Preventive migraine treatment in mitochondrial diseases: a case report of erenumab efficacy and literature review

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Abstract
Migraine is a common condition in mitochondrial diseases, with a higher prevalence than in the general population. Although several clinical studies support the hypothesis that mitochondrial dysfunction plays a central role in the pathophysiology of migraine, currently there are few data in the literature regarding the efficacy and safety of drugs for the treatment and prophylaxis for this condition in patients with primary mitochondrial disorders. We report a 37-year-old woman affected by mitochondrial disease with progressive external ophthalmoplegia phenotype (PEO) associated with POLG mutation effectively treated with erenumab, in the absence of side effects. Monoclonal antibodies against the calcitonin gene-related peptide (CGRP) or against its receptor are innovative and specific therapies for migraine prophylaxis. This class of drugs is particularly suitable for subjects, such as those suffering from genetically determined mitochondrial dysfunction, in which pharmacological management can represent a challenge due to the nature of these neurogenetic disorders and/or the frequently associated comorbidities.

Keywords Erenumab · CGRP · Migraine · Mitochondrial diseases · POLG · Case report

Introduction
Migraine is a frequent condition in patients suffering from mitochondrial diseases, with a higher prevalence than in the general population [1]. The overall prevalence of migraine in the mitochondrial population observed in our Neuromuscular Centre was 35.5% [1]. The therapeutic approach in subjects affected by these neurogenetic disorders can be particularly difficult, due to frequent comorbidities and possible poor tolerance to drugs commonly used for headache [2, 3].

Here, we report the case of a patient affected by a mitochondrial disease who was safely and effectively treated with erenumab for migraine prophylaxis.

Case presentation
A 37-year-old woman presenting progressive external ophthalmoplegia (PEO) phenotype associated with heterozygous pathogenic variant in POLG gene (c.2864A>G; p.Tyr955Cys), followed at the Division of Neuromuscular Medicine of the Fondazione Policlinico Universitario Agostino Gemelli IRCCS, was evaluated by the headache specialists for a typical history of migraine without aura, which began in adolescence and was characterized by recurrent attacks of unilateral severe pain with pulsating quality and associated with nausea, vomiting, and photophobia. Over the past 15 years, migraine had a high frequency episodic pattern and, in the last 6 months, it had further increased and was associated with recurrent use of symptomatic drugs. Regarding mitochondrial disease, the onset was around the age of 25 and, in addition to progressive external ophthalmoplegia, the main clinical features were muscle weakness, exercise intolerance, peripheral neuropathy, sensorineural hearing loss, and premature ovarian insufficiency. The patient was on medication with coenzyme Q10 (200 mg/day) and riboflavin (100 mg/day) for the mitochondrial myopathy. Over her long history of migraine, the patient had undergone several first-line prophylaxis treatments belonging to...
different pharmacological categories, which had proved ineffective or were poorly tolerated. In particular, among the pharmacological approaches, the patient was treated with amitriptyline (20 mg per day) and propranolol (up to 80 mg per day), both ineffective; cinnarizine (50 mg per day), discontinued for a marked increase in daytime sleepiness; flunarizine (5 mg per day) suspended after about 10 days for akathisia, which persisted for more than 1 month after discontinuation of this drug. Non-pharmacological treatments have not been used. Furthermore, symptomatic therapies both specific (zolmitriptan and eletriptan, effective but with high recurrence of the attacks) and non-specific (paracetamol and ketoprofen were poorly effective, while ibuprofen was effective) have been tried.

On the basis of her clinical history, a treatment with subcutaneous monthly administration of erenumab 70 mg was started.

**Average monthly migraine days and average monthly number of symptomatic drugs at baseline**

The diary, filled out for 4 months before the start of the treatment with erenumab, showed a monthly migraine days (MMD), such as the mean number of disabling migraine days per month, of 18.25 ± 1.26 (Fig. 1, panel A). The patient took an average number of 21 ± 1.16 symptomatic drugs per month (Fig. 1, Panel B).

Therefore, at the time of treatment with erenumab, the patient had a clinical pattern consistent with the International Classification of Headache Disorders - 3rd edition (ICHD-3) diagnosis of medication-overuse headache (MOH) [4].

**Average monthly migraine days and average monthly number of symptomatic drugs during treatment**

During the treatment with erenumab, there was a change in MMD from 18.25 ± 1.26 at baseline to 8.58 ± 2.35 drugs per month over 12 months of treatment, and 8.33 ± 2.08 drugs per month in the last 3 months of treatment) (Fig. 1, panel B).

During the treatment period, the patient reported an increase in the efficacy of symptomatic drugs and a concomitant reduction in the average duration of migraine crises. In this period, the patient did not fulfill the criteria for MOH. The average intensity of the migraine attacks decreased (the mean score of the visual analog scale of the attacks decreased from 9 at the baseline to 6 at the twelfth month of treatment).

The patient also reported a significant improvement in the quality of life, which was documented by the notable reduction in the score of the Migraine Disability Assessment (MIDAS) questionnaire [5] (the score changed from 115 at baseline to 39 at the third month of treatment, 12 at the sixth month of treatment, 25 at the ninth month of treatment, and 3 at the twelfth month of treatment) and headache impact test-6 (HIT-6) [6] (from 74 at baseline to 59 during the twelfth month of treatment).

Finally, no serious or mild adverse events occurred during the treatment with erenumab, and the treatment was overall well tolerated.

The ocular symptoms associated with the mitochondrial myopathy did not change with erenumab treatment.

**Discussion**

This report describes the efficacy and tolerability of the prophylaxis treatment with erenumab at a dosage of 70 mg per month in a patient affected by mitochondrial disease associated with POLG mutation.

Before the start of erenumab, the patient presented a clinical pattern that can be classified as chronic migraine associated with medication overuse, and she had experienced poor efficacy and tolerability of first-line drugs for prophylaxis.

Even if migraine is highly prevalent in patients with mitochondrial disorders, to date, only few reports on the treatment of this condition have been described in the literature, and a consensus guideline driving the therapeutic choices is lacking.
Table 1  Articles reporting data on pharmacological treatments for migraine prophylaxis in mitochondrial diseases

| Author (year)          | Case | Sex | Median age | Phenotype                      | Genotype            | Brain MRI findings | Migraine type | Migraine frequency | Symptomatic treatment (dosage) | Efficacy symptomatic treatment | AEs symptomatic treatment | Prophylactic treatment (dosage) | Efficacy prophylactic treatment | AEs prophylactic treatment |
|------------------------|------|-----|------------|--------------------------------|---------------------|-------------------|----------------|-------------------|-------------------------------|-----------------------------|------------------------|------------------------------|-------------------------------|-----------------------------|
| Tiehuis et al. (2020) [7] | Case series | 5 M; 24 F | 44 | MELAS, MIDD, MERRF, Leigh syndrome, Other phenotypes | m.3243A>G, OPA1, POLG | N/A | MA (12); MO (17) | PCT; PCT/codeine; PCT/caffeine; PCT/propyphenazone/caffeine; SMT; FRV; NRT; RZT | Triptans effective in 5/8 cases (63%) | N/A | PRP; MTP | N/A |
| Prasad et al. (2014) [8] | I | M | 18 | MELAS | m.3243A>G | T2 hyper-intensity in left occipital lobe | MA | N/A | N/A | N/A | PZT | N/A |
| Naegel et al. (2021) [9] | II | F | 20 | MELAS | m.3243A>G | Normal | MO | 30/month | N/A | NRT (2.5 mg); SMT (100 mg) | Effective | N/A | TPM; FZ; BoNTA (155/195 IU); erenumab (70 mg) | N/A | FZ (side effects) |
| | I | F | 25 | MELAS | m.3243A>G | T2 and DWI hyper-intensity in right occipital lobe | MO | 20/month | N/A | N/A | FZ (side effects) |

AEs adverse events, BoNTA onabotulinum toxin A, FRV frovatriptan, FZ flunarizine, MA migraine with aura, MO migraine without aura, MTP metoprolol, N/A not applicable, NRT naratriptan, PCT paracetamol, PRP propranolol, PZT pizotifen, RZT rizatriptan, SMT sumatriptan, TPM topiramate, MELAS mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes, MIDD maternally inherited diabetes and deafness, MERRF myoclonus epilepsy with ragged-red fibers
To explore the existing medical literature on the prophylactic treatment of migraine in mitochondrial disorders, we reviewed the literature in the Pubmed database. The last search was conducted on June 1, 2022. The search allowed to retrieve 329 papers, of which only three papers resulted to be relevant to the topic [7–9] (Table 1). Notably, erenumab 70 mg was reported to be an effective migraine prophylaxis in a female patient with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS; m.3243A > G mutation) [9]. This patient had been previously treated with topiramate and onabotulinumtoxinA, which were both discontinued due to inefficacy, and flunarizine which was not tolerated due to side effects. Topiramate was reported as a treatment for migraine in another patient affected by MELAS and m.3243A > G mutation, but no data are available on its efficacy or tolerability [8]. So far, other drugs used by patients with mitochondrial disorders are propranolol, metoprolol [7], and pizotifen [8], but no information is available on their efficacy and safety. Based on the data currently available, there are no specific indications in the choice of preventive treatments in patients with genetically determined mitochondrial dysfunction, except avoiding valproic acid in the case of subjects with pathogenic variants in POLG.

Although both in the previously published case and in our patient no adverse events were reported, based on the current knowledge of the physiological actions of CGRP, we can speculate on the possible risks associated with such treatments for patients with mitochondrial disease. In particular, antibodies targeting CGRP or its receptor can interfere with the function of the small and large intestine regarding the peristaltic motor activity, the intestinal transit, and the ion and water secretion [10]. Therefore, these drugs should be administered with caution in mitochondrial patients with gastrointestinal dysfunction, frequently reported in these neurogenetic disorders [11]. At the same time, subjects with primary mitochondrial dysfunction characterized by respiratory and cardiovascular involvement should be carefully monitored during the administration of anti-CGRP-monoclonal antibodies [12].

To the best of our knowledge, this is the first case of a patient with autosomal dominant PEO phenotype associated with a pathogenic variant in POLG to be treated with monoclonal antibody against the CGRP receptor. In our patient, therapy with erenumab has proven to be remarkably effective, significantly reducing the frequency of migraine crises and the use of symptomatic medications and resulting in a substantial modification of the migraine pattern which, after 12 months of treatment, could be classified as episodic migraine. The prophylaxis treatment also resulted in a drastic reduction in the monthly intake of symptomatic drugs. Finally, the treatment was well tolerated.

Conclusion

Our report confirms a good profile of safety and efficacy of erenumab in subjects with poor tolerability or contraindications to some prophylactic therapies, such as patients with complex comorbidities and/or diseases, including primary mitochondrial disorders.

Abbreviations

PEO: Progressive external ophthalmoplegia; CGRP: Calcitonin gene-related peptide; MMD: Monthly migraine days; MOH: Medication overuse headache; MIDAS: Migraine disability assessment; HIT-6: Headache impact test-6; MELAS: Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

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Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Ethical approval

This study was conducted in accordance with the principles of Helsinki Declaration and approved by the Ethics Committee of the Università Cattolica del Sacro Cuore (Rome, Italy). We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Consent for publication

We obtained written informed consent from the patient for participation in the study and publication of data.

Conflict of interest

The authors declare no competing interests.

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