BRIDGING NEUROPHYSIOLOGY AND IMMUNOLOGY IN CHRONIC HEADACHE: INSIGHTS FROM A CLINICAL COHORT STUDY

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Abstract: Chronic headache disorders, particularly chronic migraine, pose substantial diagnostic and therapeutic challenges due to their multifaceted neurobiological mechanisms. The present study investigates the clinical, neurophysiological, and neuroimmunological profiles of major chronic headache forms and develops individualized, optimization-oriented treatment strategies. A cohort of patients with chronic migraine and other persistent cephalalgic syndromes underwent an integrated assessment protocol comprising EEG-based neurophysiological evaluation, autonomic function testing, and detailed immunological profiling. The analysis identified distinct neurophysiological signaturesincluding disrupted cortical excitability patterns and autonomic dysregulationthat differentiated chronic migraine from other chronic headache subtypes. Concurrently, immunological assessments revealed characteristic cytokine patterns correlating with headache frequency, intensity, and chronicity, reinforcing the role of neuroinflammatory mechanisms in sustaining the disorder. Implementation of tailored therapeutic regimens, combining pharmacological therapy with neuromodulatory and lifestyle-based interventions, resulted in markedly superior clinical outcomes compared with standard treatment approaches. These findings underscore the clinical necessity of a multimodal, biologically informed diagnostic and therapeutic framework for the effective management of chronic headaches.

Keywords: Chronic headache, migraine, neurophysiology, neuroimmunology, optimization, treatment

INTRODUCTION

Chronic headache disorders, with chronic migraine at the forefront, represent one of the most prevalent and disabling groups of neurological conditions worldwide. Their high recurrence, refractoriness to standard therapies, and profound influence on functional capacity create substantial medical, social, and economic burdens. The complexity of these disorders arises from multidimensional neurobiological mechanisms that extend far beyond classical vascular explanations, encompassing cortical, brainstem, autonomic, and immune-mediated pathways. According to the ICHD-3 criteria, chronic migraine is defined as ≥15 headache days per month for more than three consecutive months, with at least eight days meeting the diagnostic criteria for migraine. This classification reflects the transformation from episodic to chronic states, a transition believed to be driven by persistent nociceptive input, central sensitization, and cumulative neuroimmune dysregulation. Within this context, the pathophysiology of chronic migraine no longer appears as a singular mechanism but as a dynamic interaction among neurophysiological instability, altered pain-modulating circuits, and sustained inflammatory signaling. To contribute to this evolving paradigm, the present research examines the clinical, neurophysiological, and neuroimmunological characteristics of various chronic headache forms within a structured patient cohort. Participants with chronic migraine and other persistent cephalalgic syndromes underwent a comprehensive, multimodal diagnostic protocol integrating three analytical pillars: (1) EEG-based functional assessment to detect disruptions in cortical excitability and network synchronization; (2) autonomic function testing, including HRV parameters, to evaluate sympathetic–parasympathetic imbalance; and (3) immunological profiling focused on cytokines such as IL-6, TNF-α, IL-10, and related markers associated with neuroinflammatory activity. Neurophysiological findings revealed reproducible alterations in thalamocortical rhythmicity, including diminished alpha power, excess theta–delta

activity, and heightened inter-regional coherence—indicative of impaired inhibitory control and cortical hyperreactivity. These patterns were more pronounced in chronic migraine compared to other chronic headache types, supporting the hypothesis of sustained cortical dysmodulation as a core feature of the disorder. Parallel immunological evaluations uncovered distinct cytokine signatures differentiating chronic migraine from tension-type and mixed headache phenotypes. Elevated IL-6 and TNF-α levels correlated with attack frequency and pain intensity, while reduced IL-10 levels suggested weakened anti-inflammatory regulation. Such findings reinforce the conceptualization of chronic migraine as a neuroimmune disorder where inflammatory processes perpetuate neural sensitization. Beyond biological markers, the study also highlights the importance of psychological and behavioral components. Anxiety, depressive symptoms, sleep disturbances, and maladaptive stress responses emerged as significant contributors to central sensitization, partly mediated through dysregulation of the hypothalamic–pituitary–adrenal axis. These factors underscore the necessity of integrating neuropsychological assessment into the diagnostic and therapeutic framework. In response to the multidimensional nature of chronic headaches, personalized treatment strategies were developed. These protocols combined pharmacological therapy with neuromodulation techniques, targeted lifestyle interventions, autonomic stabilization, sleep regulation, and stress-management approaches. Clinical outcomes demonstrated that individualized, multimodal regimens achieved more substantial reductions in headache frequency and intensity compared with conventional treatment models, reflecting the therapeutic value of tailoring interventions to neurobiological and psychophysiological profiles.

Collectively, these findings emphasize that effective management of chronic headaches requires a shift from linear, symptom-oriented approaches to biologically informed, system-level strategies. By integrating neurophysiology, immunology, and clinical phenotyping, this study contributes to the growing evidence supporting a

multimodal, personalized approach as the most effective pathway for improving patient outcomes in chronic headache disorders.

MATERIALS AND METHODS

This observational clinical study included 112 patients aged 18 to 60 years diagnosed with chronic headache forms, primarily chronic migraine, based on the International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria. The cohort was recruited from the neurology departments of regional medical centers between 2021 and 2023. Participants were grouped according to headache subtype and duration, with additional stratification by comorbid factors such as anxiety and sleep disturbances.All patients underwent a comprehensive clinical neurological examination, including detailed headache history, pain intensity assessment using the Visual Analog Scale (VAS), and headache-related disability evaluated through the Migraine Disability Assessment (MIDAS) questionnaire. Neurophysiological investigations comprised resting-state electroencephalography (EEG), brainstem auditory evoked potentials (BAEP), and heart rate variability (HRV) analysis to assess central and autonomic nervous system function. Neuroimmunological evaluation involved serum analysis of pro-inflammatory and anti-inflammatory cytokines (IL-1β, IL-6, IL-10, TNF-α), immunoglobulin profiles (IgG, IgA, IgM), and lymphocyte subset profiling via flow cytometry. Laboratory procedures followed standardized ELISA and immunophenotyping protocols, with samples processed in certified immunology laboratories. Patients received individualized treatment regimens based on clinical and instrumental findings, including pharmacological therapy (antiepileptics, antidepressants, monoclonal antibodies against CGRP), neuromodulation techniques (transcranial magnetic stimulation), and behavioral interventions (CBT, sleep hygiene education). Treatment efficacy was monitored over a 6-month follow-up period through monthly VAS scores, reduction in attack frequency, and patient-reported outcome measures.Statistical analysis was performed using SPSS software (version 25.0), with significance set at $p<0.05$. Parametric and non-parametric tests were applied as appropriate, including ANOVA,

chi-square, and Spearman's correlation to explore associations between clinical variables, neurophysiological markers, and immunological parameters.

RESULTS

Among the 112 patients evaluated, 68 (60.7%) were diagnosed with chronic migraine, while 44 (39.3%) presented with other chronic headache forms, including tension-type and mixed-type headaches. The average duration of headache history was 7.4 ± 2.1 years. Clinical assessment revealed a statistically significant higher frequency of severe pain episodes and functional disability in the chronic migraine subgroup ($p<0.01$), with a mean VAS score of 7.9 ± 1.1 and MIDAS score of 32.5 ± 6.4. Neurophysiological findings showed that 74% of chronic migraine patients exhibited diffuse EEG slowing in the alpha range, with increased cortical excitability indicated by enhanced photic stimulation responses. BAEP recordings revealed delayed interpeak latencies (I–V) in 36% of cases, suggesting brainstem dysfunction. HRV analysis demonstrated parasympathetic underactivity and heightened sympathetic tone, particularly in patients with comorbid anxiety.Neuroimmunological profiling identified elevated levels of pro-inflammatory cytokines—especially IL-6 and TNF-α—in chronic migraine patients compared to controls ($p<0.05$), alongside a reduction in regulatory cytokine IL-10. Immunoglobulin analysis showed a moderate increase in IgA and IgG titers, while flow cytometry revealed an imbalance in CD4+/CD8+ T-cell ratios and reduced B-cell populations in a subset of patients with prolonged migraine history.Treatment outcomes indicated that personalized, multimodal interventions led to a ≥50% reduction in headache frequency in 62.5% of patients over six months. Combination regimens incorporating CGRP monoclonal antibodies, neuromodulation, and cognitive behavioral therapy yielded the highest efficacy. Patients receiving only pharmacological monotherapy showed significantly lower improvement rates ($p<0.01$), underscoring the importance of individualized, integrative treatment approaches.

DISCUSSION

The findings of this study emphasize the multifactorial pathophysiology of chronic headaches, particularly chronic migraine, which is increasingly recognized as a disorder involving complex interactions between neural excitability, autonomic imbalance, and immune dysregulation. The observed EEG alterations, including diffuse alpha slowing and photic hypersensitivity, support existing literature suggesting cortical hyperexcitability as a hallmark of migraine chronification. These neurophysiological disturbances align with previous studies indicating disrupted thalamo-cortical processing and impaired inhibitory control in chronic migraine patients [3].Furthermore, brainstem auditory evoked potential delays and HRV data point to significant dysfunction within the brainstem-autonomic axis, corroborating reports that highlight its role in modulating pain pathways and vascular tone [4]. These disturbances may underlie the persistence and intensification of headache episodes, especially in patients with comorbid anxiety, as supported by our findings.Immunologically, elevated pro-inflammatory cytokines (IL-6, TNF-α) and reduced IL-10 levels indicate an ongoing inflammatory state, potentially contributing to central sensitization and neuronal hyperresponsiveness. Such immune imbalances mirror findings in recent neuroimmunology research that associates migraine with systemic and neurogenic inflammation [5]. The observed T-cell and B-cell profile changes suggest immune exhaustion or compensatory modulation in chronic headache sufferers, though causality remains to be elucidated.Importantly, our study demonstrated that individualized, multimodal treatment regimens—particularly those integrating neuromodulation and behavioral interventions alongside pharmacotherapy—significantly outperformed standard monotherapy approaches. This supports a paradigm shift toward personalized headache management, consistent with emerging clinical guidelines advocating for stratified care models based on neurobiological profiles.However, limitations include a relatively small sample size and the observational design, which may constrain generalizability.

Future randomized controlled trials are warranted to validate these findings and further delineate the mechanistic pathways involved in chronic headache disorders.

CONCLUSION

This study provides compelling evidence that chronic headache disorders, especially chronic migraine, are characterized by a confluence of neurophysiological instability, autonomic dysfunction, and immune system dysregulation. The identification of specific EEG changes, brainstem processing delays, and cytokine imbalances underscores the need for a comprehensive diagnostic framework that extends beyond symptomatic assessment. Importantly, the demonstrated efficacy of individualized, multimodal treatment strategies highlights the clinical value of integrating neurophysiological and neuroimmunological findings into therapeutic planning. These insights advocate for a shift toward personalized medicine in chronic headache management, aiming to enhance patient outcomes through targeted interventions. Future investigations, particularly those employing longitudinal and interventional designs, are essential to validate and refine this integrative model.

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