A prospective, multicentric study indicates a new feature of cluster headache attacks

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A prospective study recently published in the journal *Cephalalgia*, the official journal of the International Headache Society, extends the idea behind cluster headache chronicity. The study, entitled "Temporal changes of circadian rhythmicity in cluster headache", was first-authored by Dr. Mi Ji Lee, from the Department of Neurology, Neuroscience Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

Cluster headache (CH) is known in the medical literature as the most intense pain experienceable by humans and is popularly known as "suicidal headache". CH consists of a primary headache disorder, classed as a Trigeminal Autonomic Cephalalgia by the 3rd Version of the International Classification of Headaches Disorders—ICHD-3. It is characterized by severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes, presenting with at least one of the following autonomic symptoms in the same side of the pain: conjunctival injection and/or lacrimation; nasal congestion and/or rhinorrhea; eyelid edema; forehead and facial sweating; miosis and/or ptosis; and a sense of restlessness or agitation.

Attacks occur with a frequency between one every other day and 8 per day. During part, but less than half, of the active time-course, attacks may be less severe and/or of shorter or longer duration. Attacks occur in series lasting for weeks or months (so-called cluster periods or bouts) separated by remission periods usually lasting months or years. Another hallmark feature of CH is its circadian, or even circannual pattern, with

up to 82% of patients reporting CH attacks around the same time each day.

In this study, Dr. Lee's and colleagues investigated prospectively the pattern of circadian rhythmicity in relation to disease course in 175 patients in the active, within-bout period from 15 hospitals in Korea. The prevalence and characteristics of circadian rhythmicity were compared between- and within-patients with different numbers of total lifetime bouts. Patients with ≥ 2-lifetime bouts were categorized as stationary (no change between bouts), developing (becomes more prominent as disease progresses), decreasing (becomes less prominent as disease progresses), and variable (different from bout to bout), with regard the changes in the pattern of circadian rhythmicity during their disease progression.

Circadian rhythmicity was reported in 86 (49.1%) patients for the current bout. Seasonal rhythmicity was more prevalent in patients with circadian rhythmicity compared to patients with no seasonal rhythmicity (66.2 % vs 37.1 %, respectively). The prevalence of circadian rhythmicity was similar between groups (deciles groups) regarding the number of total lifetime bouts, while changes in circadian rhythmicity between bouts throughout the disease course were reported by 45.3% of patients. Patients without circadian rhythmicity showed a more variable pattern compared to patients with circadian rhythmicity (35.2% vs 8.8 %), whereas a stationary pattern was more common among patients with circadian rhythmicity in the current bout (64.7 % vs 40.9 %) compared to those without rhythmicity.

Regarding the time of CH attacks, 10 am and 3 pm, followed by 10 pm and 2 am, were the most common attack time recorded, and this was true either in the whole patients' sample as for patients with circadian rhythmicity. Concerning the time of day for cluster headache attacks in relation to the number of total lifetime bouts, with disease progression, a

trend to a dichotomic distribution was observed for hypnic and midday occurrence in the current bout.

A greater variance was observed in the afternoon (1 pm to 6 pm) and hypnic (1 am to 6 am) groups, whereas the evening (7 pm to 12 am) group had the least variance, implicating that afternoon and hypnic attacks occur throughout the disease course, whereas evening attacks are prominent only during the earlier disease course.

The nighttime predilection was predominant in the earliest (1st to 2nd deciles) disease duration group, that is, those with ≤ 2 lifetime CH attacks, reduced as the disease progressed (up to the 7th decile), and increased again at the 8th and 10th deciles (mean of 44.1 total lifetime bouts in the 10th decile).

These data indicate that CH may not have fixed rhythmicity throughout the disease course, there is individual variability, and interpretations are as follows:

- The suprachiasmatic nucleus may be additional, but not essential to in the pathophysiology of CH;
- Internal/External homeostasis or treatment effects may influence as well;
- Temporal evolution of CH rhythmicity should be further investigated;
- Whether this circadian rhythmicity evolution is a marker of active disease progression merits additional research;

Many studies are needed indeed to clarify this new CH rhythmicity feature, as the authors conclude "This pattern may indicate a possible evolvement and regression of diurnal expression of CH, the biological implication of which has not yet been determined".

More information: Mi Ji Lee et al, Temporal changes of circadian rhythmicity in cluster headache, *Cephalalgia* (2019). DOI: 10.1177/0333102419883372