

The majority of patients were experiencing migraine-type headache-like symptoms (44.3%) in both groups, followed by atypical, tension-type and TAC-type headache-like characteristics (28.1%, 26.2% and 1.4%, respectively). In this study, the onset of temporal headache and the establishment of an autoimmune disease diagnosis were also observed.

*Table 2* shows that the predominant portion of the patients with headache had autoimmune diseases related to connective tissues (61.7%), and over half of them reported their initial headache occurring after the confirmation of the autoimmune diagnosis (metachronous) with a median onset of headaches of 4 years (ranging from 0 to 10). In patients with autoimmune disease, the clinical features of headaches include a median frequency of 14 times per month, a median duration of 4 h and a pain intensity score of 5 on the numeric rating scale (NRS). The patients commonly identified triggers such as fatigue (32.1%), light (25%) and physical activities (21.4%). The most frequently reported additional symptoms were nausea–vomiting (66.7%) and photophobia (40.7%). Non-specific abortive medications were administered to 83% of patients for their headaches, and prophylactic drugs were given to 70.2% of patients.

As much as 61.7% of patients with headache who have autoimmune disease had metachronous onset, which was described as the onset of headache observed more than 3 months after the establishment of diagnosis in patients with autoimmune disease.

As shown in *Table 3*, bivariate analysis was conducted to observe the significance between headache and autoimmune status in patients. Confounding factors were also included in this analysis. The comparison results showed that age, age group and sex were significantly related ($p<0.05$) to autoimmune status in patients with headache of this study. The type of headache between patients with headache who have and

Table 1: Characteristics of the study subjects (n=210)

| Variable | Total (n) | % |
|---|---|---|
| Age [mean (SD)] years | 43.83 (±0.955) | |
| **Age group** | | |
| <18 years old | 1 | 0.5 |
| 18–45 years old | 106 | 50.5 |
| 46–59 years old | 75 | 35.7 |
| ≥60 years old | 28 | 13.3 |
| **Gender** | | |
| Female | 163 | 77.6 |
| Male | 47 | 22.4 |
| **Marital status** | | |
| Married | 135 | 64.3 |
| Single/unmarried | 58 | 27.6 |
| Divorce/separated | 17 | 8.1 |
| **Jobs** | | |
| Unemployed | 131 | 62.4 |
| Employee | 49 | 23.3 |
| Student | 11 | 5.2 |
| Others | 10 | 4.8 |
| Self-employed | 9 | 4.3 |
| **Types of headache** | | |
| Migraine-type headache-like | 93 | 44.3 |
| Atypical | 59 | 28.1 |
| Tension-type headache-like | 55 | 26.2 |
| Trigeminal autonomic cephalgias-type headache like | 3 | 1.4 |

*SD = standard deviation.*

do not have autoimmune disease is also significantly different ($p<0.05$) through having significant relationships that could be observed or conducted in further study.

This observational study showed characteristics of patients with headache who have autoimmune disease in Cipto Mangunkusumo National General Hospital. These findings show the exciting factors that could be further studied and conducted to give a clearer image of headaches related to autoimmune disease. The association between the onset of temporal headache and autoimmune status, as well as the association between headache characteristics and autoimmune status, is recommended as a topic for further prospective studies.

## Discussion

The findings of this study highlight important characteristics and distinctions between patients with headache who have and do not have autoimmune diseases. The prevalence of headaches among patients with autoimmune diseases in this study was 22.4%, which aligns with previous studies.[1] For instance, in patients with antiphospholipid syndrome, migraine is the most common type of headache, with a prevalence of 20%.[1] In patients with multiple sclerosis (MS), the most frequently reported type of headache is migraine, with a prevalence ranging from 2 to 67%, followed by tension-type headaches, with a prevalence ranging from 12.2% to 55%.[6] Meanwhile, in patients with giant cell arteritis, the incidence of headaches is higher, occurring in 70–80% of patients, typically presenting with severe intensity and atypical headache types.[7]

Interestingly, we did not find any patients diagnosed with autoimmune thyroiditis, such as Hashimoto's thyroiditis, in our study, even though this condition is known as the most common autoimmune disease, especially in women. Some studies, including a recent one, have shown a possible link comparing autoimmune thyroid disease and headaches, particularly migraines.[8] The absence of such cases in our data may be due to the nature of our neurology clinic, which mainly receives patients with more complex or clearly neurological autoimmune conditions. It is also possible that patients with autoimmune thyroiditis and headache were treated in other clinics, such as internal medicine or endocrinology, and therefore were not captured in our data. Future research with broader inclusion criteria or specific screening for thyroid autoimmunity in patients with headache may help explore this relationship further.

The demographic analysis revealed that the majority of patients with autoimmune-related headaches were females (77.6%) aged between 18 and 45 years (50.5%). This is consistent with existing literature, where autoimmune diseases and primary headaches, particularly migraines, show a higher prevalence in females. Previous data indicate that headaches in patients with MS are more common in women, with a female-to-male ratio of 2:1, independent of age, and often beginning before the diagnosis of MS (78.8%).[9] In another study, with 68% women and 32% men, the ratio of women to men in the headache group among patients with MS was greater than 2.5:1.[10] In other connective tissue autoimmune disease, such as Sjögren's Syndrome (SS), the prevalence ranges from 1% to 3% in the general population, with a female-to-male ratio of approximately 9:1 in the 40–50 year age group, and the most common headache type being migraine.[1]

Headaches in patients with autoimmune diseases were predominantly of the migraine type (44.3%), characterized by moderate intensity,

Table 2: Types of autoimmune diseases and their onset (n=47)

| Variable | Total (n) | % |
|---|---|---|
| **Types of autoimmune diseases** | | |
| Connective tissue disease | 29 | 61.7 |
| Mixed types of autoimmune diseases | 11 | 23.4 |
| Vasculitis | 3 | 6.4 |
| Other autoimmune disorders | 4 | 8.5 |
| Onset [median (IQR)] years | 4 (0–10) | |
| **Onset of autoimmune disease and complaints of headaches** | | |
| Metachronous | 29 | 61.7 |
| Prechronous | 16 | 34 |
| Synchronous | 2 | 4.3 |
| Frequency [median (IQR)] times/month | 14 (1–30) | |
| Duration [median (IQR)] hours | 4 (0.02–24) | |
| NRS | 5 (0–10) | |
| **Trigger factors** | | |
| Movement | 9 | 32.1 |
| Light | 7 | 25 |
| Activities | 6 | 21.4 |
| Sound | 5 | 17.9 |
| Fatigue | 5 | 17.9 |
| Lack of Sleep | 5 | 17.9 |
| Menstruation | 3 | 10.7 |
| Stress | 2 | 7.1 |
| Others | 1 | 3.6 |
| **Additional symptoms** | | |
| Nausea–vomiting | 18 | 66.7 |
| Photophobia | 11 | 40.7 |
| Phonophobia | 10 | 37 |
| Neck pain | 3 | 11.1 |
| Others | 3 | 11.1 |
| Dizziness | 1 | 3.7 |
| Paresthesia | 0 | 0 |
| **Treatments** | | |
| Non-specific abortive | 39 | 83 |
| Prophylaxis | 33 | 70.2 |
| Specific abortive | 11 | 23.5 |
| Adjuvant | 0 | 0 |

*IQR = interquartile range; NRS = numeric rating scale.*

frequent occurrences and common triggers such as fatigue (32.1%), light sensitivity (25%) and physical activities (21.4%), which is consistent with migraine triggers identified in the general population.[11,12] This suggests that the pathophysiology of headaches in these patients might involve a complex interplay between autoimmune inflammatory processes and the mechanisms underlying migraine, such as trigeminovascular system activation and cytokine release.

In migraines, the activation of the trigeminovascular system plays a crucial role in the pathophysiology of headaches, evidenced by its induction of local neurogenic inflammation involving the dural and pial blood vessels. This leads to the extravasation of plasma proteins due to increased meningeal vascular permeability and the activation of immune cells, namely, mast cells and macrophages, around the dural afferents.[1] Activated mast cells produce several inflammatory mediators, including serotonin, histamine, heparin, proteases, arachidonic acid products, proinflammatory cytokines and chemokines. All these substances are highly involved in the sensitization of peripheral trigeminal nerve endings. Sensitized trigeminal C fibres release calcitonin gene-related peptide (CGRP), which interacts with its receptors on dural vessels. Peripheral sensitization of primary afferent trigeminal ganglion (TG) neurons subsequently leads to central sensitization of second-order neurons in the trigeminal nucleus caudalis (TNC), which, upon activation, induces sensitization of third-order neurons in the thalamus.[1]

In the TG, CGRP binds to TG A delta neurons that express CGRP receptors and facilitates nociceptive transmission to second-order neurons in the TNC. Resident glial cells and astrocytes also have CGRP receptors. The interaction of CGRP with its receptors on these cells induces the release of several proinflammatory cytokines, such as tumour necrosis factor

Table 3: Bivariate analysis characteristics of patients with headache who have autoimmune diseases

| Variable | Autoimmune disease | | p-value |
|---|---|---|---|
| | Yes (n=47) n (%) | No (n=54) n (%) | |
| Age (years) | 46.98 (±1.862) | 38.98 (±1.538) | **<0.05*** |
| **Age group** | | | **<0.05†** |
| <18 years old | 0 (0) | 0 (0) | |
| 18–45 years old | 32 (68.1) | 23 (42.6) | |
| 46–59 years old | 15 (31.9) | 19 (35.2) | |
| ≥60 years old | 0 (0) | 12 (22.2) | |
| **Gender** | | | **<0.05‡** |
| Female | 44 (93.6) | 38 (70.4) | |
| Male | 3 (6.4) | 16 (29.6) | |
| **Marital status** | | | 0.87† |
| Married | 30 (63.8) | 35 (64.8) | |
| Single/unmarried | 16 (34) | 14 (25.9) | |
| Divorce/separated | 1 (2.1) | 5 (9.3) | |
| **Jobs** | | | 0.79† |
| Homemakers | 30 (63.8) | 32 (59.3) | |
| Employee | 12 (25.5) | 13 (24.1) | |
| Self-employed | 0 (0) | 4 (7.4) | |
| Student | 3 (6.4) | 1 (1.9) | |
| Others | 2 (4.3) | 4 (7.4) | |
| **Types of headache** | | | **<0.05†** |
| *Tension-like* | 12 (25.5) | 14 (25.9) | |
| *Migraine-like* | 32 (68.1) | 18 (33.3) | |
| Atypical | 2 (6.4) | 22 (40.7) | |
| Onset [median (IQR)] years | 4 (0–10) | 2 (0–8) | **0.01†** |
| Frequency [median (IQR)] times/month | 14 (1–30) | 14.5 (5–31.5) | 0.189† |
| Duration [median (IQR)] hours | 4 (0.1–24) | 7 (0.02–24) | 0.892† |
| NRS | 5 (0–10) | 7 (4–10) | <**0.01†** |
| Trigger factors | | | N.A. |
| Light/heat | 7 (70) | 3 (30) | |
| Sound | 5 (83.3) | 1 (16.7) | |
| Movement | 5 (31.3) | 11 (68.8) | |
| Fatigue | 9 (47.4) | 10 (52.6) | |
| Lack of sleep | 5 (55.6) | 4 (44.4) | |
| Activities | 6 (50) | 5 (50) | |
| Stress | 2 (16.7) | 10 (83.3) | |
| Menstruation | 3 (42.9) | 5 (57.1) | |
| Others | 1 (9.1) | 10 (90.9) | |
| **Dromal symptoms** | | | N.A. |
| Nausea–vomiting | 18 (51.4) | 17 (48.6) | |
| Aura | 2 (50) | 2 (50) | |
| Photophobia | 11 (64.7) | 6 (35.3) | |
| Phonophobia | 10 (66.7) | 6 (33.3) | |
| Neck pain | 3 | 11 (80) | |
| Dizziness | 1 (7.7) | 12 (92.3) | |
| Paresthesia | 0 (0) | 16 (100) | |
| Others | 3 (16.7) | 15 (83.3) | |
| **Treatments** | | | N.A. |
| Specific abortive | 11 (61.1) | 7 (38.9) | |
| Non-specific abortive | 39 (50) | 39 (50) | |

Continued

Table 3: Continued

| Variable | Autoimmune disease | | p-value |
|---|---|---|---|
| | Yes (n=47) n (%) | No (n=54) n (%) | |
| Prophylaxis | 33 (66) | 17 (34) | |
| Adjuvant | 0 (0) | 22 (100) | |

**Independent t-test.*
*†Mann–Whitney test.*
*‡Chi-square.*
*IQR = interquartile range; N.A. = not attainable; NRS = numeric rating scale.*

(TNF)-α and Interleukin (IL)-1ß, which significantly amplify trigeminal nociception.[1]

Autoimmune diseases are multifactorial, involving both genetic and environmental factors. This is similar to headaches, whose occurrence is also caused by multiple factors. By understanding the pathophysiology of headaches as outlined above, the relationship with autoimmune diseases can be further explained.[13] Polymorphisms in genes encoding human leucocyte antigen and cytokines are considered risk factors for autoimmune diseases. Some studies have found that the same genes are involved in the pathogenesis of migraines. These findings suggest that the genetic background may render patients more susceptible to migraines and immunological disorders, and that certain immunological changes, such as alterations in inflammatory cytokine levels, may play a role in the pathophysiology of migraines.[13]

In this case, a significant increase in peripheral proinflammatory cytokines, such as TNF-α, IL-1β, IL-6 and IL-8, whose involvement in many autoimmune diseases is well known, has been found in patients with migraine, both during interictal and ictal periods. The elevation of cytokines and chemokines in migraines, particularly between attacks, indicates an underlying proinflammatory status in migraines regardless of the acute phase of the disease.[13] This may explain the association between migraines and certain inflammatory/autoimmune diseases. These findings are crucial as they suggest that patients with autoimmune diseases who have headaches might benefit from migraine-specific treatments, in addition to managing their underlying autoimmune condition.[13]

The metachronous onset of headaches in over half (61.7%) of the patients suggests that these headaches may develop as a consequence of chronic autoimmune activity, rather than being an early manifestation of the disease. While recent studies (e.g. Samy et al., 2024 and Ha & Chu, 2024) have begun exploring immune-mediated headache mechanisms, our data provide novel insights into the predominance of migraine-like headaches and their delayed onset post-diagnosis (a median of 4 years), suggesting a potential role of chronic inflammation in headache pathogenesis.[13,14] These findings are timely, given the global rise in autoimmune diseases based on the GBD study in 2021 and emerging evidence linking cytokine dysregulation (e.g. TNF-α and IL-6) to migraine chronification. Clinically, this underscores the need for heightened vigilance in patients with autoimmune diseases developing new headaches, as early immunomodulatory or migraine-specific interventions (e.g. CGRP antagonists) may improve outcomes.[13–15] Headaches can also be an initial sign of central nervous system (CNS) involvement in systemic autoimmune diseases, including vasculitis.[16] This highlights the importance of recognizing headaches as a potential symptom and establishing a prompt diagnosis. It is particularly crucial because CNS vasculitis often leads to serious neurological complications, such as ischaemic and haemorrhagic strokes and even blindness.[16] This temporal relationship indicates that clinicians should closely monitor for the development of headaches as a possible complication in patients with long-standing autoimmune diseases.

Moreover, the widespread use of non-specific abortive and prophylactic medications in the majority of these patients highlights a gap in the targeted management of headaches within this population. Many migraine sufferers often turn to alternative or complementary treatments out of desperation. The biggest challenge in migraine research lies in the complex, multifactorial pathogenesis of migraine headaches, which are triggered by a combination of genetic, endocrine, metabolic and environmental factors. As a result, the exact pathology leading to migraine attacks remains poorly understood.[17]

Previous studies have indicated that migraine headaches are a manifestation of neurogenic inflammation, involving the activation and sensitization of trigeminovascular afferent nerves, which project to second-order neurons in the brainstem. However, identifying the initial cause and developing effective treatments remains elusive.[17]

The repeated use of acute medications is a major risk factor for developing chronic migraine, with many suggested mechanisms for this phenomenon. The fact that withdrawal or detoxification procedures can often revert chronic migraines to an episodic pattern in a large majority of patients strongly supports the idea of a causative role.[18] The frequent use of acute medications, such as ergotamine, opioids, triptans, simple analgesics and combination analgesics containing caffeine or codeine, is believed to cause rebound headaches.[19] Considering the higher likelihood of migraine-type headaches in patients with autoimmune diseases, introducing more specific migraine treatments could potentially improve patient outcomes.

This study also underlines the importance of distinguishing between primary headaches and those secondary to autoimmune conditions. Accurate classification is essential for guiding treatment strategies and improving patient quality of life. The significant association between age, gender and headache type with autoimmune status in this study suggests that these factors could serve as clinical indicators for suspecting autoimmune involvement in patients presenting with new-onset headaches. This study revealed significant associations between autoimmune status and patient demographics, as well as headache phenotype ($p<0.05$). Patients with autoimmune disease were significantly more likely to be older and female compared with those without, consistent with the known epidemiology of autoimmune disorders and primary headache syndromes.[1] Notably, certain headache phenotypes (particularly migraine and tension-type headache) were disproportionately represented in the autoimmune group, aligning with Samy et al. (2024), who found that tension-type and migraine headaches were specifically linked to mucocutaneous manifestations in patients with SLE.[14] Clinically, these findings suggest that an older

female presenting with new-onset migraine or tension-type headache should prompt consideration of underlying autoimmune pathology and may warrant targeted evaluation (e.g. autoimmune serologies or rheumatology referral), illustrating how such demographic and phenotypic features can inform clinical decision-making. However, the retrospective design and potential confounders (such as comorbidities or medications) limit causal inference, and these associations should be validated in prospective studies.

Despite the observed predominance of migraine-type headaches (44.3%) among patients with autoimmune diseases in this study, it is important to acknowledge that this finding may be influenced by the demographic characteristics of our study population. The high proportion of females aged 18–45 years, who are inherently at increased risk for primary headache disorders such as migraines, presents a potential confounding factor. Therefore, while autoimmune mechanisms, including chronic inflammation and cytokine dysregulation, are plausible contributors to headache pathogenesis, the current retrospective and cross-sectional design does not allow for establishing a direct causal relationship between autoimmune status and headache type. The association observed in this study may partly reflect an overlap of prevalent demographics between autoimmune diseases and primary headaches rather than a direct pathophysiological link. Prospective studies with matched control groups and stratified analyses are needed to disentangle demographic influences from disease-specific effects in this context.

From a clinical perspective, these findings underscore the importance of considering autoimmune screening in patients with chronic or refractory headaches of unclear aetiology, particularly when accompanied by systemic features. Recognizing such patterns may lead to more personalized headache management, involving closer collaboration between neurology and rheumatology, and possibly incorporating immunomodulatory therapies in select cases. Given the cross-sectional nature of this study, future longitudinal research is warranted to explore causal relationships between autoimmune activity and headache development, assess the predictive value of immunological markers and determine the impact of specific autoimmune treatments on headache characteristics and therapeutic outcomes.

## Conclusions

This study demonstrates that age, gender and headache type are significantly associated with autoimmune status among patients with primary headaches. These findings highlight the potential utility of demographic and clinical headache characteristics as preliminary indicators for underlying autoimmune involvement, particularly in patients presenting with new-onset migraine or tension-type headaches. The integration of these indicators into clinical evaluation may facilitate earlier identification and management of autoimmune comorbidities. Further prospective studies are needed to confirm these associations and explore their diagnostic value in broader and more diverse populations. ❑


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