The prevalence of migraine is three-fold higher in women than in men. It is well known that the calcitonin gene-related peptide (CGRP) is involved in migraine pathophysiology. It is released from the trigeminal afferent nerve fibers during migraine attacks, causing vasodilation and inflammatory response. The researchers from Germany conducted this study to investigate whether the concentration of the neuropeptide CGRP during the menstrual cycle phases differs between women who suffer from migraines and women without migraines.

According to the "estrogen withdrawal hypothesis", the fluctuation of endogenous steroids is involved in the complex pathophysiology of migraine attacks. A decrease in plasma estrogen concentrations may trigger migraine attacks, activating the trigeminal-vascular system and releasing CGRP. The estrogen receptors are highly expressed in CGRP-positive neurons in the trigeminal-vascular system, so, fluctuations in hormonal concentrations can modulate their excitability. Previous data have demonstrated that women suffering from migraine attacks have significantly elevated plasma CGRP concentrations.



About the Study and Results

The research team investigated a difference in the CGRP concentration during the menstrual cycle phases between women who suffer from migraines and women without migraines. They also investigated whether a decrease in the concentrations of endogenous sex steroids, caused by oral contraceptives (combining estrogen and progesterone) or menopause, alters the CGRP concentration.

The study included 180 women who were diagnosed with episodic migraine, and categorized into three distinct groups: 1. women with a regular menstrual cycle, 2. women taking oral contraceptives combining estrogen and progesterone, and 3. postmenopausal women. Three control groups included age-matched women who did not suffer from episodic migraine.

During menstruation (a phase of low estrogen levels), the CGRP concentrations were significantly higher in plasma and tear fluid from women with regular menstrual cycles who suffered from migraine than in women without migraine. In addition, the CGRP concentrations were higher only in tear fluid (not in plasma) from women with regular menstrual cycles who suffered from migraine than in women who suffered from migraine and were taking combined oral contraceptives.

Conclusion

These results suggest that the relationship between changes in plasma and tear fluid CGRP concentrations and the endogenous sex hormone levels was found only in women with regular menstrual cycles who suffered from migraine. The authors noted that the feasibility of CGRP plasma concentrations as a biomarker for migraines remains a matter of debate. However, the biomaterials closer to the trigeminal CGRP source, such as tear fluid, may represent a better and more direct approach.

Accordingly, the increased CGRP release from the trigeminal-vascular system during menstruation could explain the biological predisposition to more frequent, severe, and prolonged migraine attacks during this period.

This article was published in Neurology.

Journal Reference

Raffaelli B. et al. Sex Hormones and Calcitonin Gene-Related Peptide in Women With Migraine: A Cross-sectional, Matched Cohort Study. Neurology. February 22, 2023. (Open Access) https://n.neurology.org/content/early/2023/02/22/WNL.0000000000207114