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The effect of calcitonin gene-related peptide monoclonal antibodies on restless legs syndrome in patients with migraine

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Abstract

Background Calcitonin gene-related peptide monoclonal antibody (CGRP mAb) effects on restless legs syndrome (RLS) are unclear.

Methods Fifteen migraine patients (aged 49.1 ± 5.8 years; 14 women) with concomitant RLS who received CGRP mAbs (2 erenumab, 3 galcanezumab, and 10 fremanezumab) were retrospectively studied. Number of monthly migraine days (MMDs) was obtained from headache diaries. The primary outcome is changes in RLS severity as assessed by the International RLS Group Rating Scale (IRLS). Headache-related disability was assessed using the Migraine Disability Assessment (MIDAS). The severity of headache and RLS was rated using the Patient Global Impression of Change (PGIC) scale. Central sensitization was evaluated with the Central Sensitization Inventory (CSI).

Results At 1, 2, and 3 months, the percentages of patients with ≥ 50% improvement in number of MMDs were 53.3%, 66.6%, and 60.0%, respectively. From baseline to 3 months, there were significant reductions in the MIDAS (25.1 ± 23.2 vs. 19.7 ± 22.8, $p = 0.005$) and CSI scores (36.3 ± 12.9 vs. 29.1 ± 12.3, $p = 0.001$). IRLS scores decreased significantly from baseline to 1 month (-8.8 ± 2.1 points) and 3 months (-11.6 ± 2.3 points) after CGRP mAb treatment. On the PGIC scale, 86.7% and 73.3% of patients reported at least "minimal improvement" in migraine and RLS severity, respectively, with 46.7% and 26.7% reporting "very much improvement". Among those with a < 50% reduction in number of MMDs at 3 months, 66.6% reported at least "minimal improvement", with 33.3% reporting "very much improvement".

Conclusion Our study revealed that 3-month CGRP mAb treatment significantly alleviated RLS symptoms, central sensitization and headache-related disability in patients with comorbid migraine and RLS.

Keywords Migraine, Calcitonin gene-related peptide monoclonal antibody, Restless legs syndrome

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Introduction

Patients with migraine experience various sleep problems, including daytime sleepiness, insomnia, parasomnia, sleep-disordered breathing and restless legs syndrome (RLS). Insomnia is observed in more than half of patients with migraine, is associated with worsening headache severity and even leads to headache chronification [1]. RLS is a sleep-related movement disorder that causes insomnia because of the urge to move the legs and abnormal sensations. Comorbid RLS in patients with migraine is associated with increased migraine severity and headache-related disability [2]. In a 12-year follow-up study of migraine patients, comorbid RLS status had a negative impact on sleep, depression, insomnia and headache-related disability [3]. Therefore, the management of RLS may be involved in improving the quality of life of migraine patients.

Calcitonin gene-related peptide monoclonal antibodies (CGRP mAbs) have been reported not only to reduce the number of migraine days and the degree of headache-related disability but also to alleviate nonheadache symptoms such as sleep quality, stress, anxiety and depressive symptoms [4–6]. However, the effects of CGRP mAbs on RLS have been evaluated in only a few reports, and the results are inconclusive, with one study showing an improvement in RLS symptoms [7] and another showing provocation of RLS symptoms [8]. In this study, we investigated the effects of CGRP mAbs on RLS in migraine patients in a single-center setting.

Methods

We retrospectively reviewed the records of patients who were diagnosed with both RLS and migraine and were treated with CGRP mAbs at our headache outpatient clinic between May 2023 and August 2024. The primary outcome is changes in RLS severity as assessed by the International RLS Group Rating Scale (IRLS). The Institutional Review Board of Dokkyo Medical University Hospital approved this study. In accordance with the principles of the Declaration of Helsinki, all participating patients were informed regarding the details of this observational study and were given the opportunity to opt out of participation. Owing to the observational nature of this study, our institutional review board waived the requirement for patients to sign informed consent forms.

Patients

The clinical records of 15 migraine patients with comorbid RLS (aged 49.1 ± 5.8 years; 14 females) who received CGRP mAbs (2 erenumab, 3 galcanezumab and 10 fremanezumab) were retrospectively reviewed. Regarding treatment for RLS, 4 patients were treated with dopamine agonists, and 3 patients were treated with alpha 2-delta ligands, but no additional medications for RLS or RLS medication dose changes were made from 1 month prior to CGRP mAb treatment to 3 months after the introduction of CGRP mAbs. Two patients discontinued their use of dopamine agonists and alpha 2-delta ligands because of their ineffectiveness. None of the patients received iron supplements.

Clinical evaluation

The diagnosis of migraine with and without aura was made according to the International Classification of Headache Disorders (ICHD)-3 criteria [9] after secondary headache was excluded via brain magnetic resonance imaging (MRI). Chronic migraine was defined as having headaches for at least 15 days per month, of which at least 8 days per month fulfilled the diagnosis of migraine, for at least 3 months. Medication overuse headache (MOH) was diagnosed according to the ICHD-3 criteria [9]. The number of monthly migraine days (MMDs) before and after CGRP mAb treatment was obtained from headache diaries. On the basis of headache diaries, percentage reductions in the number of MMDs were grouped as less than 30%, 30–50%, 50–75%, and 75–100%. Headache-related disability was assessed using the Migraine Disability Assessment (MIDAS) at baseline and 3 months after CGRP mAb treatment [10]. The clinical characteristics of the patients, including duration of migraine, aura, photophobia, phonophobia, osmophobia, nausea, allodynia and body mass index, were obtained from clinical records. Central sensitization was assessed by the Central Sensitization Inventory (CSI), which includes 25 items on somatic symptoms related to central sensitization [11].

RLS was diagnosed according to established criteria via face−to-face interviews [12]. Briefly, four essential features over the past year were required for the diagnosis of RLS: (1) an urge to move the legs, usually accompanied by an uncomfortable or unpleasant leg sensation; (2) onset or worsening of the symptoms at rest or with inactivity; (3) partial or total relief of the symptoms by movements; and (4) the symptoms occur only in the evening or night or are worse in the evening or night than during the day. After careful differential diagnosis and exclusion of RLS mimics, a definitive diagnosis of RLS was made. The International RLS Group Rating Scale (IRLS) is a 5-point, 10-item rating scale used to assess RLS severity, with scores for each item ranging from 0 to 4. Each question is designed to inquire about the patient's experience with RLS symptoms in the past week, including the intensity, frequency and duration of RLS, sleep disturbances, daytime fatigue, and impact on daily life and mental health [13]. The total score ranges from 0 to 40, with scores ranging from 0 to 10 indicating mild RLS, 11–20 indicating moderate, 21–30 indicating severe, and 31–40 indicating the most severe. The IRLS was utilized to assess

Table 1 Clinical characteristics of patients with migraine

	Migraine patients
n (M/F)	15 (1/14)
Age, years	49.1 ± 5.8
Disease duration, years	30.0 ± 8.4
Type of CGRP mAbs, n (%)	
Galcanezumab	3 (20.0)
Fremanezumab monthly	5 (33.3)
Fremanezumab quarterly	5 (33.3)
Erenumab	2 (13.3)
Chronic migraine, n (%)	5 (33.3)
Body mass index (kg/m^2)	23.4 ± 3.0
Migraine with aura, n (%)	4 (26.7)
MOH, n (%)	3 (20.0)
Accompanying symptoms, n (%)	
Photophobia	12 (80.0)
Phonophobia	9 (60.0)
Osmophobia	10 (66.7)
Nausea	13 (86.7)
Allodynia	5 (33.3)
Baseline number of MMDs	14.9 ± 6.9
MIDAS score	25.1 ± 23.2
CSI score	36.3 ± 12.9
IRLS score	20.4 ± 11.3

M = male; F = female; CGRP mAbs = calcitonin gene-related peptide monoclonal antibodies; MOH = medication overuse headache; MMDs = monthly migraine days; MIDAS = Migraine Disability Assessment; CSI = Central Sensitization Inventory; IRLS = International RLS Group Rating Scale

symptom severity at baseline and at 1 and 3 months after CGRP mAb treatment.

In addition, the severity of headache and RLS was assessed using the Patient Global Impression of Change (PGIC) scale, which is a self-rated seven-point scale with scores ranging from 1 ("much better") to 7 ("much worse") after CGRP mAb treatment.

Statistical analysis

Sample size calculations were not performed because of the exploratory nature of the study. The Wilcoxon signed rank test was used to compare the MIDAS score before and 3 months after CGRP mAb treatment. Spearman rank correlation coefficients were used to analyze the correlation between changes in the MIDAS and IRLS scores before and 3 months after CGRP mAb treatment. A generalized linear mixed effects model with repeated measures followed by Bonferroni post hoc test was employed to assess whether the IRLS score and number of MMDs were significantly different from baseline to 1 and 3 months after CGRP mAb treatment. A two-sided $p < 0.05$ was considered to indicate statistical significance. IBM SPSS Statistics version 29 (IBM SPSS, Tokyo, Japan) was used for the statistical analyses. GraphPad Prism for Mac (Version 8; GraphPad Software, San Diego, USA) was used to create the figures.

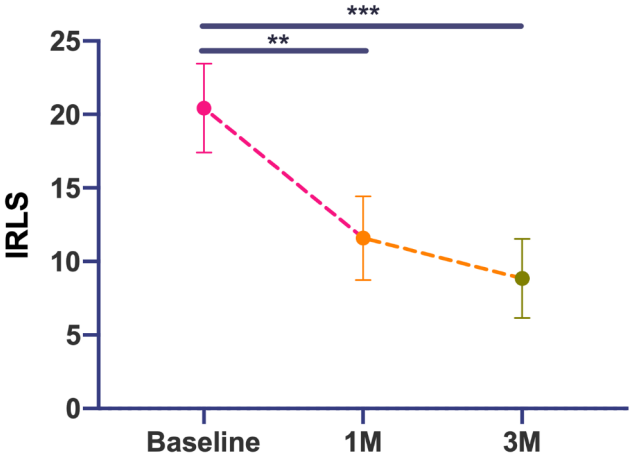

Fig. 1 Changes in IRLS scores before and after CGRP mAb treatment. IRLS = International RLS Group Rating Scale; CGRP mAb = calcitonin gene-related peptide monoclonal antibody. ** $p < 0.01$, *** $p < 0.001$, compared with baseline using a generalized linear mixed effects model with repeated measures followed by a Bonferroni multiple comparison test

Results

The clinical characteristics of 15 migraine patients with comorbid RLS who received CGRP mAb for migraine preventive treatment are shown in Table 1. The mean duration of migraine was 30.0 ± 8.4 years, and 33.3% of patients had chronic migraine. The baseline number of MMDs was 14.9 ± 6.9, the MIDAS score was 25.1 ± 23.2, and the IRLS score was 20.4 ± 11.3. After CGRP mAb treatment, the number of MMDs at 1, 2, and 3 months significantly decreased. The mean change in the number of MMDs was -6.6 ± 4.3 at 1 month, -7.5± 4.6 at 2 months and -6.8± 4.0 at 3 months (Supplementary Fig. 1). The proportions of responders at 1, 2 and 3 months are shown in Supplementary Fig. 2. The percentages of patients with ≥ 50% response rates in terms of number of MMDs at 1, 2 and 3 months were 53.3%, 66.6% and 60.0%, respectively. From baseline to 3 months, significant reductions in the MIDAS (25.1 ± 23.2 vs. 19.7 ± 22.8, $p = 0.005$) and CSI scores (36.3 ± 12.9 vs. 29.1 ± 12.3, $p = 0.001$) were observed. The IRLS score significantly decreased from baseline at 1 month (-8.8 ± 2.1 points) and 3 months (-11.6 ± 2.3 points) after CGRP mAb treatment (Fig. 1). No patient had an IRLS score after treatment that was worse than that before treatment. On the PGIC scale, 86.7% and 73.3% reported at least "minimal improvement" in migraine and RLS severity, with 46.7% and 26.7% reporting "very much improvement", respectively (Fig. 2). Among nonresponders (< 50% reduction in number of MMDs; $n = 6$) at 3 months, 66.6% reported at least "minimal improvement" with 33.3% reporting "very much improvement", and 33.3% reported "no change". There was no significant correlation between changes in the IRLS score and the MIDAS score (r=-0.41, $p = 0.140$)

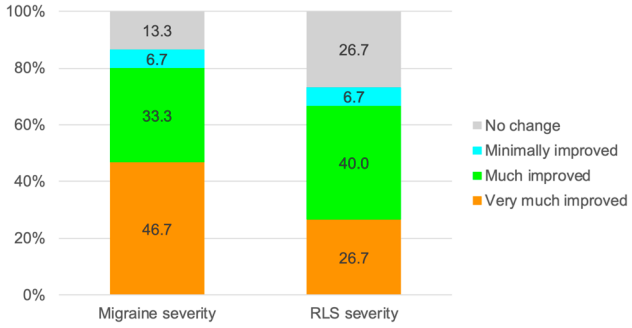

Fig. 2 PGIC scale scores for migraine and RLS severity following CGRP mAb treatment. PGIC = Patient Global Impression of Change; RLS = restless legs syndrome; CGRP mAb = calcitonin gene-related peptide monoclonal antibody

or CSI score (r=-0.50, p = 0.086) from baseline to 3 months.

Discussion

In this study, we investigated the effect of CGRP mAbs on 15 migraine patients with comorbid RLS over 3 months. The number of MMDs and MIDAS score decreased after CGRP mAb initiation. Additionally, RLS severity (IRLS score) significantly decreased 1 and 3 months after CGRP mAb treatment, and 73.3% of patients reported at least some improvement in RLS symptoms (Fig. 2). We found no significant correlation between changes in the IRLS and MIDAS scores before and 3 months after CGRP mAb treatment, and 66.6% of nonresponders who did not achieve a 50% reduction in the number of MMDs after 3 months presented at least some improvement in RLS symptoms. However, whether or not a decrease in IRLS score is associated with a reduction in headache severity following CGRP mAb treatment requires further research. Although two cases of migraine patients in whom RLS symptoms were induced after treatment with erenumab or galcanezumab have been reported [8], the results of the present study, in which three types of CGRP mAbs were included, confirm the findings of our single case report of a migraine patient in whom RLS symptoms were mitigated after treatment with galcanezumab [7] and may suggest class effects of CGRP mAbs for RLS.

Clinical trials have validated that the minimum clinically meaningful change in IRLS score is 3–6 points [14, 15]. In this study, the change in IRLS score was -8.8 ± 2.1 points after 1 month and -11.6 ± 2.3 points after 3 months of CGRP mAb treatment, suggesting a significant clinical improvement in the IRLS scores. No patients discontinued or tapered their RLS medications after starting CGRP mAb treatment; however, CGRP mAb treatment was effective in two patients who previously had no response to dopamine agonists or alpha2-delta ligands. Although these observations suggest that CGRP mAb may be an option for the treatment of RLS, future studies on its efficacy in severe cases of RLS and in RLS patients without migraine are needed.

A bidirectional association between migraine and RLS has been suggested [2]. A recent 12-year prospective study revealed that comorbid RLS increases migraine-related disability, insomnia and depressive symptoms in patients with migraine [3]. Pathophysiological mechanisms common for both disorders include changes in the levels of neurotransmitters such as dopamine, glutamate [16] and adenosine [17]; brain iron impairment; and genetic factors [18]. CGRP, which is involved in pain transmission, vasodilation and the development of neurogenic inflammation [19], may also be an important neurotransmitter involved in both migraine and RLS. The A11 region of the hypothalamus provides the only descending dopaminergic pathway involved in the pathogenesis of RLS [20], and all dopaminergic neurons in that nucleus co-express CGRP, but there are also several non-dopaminergic neurons that only express CGRP. The muscles of the lower limbs are predominantly innervated by CGRP-containing neurons from the dorsal root ganglion [21], and CGRP may be involved in the worsening of abnormal leg sensation in RLS. CGRP and its receptors are widely distributed in the central nervous system and trigeminal ganglion, a key structure for the pathophysiology of migraine, as well as in the dorsal root ganglion, peripheral sensory nerves, neuromuscular junctions, motor neuron and muscles [22, 23]. Excitability of peripheral motoneurons has been described in patients with RLS [24]. Although the hypothalamic median eminence lacks a blood-brain barrier, only small amounts of CGRP-mAbs cross the blood−brain barrier [25]. Thus, the main possible site of action of CGRP mAbs on RLS appears to be the periphery, where CGRP antagonism could inhibit excitation of sensory nerves and high-threshold muscle afferents [26].

Interestingly, there have been reports of patients with RLS refractory to conventional therapy who responded to botulinum toxin type A [27]. The mechanism of action of botulinum toxin includes blocking the release of excitatory neurotransmitters such as acetylcholine, glutamate, CGRP, and substance P from the peripheral terminals of sensory nerves and the dorsal root ganglion [28]. The findings of this study may indirectly support the effect of CGRP mAbs on RLS.

In contrast, the central effects of CGRP mAbs for migraine prevention are suggested by the decrease in hypothalamic activation after treatment with erenumab in migraine patients [29] and by the improvement in premonitory/accompanying symptoms, suggestive of hypothalamic involvement, and aura following CGRP mAb administration [5]. In addition, the improvement in RLS symptoms could result from the suppression of central sensitization following CGRP mAb treatment. In a study

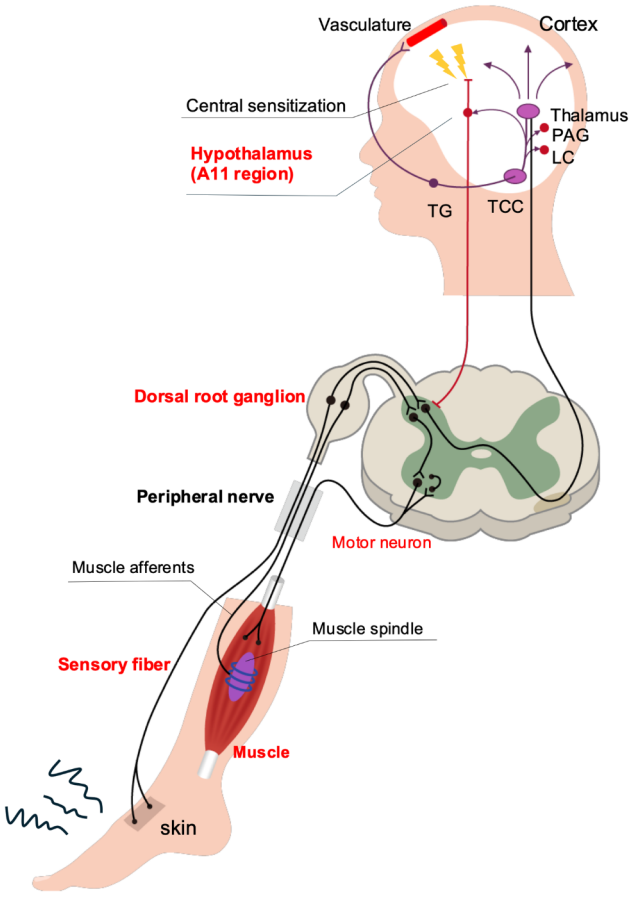

Fig. 3 Possible mechanism of CGRP mAbs on RLS. Possible sites of CGRP mAb action (highlighted in red text) and the associated neural pathways are shown. As a peripheral mechanism, in RLS, sensory inputs to dorsal root ganglion neurons are disinhibited, resulting in abnormal sensations in the lower extremities and focal akathisia in the muscles. The localization of CGRP and CGRP receptors suggests dorsal root ganglia, muscles and sensory nerves as possible peripheral sites of CGRP mAb action. Since CGRP also localizes to motor neurons, its antagonism may suppress motor excitability and contribute to improvement in RLS symptoms (motor restlessness). A small percentage of CGRP mAbs that cross the blood-brain barrier may contribute to central sensitization improvement. The hypothalamic A11 nucleus has inhibitory projections to the spinal dorsal horn and cortex. The A11 nucleus coexpresses CGRP and contains dopaminergic neurons, and non-dopaminergic neurons contain CGRP. CGRP antagonism by CGRP mAbs in this region may affect descending pathways to the spinal cord involved in RLS. TG = trigeminal ganglion; TCC = trigeminal cervical complex; LC = locus coeruleus; PAG = periaqueductal gray; RLS = restless legs syndrome; CGRP mAb = calcitonin gene-related peptide monoclonal antibody

of 186 migraine patients, the presence of RLS was one of the determinants of central sensitization [30]. In our study, as in the study by Danno et al. [31], the CSI score significantly decreased after treatment with CGRP mAbs. In a study of 36 migraine patients with 15.2 ± 4.7 days of migraine per month at baseline, the volumes of the right anterior cingulate cortex, bilateral orbitofrontal cortex, and left inferior frontal gyrus decreased after 3 months of treatment with galcanezumab [32]. The authors speculate that CGRP mAbs inhibit the activation of nociceptors in the meninges and reduce the number of nociceptive signals transmitted to the brain, normalizing the hyperexcitability of the patients' brains.

Central sensitization is a condition in which the hyperactivity of neurons and circuits in the nociceptive pathway is associated with the plasticity of the somatosensory nervous system in response to chronic pain, which is involved in the pathophysiology of migraine chronification [33]. In RLS, central sensitization of the spinal cord is associated with the development of clinical symptoms [34]. Alterations in sensorimotor cortices have been reported in patients with RLS [35] and migraine [36], respectively. Furthermore, migraine and RLS patients exhibit shared characteristic changes in their gray matter [37]. Thus, central sensitization may be involved in the exacerbation and expansion of pain or abnormal sensations in patients with both migraine and RLS. Figure 3 shows a possible mechanism of CGRP mAbs on RLS.

The study limitations include the small sample size, retrospective nature of the study, and lack of a CGRP mAb-untreated group as a control group. IRLS scores were available at baseline and at 1 and 3 months but not at 2 months after the initiation of CGRP mAb treatment. No comparison could be made between CGRP ligand (galcanezumab and fremanezumab) and receptor mAbs (erenumab) in terms of differences in their effects on RLS symptoms. Further studies with a larger number of patients with migraine and RLS are needed to confirm our findings.

In conclusion, our study revealed significant improvements in RLS symptoms, migraine severity and central sensitization following 3 months of CGRP mAb treatment in migraine patients with comorbid RLS. Our findings may be useful in elucidating the pathogenesis of comorbid migraine and RLS.

Abbreviations

CSI	Central Sensitization Inventory
CGRP mAb	calcitonin gene-related peptide monoclonal antibodies
IRLS	International RLS Study Group Rating Scale
MIDAS	Migraine Disability Assessment
MMD	Monthly migraine days
MOH	Medication overuse headache
PGIC	Patient Global Impression of Change
RLS	Restless legs syndrome

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s10194-025-01976-7.

Supplementary Material 1

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Author contributions
All the authors contributed to the acquisition and interpretation of the data for this study. KS drafted the manuscript. KS performed the statistical analysis. SS, HF, SK, MS, RH and KH performed a critical review of important intellectual content. All the authors approved the final manuscript.

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Data availability
The datasets from this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in compliance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Dokkyo Medical University Hospital (approval number: R-89–1 J). The Institutional Review Board of Dokkyo Medical University Hospital waived the requirement for patients to sign informed consent forms on the basis of the retrospective, observational nature of the study.

Consent for publication
Not applicable.

Competing interests
The authors declare the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. K Suzuki received lecture fees from Eli Lilly Japan, Daiichi Sankyo and Otsuka Pharmaceutical Co., Ltd., during the study. S Suzuki received lecture fees from Eli Lilly Japan, Daiichi Sankyo, Amgen and Otsuka Pharmaceutical Co., Ltd., during the study. H Fujita, S Kobayashi, M Shioda and R Hida have nothing to disclose. K Hirata received lecture fees from Eli Lilly Japan, Daiichi Sankyo, Amgen and Otsuka Pharmaceutical Co., Ltd., during the study.

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