CASE

Treating chronic migraine in CADASIL with calcitonin gene-related peptide receptor antagonism

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PRACTICAL IMPLICATIONS

CGRP receptor monoclonal antibodies may be safe for preventing migraine therapy in those with CADASIL; systematic study of safety and efficacy are needed before this approach to migraine prevention can be recommended.

Case

A 58-year-old right-handed man is being routinely monitored in the outpatient neurology clinic with a genetically confirmed diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (heterozygous transition G>A, nucleotide position 272, codon 65 of the *NOTCH3* gene) and without baseline neurologic deficits, cognitive impairment, or comorbid psychiatric illness. He describes a long-standing history of chronic migraine beginning at the age of 47 with various accompaniments, namely visual polychromatic photopsia and confusional aura, which pre-dated stroke onset by roughly 10 years. Photopsia would last 3–4 hours and abate spontaneously, whereas the confusional aura would occur suddenly and last for 10–15 minutes. He had migraines 3–4 times per week, lasting up to 5 hours each, and described them as an alternating hemicranial pounding sensation. A Migraine Disability Assessment[1] (MIDAS) Questionnaire revealed severe migraine-related disability (score of 26). He had attempted multiple abortive and prophylactic medications including amitriptyline, topiramate, various triptans, and at present, verapamil 180 mg daily without improvement in headache burden.

An outside physician prescribed the calcitonin gene-related peptide receptor (CGRP) antagonist, erenumab-aooe[2] (Aimovig; Amgen Inc.), at a dose of 70 mg subcutaneous injection monthly shortly after the drug was approved by the Food and Drug Administration for the treatment of chronic migraine on May 17, 2018. The patient initially described substantial worsening of headache and migraine accompaniments for an estimated 1–2 weeks, at which point he was required to wear an eyepatch because of intense photophobia. Over the subsequent months, he had gradual improvement in both headache severity and aura length, estimating only having 1 migraine every 2 weeks. Repeat MIDAS about 6 months after his first dose was 9, indicating mild migraine-related disability. The Headache Impact Test-6[3] score was 52 (score range: 36–78), and a Questionnaire for Verifying Stroke-Free Status[4] was without new symptoms since erenumab-aooe initiation.

Discussion

CADASIL is a rare microangiopathy inherited in an autosomal dominant fashion from the mutation of the *NOTCH3* gene on chromosome 19. Those with CADASIL classically develop recurrent microvascular ischemic strokes, cognitive decline, psychiatric disturbances, and migraine. Migraine, typically with visual aura, tends to be the heralding symptom of CADASIL and is present in 75% of cases. Migraines in CADASIL are particularly debilitating and refractory to prophylactic medications.[5]

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Mutation of the *NOTCH3* gene leads to patchy degradation of vascular smooth muscle cells, yielding impaired vascular autoregulation primarily of the arterioles and small penetrating subcortical vessels.[6] Calcitonin gene-related peptide is one of many nociceptive neuropeptides, although has the added property of being a potent intracerebral vasodilator.[7] One may anticipate that for those with CADASIL, who intrinsically are in a precarious state of cerebral autoregulation, modulation of CGRP may impart an added risk of parenchymal damage or perhaps acceleration of the ischemic process. Although speculative, we hypothesize that the initial worsening of headaches after CGRP receptor modulation suggests that those with CADASIL are particularly susceptible to changes in CGRP activity. Furthermore, the gradual and sustained improvement in migraines without interval symptoms of stroke or transient ischemic attack suggests that a compensatory alternative non-nociceptive vasoactive neuropeptide is upregulated.

Although stroke and vascular dementia are the most feared consequences of CADASIL, migraine, which typically characterizes the early phase of disease, can by itself generate considerable disability as our case illustrates. To date, there have been no randomized trials of abortive or prophylactic therapies for migraine in CADASIL. It is not known with certainty what, if any, role CGRP plays in the generation of migraines, specifically in patients with CADASIL. It remains to be seen whether the observed pattern of worsening, followed by improvement is a consistent finding in patients with CADASIL on initiation of therapy with a CGRP inhibitor. It is important that clinicians are aware of this possibility so that the medication not be declared a failure and abandoned prematurely. Last, it is reassuring that our patient reported no interval neurologic deficits after the initiation of the CGRP inhibitor. Whether the drug has positive or negative effects on new vascular damage in CADASIL would require controlled studies, preferably with imaging surveillance.

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Name	Location	Role	Contribution
Eric D Goldstein, MD	Mayo Clinic, Jacksonville, FL	Author	Design and conceptualized study, analyzed the data, and drafted the manuscript for intellectual content
Mohammed K. Badi, MD	Mayo Clinic, Jacksonville, FL	Author	Design and conceptualized study, analyzed the data, and revised the manuscript for intellectual content
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