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CGRP as a Biochemical Biomarker in Migraine Diagnosis: A Systematic Review

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ABSTRACT

Introduction. Migraine is one of the leading causes of disability worldwide, particularly among young women. Due to the key role of calcitonin gene-related peptide (CGRP) in the activation of the trigeminovascular pathway, this molecule has emerged as a major candidate for a biochemical marker that could facilitate precise diagnosis and classification of patients.

Aim. The aim of this review is to systematize the most recent evidence regarding the potential of CGRP as a diagnostic biochemical biomarker of migraine.

Methods. The study was conducted in accordance with PRISMA guidelines, with a systematic search of MEDLINE, Web of Science, and Embase databases for publications from the last six years. A total of 166 records were identified, of which 13 articles were included in the final analysis following rigorous selection.

Results. Most of the analyzed studies confirm that CGRP levels are significantly elevated in patients with migraine, particularly during the ictal phase. This has been demonstrated in serum, plasma, saliva, and tear fluid. CGRP levels were found to correlate with pain intensity and the severity of clinical symptoms. Higher concentrations were observed in chronic migraine (CM) compared to episodic migraine (EM). However, findings regarding interictal levels remain inconsistent, with some studies showing no significant differences between patients and healthy controls.

Conclusions. CG RP remains a promising, yet still imperfect, diagnostic biomarker. Its clinical utility is limited by considerable methodological heterogeneity and the influence of individual factors such as sex, age, and comorbidities.

Keywords: Migraine; CGRP; Biomarker; Calcitoningene-relatedpeptide; diagnosis

1. Introduction

According to the Global Burden of Disease study, migraine is the second leading cause of disability worldwide, and ranks first among young women [1]. The term "migraine" derives from the Greek word hemicranias, meaning "half of the head," which reflects the typical clinical presentation of the disorder, characterized by unilateral head pain in the majority of patients [2]. Migraine (MH) is a prevalent disorder affecting approximately 18% of women and 6% of men, while chronic migraine (CM) occurs in about 2% of the global population [3]. The condition is particularly debilitating, as it significantly reduces the quality of life and impairs functioning in occupational, familial, and social domains [3]. MH is most prevalent among individuals aged 18–44 years. In subsequent age cohorts, its prevalence declines to 15.9% among those aged 45–64 years, 7.3% in those aged 65–74 years, and 5.1% in the population over 75 years of age [4, 5]. Research further indicates that women are more susceptible to developing MH than men [4].

The exact mechanisms underlying the pathogenesis of MH remain unknown. Historically, it was assumed that the pain during an attack resulted first from the constriction, and subsequently the dilation, of cerebral arteries [6, 7]. However, this hypothesis has been refuted, and studies by Amin et al. demonstrated that extracranial arterial dilation does not play a significant role in the development of MH [4, 6]. Currently, the neurovascular hypothesis is widely accepted, according to which the source of pain is the activation of the trigeminovascular system, responsible for transmitting pain signals from meningeal blood vessels to higher structures of the central nervous system [7]. The activation of trigeminal sensory fibers leads to the release of vasoactive neuropeptides, such as CGRP (calcitonin gene-related peptide), neurokinin A, and substance P, which results in vasodilation and subsequently leads to neurogenic inflammation [8, 9]. Serotonin receptors also play a role in the pathogenesis of MH, as well as genetic factors in a subset of patients, most commonly characterized by polygenic inheritance [10].

A typical MH attack lasts from 4 to 72 hours, is unilateral, pulsating in nature, and is characterized by moderate or severe intensity that is aggravated by physical activity. The attack is accompanied by nausea or vomiting, as well as sensitivity to light, noise, or odors [9]. The course of a MH attack encompasses a sequence of several phases: the prodromal phase, aura (affecting approximately one-third of patients), the headache phase itself, the resolution phase, and the postdromal phase [9]. The primary tool used for diagnosing and categorizing migraines and other types of headaches is the International Classification of Headache Disorders (ICHD),

developed by the International Headache Society (IHS) [11]. It distinguishes between episodic migraine (EM) and chronic migraine (CM), and also divides cases into those with aura (MA) and without aura (MO).

The occurrence of a MH attack is influenced by numerous risk factors. Among non-modifiable factors, sex, age, and genetic predispositions play a crucial role. Conversely, modifiable factors include, among others, circadian rhythm disturbances, meteorological fluctuations, emotional stress, hormonal changes, as well as dietary habits (e.g., consumption of chocolate, coffee, or alcohol), and the use of certain medications, including oral hormonal contraception [5, 12, 13].

According to the definition proposed by the National Institutes of Health (NIH), biomarkers are substances identifiable in blood or tissues, the presence of which indicates underlying pathological alterations or disease processes. Certain biomarkers play a significant role in predicting the clinical course of diseases. Research into novel biomarkers contributes to advancements in the diagnostics and treatment of various diseases [14].

To date, no reliable biomarkers measurable in blood or cerebrospinal fluid have been identified that could be associated with EM or CM [15, 16]. Most studies thus far have focused on vasoactive neuropeptides that play a role in MH attacks; these include calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide (PACAP).

Due to the ease and speed of obtaining results, the development of specific and sensitive biochemical biomarkers remains a priority. Their clinical implementation could significantly facilitate patient differentiation and diagnosis in clinically ambiguous cases.

Calcitonin gene-related peptide (CGRP) is a 37-amino acid neuropeptide belonging to the calcitonin family. In humans, two forms of this compound are identified: alpha-CGRP and beta-CGRP. They are encoded by distinct genes (CALCA and CALCB, respectively), and their sequences differ by three amino acids [17]. Both peptides are widely expressed in the central and peripheral nervous systems, whereas beta-CGRP is particularly abundant in the enteric nervous system [18].

Preclinical studies confirm that CGRP activity within both the central and peripheral nervous systems plays a fundamental role in the mechanisms of MH pathogenesis [19]. This peptide interacts with glial cells, mast cells, as well as blood vessels and trigeminal fibers within the

meninges and trigeminal ganglia [20]. By initiating neurogenic inflammation and the release of sensitizing agents, CGRP potentiates vasodilation in the meninges [21]. This potent vasoactive mediator is essential in the stimulation of the trigeminal pathway, which is responsible for pain perception during an attack [18, 22].

The objective of this review is to systematize the latest reports regarding the potential of CGRP as a diagnostic biochemical biomarker for MH.

2. Methods

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The research process was initiated by conducting a comprehensive search of the MEDLINE (via the PubMed platform), Web of Science, and Embase electronic databases, restricting the search scope to English-language publications issued over the past six years. The search strategy utilized MeSH descriptors for the PubMed database, combining selected keywords into a Boolean query (migraine AND biomarkers AND CGRP).

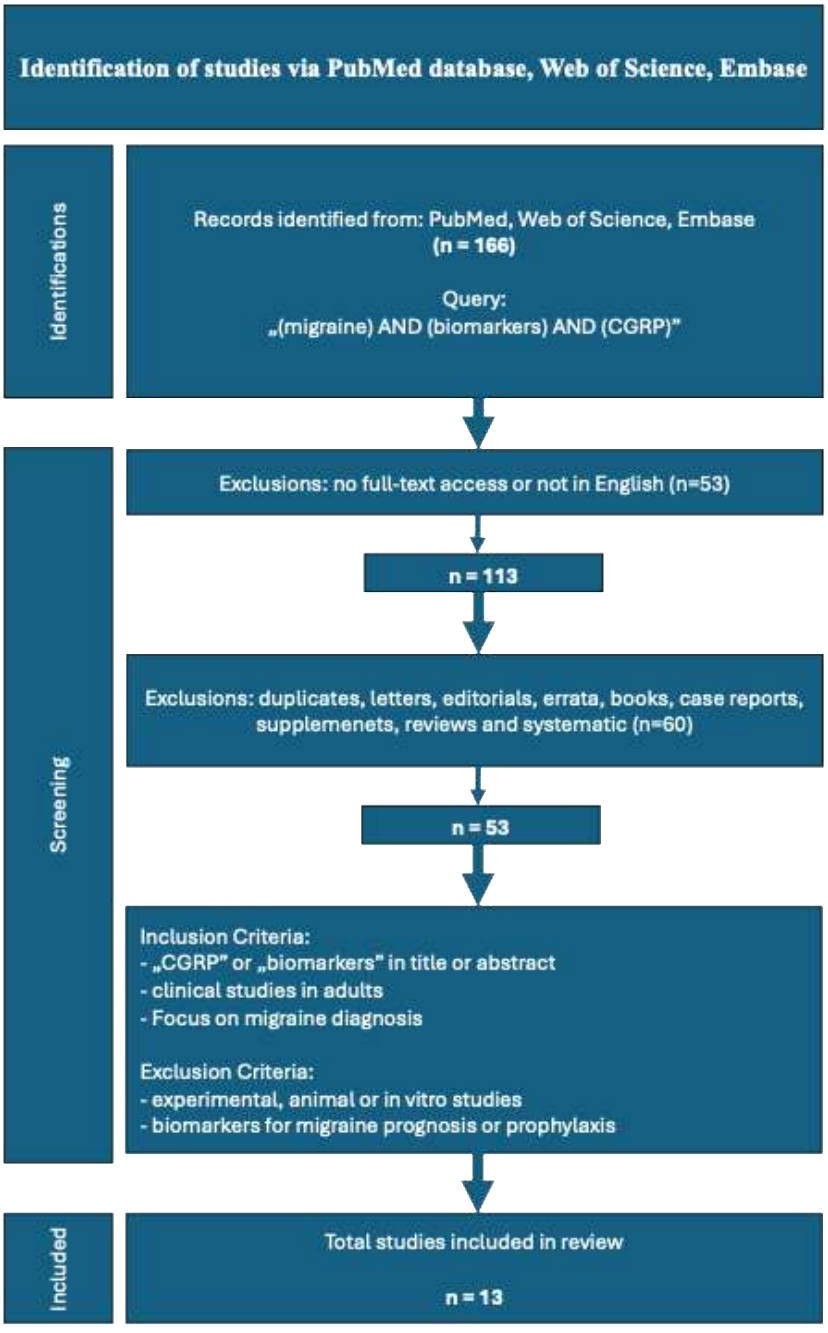
The initial search yielded 166 publications. Articles lacking full-text access and those not published in English were excluded (n = 53). Furthermore, duplicate records, letters to the editor, commentaries, errata, books and documents, case reports, supplementary materials, as well as review articles and systematic reviews were excluded (n = 60). Only original research, including randomized controlled trials, non-randomized trials, and observational studies (cohort, case-control, and cross-sectional), was qualified for further analysis.

The remaining 53 publications underwent a detailed evaluation according to the established inclusion and exclusion criteria. The inclusion criteria were as follows: (1) the presence of the terms "CGRP" or "biomarker" in the title or abstract, (2) clinical studies conducted in an adult population, and (3) studies focused on the diagnosis of MH. The exclusion criteria encompassed: (1) experimental, in vitro, and animal studies, and (2) publications regarding biomarkers in the context of other aspects of MH (e.g., prognosis or prophylactic treatment) that did not directly relate to the diagnosis of the disease.

Following a rigorous full-text review, 13 articles were ultimately selected, which form the basis of the present review (Fig. 1). Key data were extracted from each of the selected studies,

including the author's name and year of publication, the number of participants, the clinical type of MH (accounting for the presence of aura, the episodic or chronic form, and the phase of the attack), as well as the methodology applied and the results obtained.

Figure 1. The flowchart for the selection process; n: number of studies.



3. Results

The first study, conducted in 1990 by Goadsby and colleagues, focused on evaluating plasma CGRP concentrations during spontaneous MH attacks [6, 23]. It was demonstrated that blood samples collected from the external jugular vein during the headache phase were characterized

by elevated CGRP levels in MH patients compared to healthy controls (HC) [23]. These findings initiated intensive research into the role of CGRP, highlighting its potential significance as a candidate biomarker for MH.

In a study conducted by Greco and colleagues, CGRP concentrations were evaluated in blood plasma collected from the antecubital vein of 27 patients with EM and 28 individuals with CM associated with medication overuse. The results demonstrated significantly higher CGRP levels in the group of patients with CM and medication overuse compared to those with EM [24]. However, no significant associations were found between CGRP concentration and factors such as sex, age, or disease duration. Additionally, a positive correlation was observed between CGRP levels and the expression of miR-382-5p and miR-34a-5p (Table 1) [24].

In a subsequent large-scale study conducted by Pereda-Perez S. and colleagues, 296 participants were enrolled, comprising 101 patients with CM, 98 with EM, and 97 individuals constituting the control group (CG). It was demonstrated that serum CGRP concentrations were significantly higher in CM patients compared to both the EM and CG groups, whereas no significant differences were noted between the EM and CG. Although interictal CGRP levels were elevated in CM patients relative to the other groups, their utility in differentiating distinct MH types proved limited [25].

In their study, Latif R. and colleagues evaluated CGRP and ApoE concentrations in 28 women aged 18–25 years, 14 of whom were diagnosed with neurologist-confirmed MH. No statistically significant differences were demonstrated in serum CGRP levels between MH patients in the interictal phase and the control group [26]. In contrast, ApoE concentration was significantly higher in both the interictal and ictal phases of MH compared to the control group. However, the authors emphasize that CGRP may exhibit "sufficient" diagnostic value in differentiating MH patients in the ictal phase from healthy individuals [26].

In a study conducted by Alpuente A. and colleagues, interictal salivary CGRP concentrations and the profile of its changes during MH attacks were evaluated in 44 women, including 22 with EM and 22 constituting the control group. It was demonstrated that salivary CGRP levels were significantly higher in MH patients during both the interictal period and an attack compared to healthy subjects. During an attack, a marked increase in CGRP concentration was observed, reaching peak values in the early headache phase [27]. Based on the dynamics of CGRP concentration changes between the pre-ictal and ictal phases, patients were divided into

CGRP-dependent (79.6%) and CGRP-independent (20.4%) attack groups. Additionally, it was found that accompanying symptoms, such as photophobia and phonophobia, were significantly more frequent in the CGRP-dependent attack group. Furthermore, a statistically significant elevation in salivary CGRP concentration during spontaneous MH attacks was noted primarily in the CGRP-dependent group [27].

In a study conducted by Vural S. and colleagues, 135 individuals participated, comprising 85 patients with MH and 50 individuals constituting the control group. Serum concentrations of CGRP and PTX-3 were evaluated. It was demonstrated that CGRP levels were significantly higher in patients during a MH attack compared to the control group. Furthermore, a positive correlation was found between CGRP concentration and the intensity of perceived pain. Conversely, no significant differences in CGRP levels depending on sex or the presence of aura were observed in subgroup analyses [28].

In a study conducted by Scher A. and colleagues, the concentrations of CGRP and nerve growth factor (NGF) were evaluated in 264 soldiers, including 230 men and 34 women. It was demonstrated that CGRP levels were approximately 60% higher in men compared to women. Simultaneously, CGRP concentrations were approximately 30% lower in participants experiencing a headache at the time of blood draw compared to individuals without a headache. In contrast to CGRP, the NGF level did not differ significantly between women and men [29].

In a study conducted by Tchivilwya I. E. and colleagues, comprising 80 participants, plasma CGRP concentrations were evaluated. No significant differences were demonstrated between CGRP levels in individuals with MH during the interictal period and the values observed in the control group (HC). However, a positive association was found between CGRP concentration and age, as well as a weak correlation with body mass index (BMI). No significant associations were observed between CGRP levels and other analyzed characteristics of the participants [30].

In a study conducted by Li C. and colleagues, serum CGRP concentrations were evaluated in patients with MA depending on the presence of a patent foramen ovale (PFO). The analysis included 153 individuals, 51 of whom were found to have a PFO. It was demonstrated that patients with MH coexisting with PFO were characterized by significantly higher CGRP levels compared to patients without this defect [31].

In a study conducted by de la Guerra-Sasian L. and colleagues, the focus was placed on analyzing the factors influencing the determination of CGRP in plasma. It was demonstrated that the addition of protease inhibitors (PI) to plasma samples significantly increased the detectability of α-CGRP, while simultaneously having a lesser impact on β-CGRP concentrations [32]. No significant correlation was found between α- and β-CGRP levels in the plasma. Furthermore, plasma samples containing PI were characterized by higher CGRP concentrations compared to serum samples. The analysis also revealed a negative correlation between age and α-CGRP levels, whereas no association was observed between α- and β-CGRP concentrations and the sex of the participants [32].

In a study by Bai Y. and colleagues, plasma and salivary CGRP concentrations were evaluated in patients with vestibular MH (VM individuals with vestibular MH). The analysis included three groups: individuals with VM corresponding to EM (VM, n = 81), patients with CM without vestibular symptoms (CM, n = 73), and healthy controls (HC, n = 59). It was demonstrated that plasma CGRP levels in VM patients were significantly lower compared to the CM group, whereas they did not differ significantly from the values observed in the control group. A similar relationship was noted in the case of salivary CGRP concentrations, which were also lower in VM than in CM, with a lack of significant differences between VM and HC. No significant correlations were found between plasma and salivary CGRP levels and clinical symptoms in both CM and VM [33]. The obtained results suggest that interictal plasma and salivary CGRP concentrations possess limited value as potential biomarkers for vestibular MH.

In a study conducted by Sreevani N. and colleagues, 296 individuals participated, comprising 266 women and 30 men. The participants were divided into three groups: patients MA (n = 101), MO (n = 98), and a CG (n = 97). Serum concentrations of CGRP, VIP, and PACAP-38 were evaluated. It was demonstrated that CGRP levels were significantly higher in MH patients compared to the control group. The highest CGRP values were recorded in the group of patients with MA, lower in the group without aura, and the lowest among healthy individuals [34].

In another large-scale study conducted by Huang Q. and colleagues, 269 individuals participated, including 184 MH patients and 85 healthy individuals constituting the control group. It was demonstrated that CGRP concentrations were significantly higher in MH patients compared to the control group [35]. Based on ROC curve analysis, a cut-off value was established at 40 pg/ml, which allowed for the stratification of the studied population into high

and low CGRP concentration groups. Comparative analysis revealed that patients with higher CGRP levels were characterized by a greater monthly frequency of MH attacks and a more frequent occurrence of pericranial tender points [35].

Kamm K. and colleagues evaluated CGRP concentration in tear fluid during spontaneous MH attacks. It was demonstrated that during the phase of maximum pain intensity, CGRP levels were significantly higher compared to both the onset of the attack and the period following its resolution. Furthermore, it was observed that the elevation in CGRP concentration was more pronounced in cases where the time elapsed since headache onset was shorter [36].

The obtained results indicate that CGRP concentration in tear fluid increases during spontaneous MH attacks, suggesting that its determination in this biological material may be reliable and potentially utilized as a biomarker for MH in the future.

Tabele 1. The recent research investigating CGRP in MH

Ref.	Year	Autor	Population	Comparison	Sample / method	Results (CGRP)
24	2020	Greco et al.	n= 55	EM (27), CM + medication overuse (28)	Plasma ELISA	↑ w CM vs EM
25	2020	Pereda-Perez S. et al.	n= 296	CM (101), EM (98), CG (97)	Serum ELISA	↑ in CM vs EM and CG
26	2021	Latif R. et al.	n = 28	Women MH (14), CG (14)	Serum ELISA	no difference interictally; ↑ during attack
27	2022	Alpuente A. et al.	n = 44	Women EM (22), CG (22)	Saliva and Plasma ELISA	↑ EM and during attacks vs CG
28	2022	Vural S. et al	n = 135	MH (85), CG (50)	Serum ELISA	↑ during attack
29	2023	Scher A et al.	n = 264	men (230), women (34) MO (37), MA (39), post-traumatic headache (35), CG (125)	Plasma ELISA	↑ in men; ↓ during headache
30	2023	Tchivilwya I. et al.	n = 80	CG (20), TMD without MH (20), migraine without TMD (20), TMD with MH (2)	Plasma ELISA	no significant difference
31	2024	Li C. et al.	n = 153	MH + PFO (51), without PFO (102)	Serum ELISA	↑ in MH with PFO
32	2025	de la Guerra-Sasian L. et al.	n = 43	CM (43)	Plasma ELISA	↑ detection in plasma with protease inhibitors
33	2025	Bai Y. et al.	n = 213	VM (81), CM (73), CG (59)	Plasma + saliva ELISA	↓ in VM vs CM
34	2025	Sreevani N. et al.	n = 296	MA (101), MO (98), CG (97)	Serum ELISA	↑ MA > MO > CG
35	2025	Huang Q. et al	n = 269	MH (184), CG (85)	Serum MP-CLIA	↑ MH
36	2025	Kamm K. et al	n = 14	MH (14)	Tear fluid ELISA	↑ during attack

MH- migraine; CM – chronic migraine, EM – episodic migraine, CG – controls group, MA – migraine with aura, MO – migraine without aura, CGRP - calcitonin gene-related peptide, TMD - chronic temporomandibular disorder, PFO - patent foramen oval, VM- individuals with vestibular migraine, MP-CLIA - magnetic particle-based chemiluminescent immunoassay, ELISA – enzyme-linked immunosorbent assay

4. Discussion

Although MH is one of the leading causes of disability worldwide, its diagnosis still relies primarily on the clinical criteria outlined in the ICHD classification. The identification of migraine-specific biomarkers would be of crucial importance in the context of precision medicine, facilitating more accurate diagnosis and a more precise classification of its subtypes. Despite years of research directed towards isolating diagnostic markers for MH, to date, no reliable biomarkers applicable in clinical practice have been identified, regardless of the type of biological material analyzed, such as peripheral blood, cerebrospinal fluid, saliva, or urine [6].

The present systematic review analyzed current evidence regarding the potential of CGRP as a diagnostic biomarker for MH. The obtained results indicate that although CGRP plays a pivotal role in the pathophysiology of MH, its clinical utility as a reliable biomarker remains limited and dependent on multiple factors.

The majority of available publications - ranging from Goadsby's groundbreaking research in 1990 [23] to the latest reports - confirm that CGRP concentration in MH patients is significantly elevated, particularly during the ictal phase [25, 27]. Higher concentrations of this peptide have been noted not only in serum and plasma but also in alternative biological materials, such as saliva or tear fluid [33, 36]. Specifically, studies have demonstrated that CGRP levels correlate with pain intensity and the severity of clinical symptoms, suggesting its involvement in the mechanisms generating and sustaining a MH attack [27, 28]. Simultaneously, it has been observed that the increase in CGRP concentration is more pronounced in specific MH phenotypes, such as CM or CGRP-dependent attacks [27].

Despite promising indications, the scientific data concerning CGRP remain heterogeneous. In a subset of analyses, no significant differences in CGRP levels were demonstrated between patients in the interictal phase and healthy individuals, which limits its application as a diagnostic marker in clinical settings [26, 30]. Additionally, in certain populations, such as patients with vestibular MH, CGRP levels did not differ significantly from the values observed

in control groups, which underscores the heterogeneity of the disease and the complexity of its pathophysiology [33].

A crucial factor influencing the interpretation of the obtained data is the substantial methodological heterogeneity across the conducted studies. CGRP concentrations may vary depending on the type of biological material (plasma, serum, saliva, tear fluid), the site of sample collection, as well as the analytical methods employed. For instance, the supplementation of plasma samples with protease inhibitors significantly enhances the measurability of this neuropeptide's levels, directly demonstrating the necessity for the standardization of laboratory procedures [32]. The lack of standardized measurement methodologies constitutes one of the primary limitations in evaluating CGRP as a biomarker.

The variability of CGRP levels is additionally influenced by individual factors, such as age, sex, the presence of comorbidities, or specific clinical characteristics of the MH. Although certain analyses indicate an association between biomarker concentration and patient age or attack frequency, other reports fail to corroborate these correlations, suggesting a high degree of complexity in the mechanisms regulating the secretion of this peptide [28, 30]. Furthermore, the discrepancies between MH with and without aura, as well as between the episodic and chronic forms, underscore the necessity of incorporating the disease phenotype into biomarker analyses [34].

It should be noted that in current research trends, CGRP is increasingly less often considered as an isolated diagnostic parameter. A growing body of scientific evidence indicates the necessity of implementing multi-component biomarker panels that, alongside CGRP, encompass other vasoactive neuropeptides, such as VIP and PACAP-38, as well as regulatory molecules, including specific microRNAs [24, 26, 28, 34]. Such an approach may enhance diagnostic sensitivity and specificity compared to a single marker.

Limitations of the present review include the relatively small number of included studies, the heterogeneity of the study populations, and differences in CGRP determination methodologies. Furthermore, the majority of the analyzed studies were observational in nature, which limits the ability to draw definitive cause-and-effect conclusions.

5. Conclusions

CGRP remains a promising yet imperfect biomarker for MH. Existing research confirms that CGRP levels are elevated in patients with MH, during both the interictal and ictal phases. However, its clinical application necessitates further investigation, particularly concerning the standardization of measurement methodologies and the identification of specific patient phenotypes for whom CGRP determination would yield the highest diagnostic value. In the future, the integration of biochemical data with imaging and clinical data may contribute to the development of more precise diagnostic and therapeutic tools.

6. Disclosure

Author's Contribution

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Supervision: Karolina Różycka

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