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Letter to the Editor

A positive effect of galcanezumab in MELAS must be proven by appropriately designed studies

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Letter to the Editor

We were interested to read the article by Kuczynski *et al*. on the effect of calcitonin gene-related peptide (CGRP) antagonists in a 31-year-old woman with MELAS (patient-1) and a 62-year-old woman with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (patient-2) [1]. Patient-1 benefited from galcanezumab (120 mg/month) and patient-2 from eptinezumab [1]. The study is remarkable, but some points should be discussed.

The first point is that the diagnosis of MELAS in patient-1 is not confirmed [1]. The patient had never suffered a seizure or stroke-like episode (SLE), and there were no focal neurological deficits or "red flags" for MELAS [1]. Therefore, it should be clarified why this patient was diagnosed with MELAS. MELAS is usually diagnosed according to the Japanese or Hirano criteria. According to the Japanese criteria, MELAS is diagnosed when there are signs of encephalopathy associated with dementia or epilepsy, SLE in early childhood, and biochemical signs of mitochondrial dysfunction, such as lactic acidemia and the presence of ragged red fibers (RRF) in the muscle biopsy [2]. Patient-1 did not fulfil any of these criteria [1]. According to the Hirano criteria, MELAS is diagnosed if SLE occurs before the age of 40 and seizures or dementia, lactic acidosis or RRFs, normal early development, recurrent headaches or recurrent vomiting are present [3]. To make a diagnosis of MELAS according to the Hirano criteria, all of the first three criteria and at least two of the second three criteria must be met. Of these criteria, patient-1 fulfilled only one, which is not sufficient for the diagnosis of MELAS. Based on these considerations, it is not justified to diagnose patient-1 with MELAS.

The second problem is that it was not reported whether the diagnosis of MELAS was confirmed by genetic testing [1]. In about 80% of cases, MELAS is due to the m.3243A>G variant in *MT-TL1* [4]. Other mtDNA variants associated with MELAS are the variants m.3271T>C and m.3252A>G in *MT-TL1* and m.13513G>A in *MT-ND5* [4]. In rare cases, MELAS is due to mutations in *MT-TH* or *MT-TV*. Knowledge of the genetic cause of MELAS is crucial for the prognosis of the course of the disease and for genetic counselling.

The third point is that we disagree with the statement that CGRP antagonists are safe and effective in mitochondrial disorders (MID) [1]. In order to be able to make such a statement, appropriate studies must first be carried out. As long as it only works in one patient, the criteria for a double-blind, placebo-controlled cross-over study is not met in order to make a statement about the effectiveness of a therapy. So far, there are only single case reports showing a positive effect of erenumab in MELAS [5], of erenumab in a patient with chronic progressive external ophthalmoplegia (CPEO) due to a *POLG1* variant [6] or of galcanezumab in an *SSBP1* mutation carrier [7]. It is also not valid to say that the therapy is safe until long-term data are available,

The fourth point is that headaches in MELAS are usually categorized as "migraine-like" and are often associated with SLE. The treatment of "migraine-like" headaches in SLEs must be distinguished from the treatment of classic migraine, which may or may not be causally related to MELAS. To confirm or rule out the presence of a stroke-like lesion (SLL), the morphologic correlate of SLE on cerebral magnetic resonance imaging (MRI) [8], it is crucial to perform a cerebral MRI. A CT scan, as performed in patient-1, may not be sufficient to detect SLL. SLEs are usually treated with NO-precursors, coenzyme-Q and other antioxidants, vitamins and co-factors.

In conclusion, this interesting study has limitations that affect the results and their interpretation. Addressing these limitations could strengthen the conclusions and support the message of the study. Appropriately designed studies are needed before the conclusion can be drawn that galcanezumab is effective for migraine in MELAS patients.

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