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Is CGRP a marker for chronic migraine?

Calcitonin gene-related peptide (CGRP) research was initiated by Poyner et al., who found that the calcitonin gene encodes the 37-amino acid neuropeptide CGRP in neuronal tissue. Within months, the Lund group produced antibodies toward α-CGRP and developed sensitive methods to study the role of this peptide in the cranial circulation. Intracranial vessels and the trigeminal ganglion harbor this potent vasodilator peptide. Functionally, CGRP has a substantial role in the trigeminovascular reflex. The calcitonin family is now well-characterized and contains 6 members: calcitonin, amylin, adrenomedullin-2, adrenomedullin, and CGRP (2 isoforms: α-CGRP and β-CGRP). The α- and β-isomers of CGRP are similar in their biological activities but show different tissue distributions. β-CGRP is mainly found in enteric nerves and in the pituitary gland, while α-CGRP is found predominantly in sensory neurons and in the CNS. CGRP causes cranial vasodilation and facilitates nociception. During a migraine attack, trigeminal activation results in the release of CGRP from presynaptic nerve terminals and induces vasodilation and neurogenic inflammation in leptomeningal and extracranial vessels, which gives rise to the typical throbbing pain of migraine. Goadsby and Edvinsson showed that plasma concentrations of CGRP are elevated in the external jugular venous blood during migraine headaches and that sumatriptan can abort the rise in CGRP and the headache. CGRP given IV causes headache only in migraine patients and CGRP antagonists are effective for the acute treatment of migraine. Until now, CGRP elevation in the plasma has not been reproduced in all studies. However, technical problems have sometimes hampered the proper measurements of CGRP.

Migraine can be episodic (fewer than 15 headache days per month) or chronic (15 or more headache days per month for at least 3 months). Chronic migraine (CM) requires that headaches fulfill migraine criteria on 8 or more days per month. In this issue of Neurology®, Cernuda-Morollón et al. determined that the interictal CGRP level in the peripheral blood of women with CM is a potential biomarker for permanent trigeminovascular activation. The authors assayed plasma samples from 103 women with CM (all older than 17 years of age) and 31 matched healthy women with no headache history, 43 matched women with episodic migraine (EM), and 14 patients with episodic cluster headache matched for age in a pain-free period. CGRP levels were determined by ELISA from blood samples obtained from the right antecubital vein outside a migraine attack and with the patient having taken no symptomatic medication the day before.

CGRP levels were increased in CM (74.90 pg/mL) compared with healthy control women (33.74 pg/mL), women with EM (46.37 pg/mL), and episodic cluster headache patients (45.87 pg/mL). Thresholds of 43.45 and 58.22 pg/mL optimize the sensitivity and specificity needed to differentiate CM from healthy controls and EM, respectively. In the CM group, CGRP levels were increased in women with a history of migraine with aura vs those who only experienced migraine without aura. Variables such as age, analgesic overuse, depression, fibromyalgia, vascular risk factors, history of triptan consumption, or type of preventive treatment did not influence CGRP levels.

That interictal CGRP levels were elevated in peripheral blood in a large series of women with CM and, to a lesser degree, in women with EM, confirms the presence of increased CGRP levels in peripheral blood in CM patients outside migraine attacks. Peripher al CGRP levels outside migraine attacks in the absence of symptomatic medication may be a biomarker for CM. It may allow monitoring a patient’s status and response to preventive treatment. Future work on the role of CGRP and its receptor in CNS and intracranial structures will be very interesting. In particular, we look forward to learning more about the effects of small-molecule CGRP antagonists and antibodies toward CGRP and the CGRP receptor on CGRP levels and clinical outcome.

AUTHOR CONTRIBUTIONS
Stephen D. Silberstein: drafting/revising the manuscript, study concept or design. Lars Edvinsson: drafting/revising the manuscript.

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REFERENCES


