

PLASMA PACAP-38 IS INCREASED IN MIGRAINE REGARDLESS OF CLINICAL PHENOTYPE: A CASE-CONTROL STUDY

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Background. Pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38) has emerged as a key neuropeptide involved in migraine pathophysiology through its vasoactive, nociceptive, and neuroinflammatory effects. Although experimental evidence strongly supports its biological role, clinical studies evaluating circulating PACAP-38 concentrations have yielded inconsistent results. We aimed to compare plasma PACAP-38 concentrations between patients with migraine and healthy controls and investigate their relationship with migraine phenotype and clinical characteristics.

Methods. We conducted a single-center cross-sectional case-control study. Plasma PACAP-38 concentrations were measured using a commercially available sandwich ELISA (BlueGene Biotech; Cat. No. E01P0585). Patients were classified according to migraine phase (ictal/interictal), migraine subtype, presence of aura, medication-overuse headache (MOH), and sex. Associations with demographic and clinical variables were evaluated using non-parametric tests with correction for multiple comparisons.

Results. Eighty-five patients with migraine (70 females, 15 males; mean age 44.7 ± 14.7 years; 42 chronic and 43 episodic migraine) and 36 healthy controls (26 females, 10 males; mean age 45.3 ± 13.0 years) were included. Plasma PACAP-38 concentrations were significantly higher in patients with migraine than in healthy controls (234.86 vs 169.72 pg/mL; $p<0.001$). Increased PACAP-38 concentrations were observed both during migraine attacks (219.21 vs 169.72 pg/mL; $p=0.003$) and in the interictal phase (233.76 vs 169.72 pg/mL; $p<0.001$), whereas no significant difference was found between ictal and interictal samples ($p=0.443$). No significant differences were observed according to migraine subtype, presence of aura, medication-overuse headache, or sex. Furthermore, plasma PACAP-38 concentrations were not associated with clinical characteristics or measures of migraine severity after correction for multiple comparisons.

Conclusions. Plasma PACAP-38 concentrations are significantly increased in patients with migraine compared with healthy controls, supporting activation of the PACAP pathway as a biological hallmark of migraine. Circulating PACAP-38 concentrations appear independent of migraine phenotype and clinical severity, suggesting that PACAP-38 may represent a trait biomarker rather than a marker of disease activity. Larger prospective studies, particularly including more patients sampled during migraine attacks, are warranted to further clarify the diagnostic and pathophysiological significance of PACAP-38.